DEEP BRAIN STIMULATION THINK TANK: UPDATES IN NEUROTECHNOLOGY AND NEUROMODULATION RESEARCH

EDITED BY: Michael S. Okun, James J. Giordano, Adolfo Ramirez-Zamora and Casey Halpern

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DEEP BRAIN STIMULATION THINK TANK: UPDATES IN NEUROTECHNOLOGY AND NEUROMODULATION RESEARCH

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BRIEF RESEARCH REPORT
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Imaging the Centromedian Thalamic Nucleus Using Quantitative Susceptibility Mapping

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The centromedian (CM) nucleus is an intralaminar thalamic nucleus that is considered as a potentially effective target of deep brain stimulation (DBS) and ablative surgeries for the treatment of multiple neurological and psychiatric disorders. However, the structure of CM is invisible on the standard T1- and T2-weighted (T1w and T2w) magnetic resonance images, which hamper it as a direct DBS target for clinical applications. The purpose of the current study is to demonstrate the use of quantitative susceptibility mapping (QSM) technique to image the CM within the thalamic region. Twelve patients with Parkinson's disease, dystonia, or schizophrenia were included in this study. A 3D multi-echo gradient recalled echo (GRE) sequence was acquired together with T1w and T2w images on a 3-T MR scanner. The QSM image was reconstructed from the GRE phase data. Direct visual inspection of the CM was made on T1w, T2w, and QSM images. Furthermore, the contrast-to-noise ratios (CNRs) of the CM to the adjacent posterior part of thalamus on T1w, T2w, and QSM images were compared using the one-way analysis of variance (ANOVA) test. QSM dramatically improved the visualization of the CM nucleus. Clear delineation of CM compared to the surroundings was observed on QSM but not on T1w and T2w images. Statistical analysis showed that the CNR on QSM was significantly higher than those on T1w and T2w images. Taken together, our results indicate that QSM is a promising technique for improving the visualization of CM as a direct targeting for DBS surgery.

Keywords: deep brain stimulation, direct targeting, gradient recalled echo, quantitative susceptibility mapping, centromedian nucleus

Abbreviations: CM, centromedian nucleus; CNR, contrast-to-noise ratio; DBS, deep brain stimulation; GRE, gradient recalled echo; MRI, magnetic resonance imaging; QSM, quantitative susceptibility mapping; T1w, T1-weighted; T2w, T2-weighted.

INTRODUCTION

The centromedian nucleus (CM) or centromedian–parafasicular nucleus complex, located in the caudal intralaminar thalamic nuclei, has been reported to be a potentially effective target for deep brain stimulation (DBS) or ablative surgeries for the treatment of various neurological and psychiatric diseases, e.g., Parkinson's disease, Tourette syndrome, generalized epilepsy, and intractable neuropathic pain (Ilyas et al., 2019). However, the surgeries targeting CM still relied on the indirect targeting method by registering a normalized atlas to the patient's magnetic resonance imaging (MRI) data and then the CM coordinates are used for target localization (Krauss et al., 2002; Kim et al., 2017; Sharma et al., 2017). This indirect targeting method may lead to suboptimal targeting since significant variations exist in brain structures between patients, and this variation causes unpredictable registration errors (Kennedy et al., 1998) and may sub-optimize treatment effect and increase the rate of surgical complications and adverse side effects (Chan et al., 2009).

Direct targeting can improve the targeting accuracy in certain aspects as revealed by some studies (Tonge et al., 2016; Fenoy and Schiess, 2018). Direct targeting requires that the anatomical locations can be visible on certain image contrast. However, direct visualization of the CM nucleus using the standard T1w and T2w MRI sequences is challenging. On one hand, the volume of the CM is small (smaller than 10 mm in most dimensions; Ilyas et al., 2019). On the other hand, the contrast between the CM nucleus and its surrounding thalamic structures is pretty low. The absence of an imaging technique for direct visualization of CM hampers the targeting accuracy of CM for DBS surgery.

Some researchers have made considerable efforts to improve the individualized depiction of thalamic substructures. Lemaire et al. (2010) reported that high-resolution T1w images could be used to image the substructures of the thalamus, which were very comparable to myelin-stained histologic sections. However, the scan time for the protocol was approximately 14 h, which is not suitable for routine clinical scans. Kanowski et al. (2010) showed that the CM is identifiable in a reasonable measurement time of 13–26 min with two-dimensional high-resolution proton-attenuation-weighted images at 3 T. However, only a few slices in axial plane covering the localized areas were acquired, which still challenges targeting localization when using the surgical planning software involving the 3D image registration procedure. Bender et al. (2011) demonstrated that the CM could be roughly identified by optimized 3D MPRAGE protocol, which would take about 20 min to be acquired; however, clear discrimination of all thalamic substructures were not achievable. If anatomic imaging-based targeting methods can be further improved, the accuracy and efficiency of target selection for DBS or ablative surgeries may further increase.

Quantitative susceptibility mapping (QSM) reconstructed from the MRI phase images of the 3D gradient recalled echo (GRE) sequences could improve tissue contrast compared to T2w images. QSM employed deconvolution of GRE phase images and removed the non-local susceptibility effects, depicting more accurate structural delineation (Liu et al., 2015). QSM has been clinically used to assess important tissue functions and disease (Wang et al., 2017), and recently it has been demonstrated for improving the depiction of DBS target structures with iron-rich nucleus (paramagnetic), e.g., the subthalamic nucleus (Liu et al., 2013; Alkemade et al., 2017) and the globus pallidus internus (Wei et al., 2019), with the surrounding white matters (diamagnetic). The thalamus contains different subregions that are known to have various iron deposits and different degrees of myelinated white matters (Morris et al., 1992; Zhang et al., 2018), which indicates that QSM, by using the susceptibility differences existing between substructures, may be a proper imaging technique to identify CM.

The aim of this study is to examine whether QSM could delineate the CM nucleus from its adjacent thalamic structures and thus generate a direct visualization of the CM.

MATERIALS AND METHODS

Human Subjects

Twelve patients (six males and six females, mean age 41.8 ± 21.2 years old) with Parkinson's disease (n = 5, mean age 61.0 ± 16.6), dystonia (n = 4, mean age 32.8 ± 8.6), or schizophrenia (n = 3, mean age 21.7 ± 10.3) were included as convenient samples in this study. Demographic information collection and neuroradiological investigation were performed by specialized movement disorder neurologists or psychiatrists. The study was approved by the ethics committee of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University. All subjects provided written consent in accordance with the Declaration of Helsinki.

Data Acquisition

Imaging was performed on a 3.0-T MR scanner equipped with a 24-channel head coil. Each subject lay supine with their head snugly fixed with foam pads. The subject was asked to keep still as long as possible. 3D T1w and axial T2w images were acquired. A multi-echo GRE sequence was also performed. Detailed imaging parameters, including the time of repetition, time of echo, field of view, voxel size, and total duration of scanning for the three imaging modalities, are summarized in **Table 1**.

Image Processing

QSM images were reconstructed from GRE phase data. The details of QSM processing has been documented in the previous articles (Wei et al., 2015, 2017). In brief, three major steps were taken for the reconstruction of the QSM image. First, the phase images of GRE were unwrapped using a Laplacian-based phase unwrapping. Afterward, the magnitude images were used to extract the brain tissue using the FMRIB Software Library Brain Extraction Tool[1]. Then, the background phases were removed using the V_SHARP method to obtain the local tissue phase images (Li et al., 2015). Finally, susceptibility maps were generated after dipole inversion using streaking artifact reduction for QSM method (STAR-QSM; Wei et al., 2015).

[1]https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET

TABLE 1 | Imaging parameters.

Parameter	3D T1w	2D T2w	3D GRE
Imaging plane	Axial	Axial	Axial
Field of vision (mm)	240 × 240	240 × 240	240 × 240
Matrix	320 × 320	320 × 320	320 × 320
Resolution (mm)	0.75 × 0.75 × 1.5	0.75 × 0.75 × 1.5	0.75 × 0.75 × 1.5
Time of repetition (ms)	7.04	3,000/4,000	32.80
Time of echo (ms)	3.47	128.60/106.03	11.00
Scan time (s)	172	346	528

Image Inspection and Data Analysis

Firstly, we compared the QSM images to a schematic drawing referenced from the overlay of Schaltenbrand and Wahren histologic atlas (Schaltenbrand et al., 1977) to confirm whether the CM can be visible on the QSM image. To calculate the contrast-to-noise ratios (CNRs), QSM and T2w images were firstly registered to the T1w image. Then, the regions of CM and the adjacent posterior thalamic tissues were manually defined as masks on the QSM image (**Supplementary Figure S1**). Afterward, the masks of CM and posterior thalamus were applied to the T1w and T2w images. The CNRs of the CM nucleus referenced to the posterior thalamus were measured: $CNR = |S_{CM} - S_{pTH}|/\sigma$, where S_{CM} and S_{pTH}, respectively, represent the mean signal intensities of the CM nucleus and posterior part of thalamus. σ represents noise measurement calculated as the standard deviation of the signal intensities in the posterior part of thalamus. The volumes of the CM nucleus were also calculated on QSM images, by multiplying the number of CM voxels and the voxel size.

Statistical Analysis

A one-way analysis of variance (ANOVA) was used to compare the difference in CNRs among the three MR image modalities (IBM SPSS Statistics, version 22). If the one-way ANOVA gave a significant result, independent two-sample *t*-tests were further used as the *post hoc* tests to reveal the CNR differences between each two modalities (T1w vs. T2w, T1w vs. QSM, and T2w vs. QSM). Two-way repeated-measure ANOVAs were also performed to examine the significance of interaction between image modality (T1w, T2w, and QSM) and patient type (Parkinson's disease, dystonia, and schizophrenia), and the significance of interaction between CM volume (left CM and right CM volumes) and patient type. The threshold of significance was set at $p < 0.05$.

RESULTS

Figure 1A shows a schematic drawing of thalamus that is referenced to the Schaltenbrand and Wahren atlas (Schaltenbrand et al., 1977). The diamagnetic CM is surrounded by the relatively paramagnetic medial, lateral, and posterior parts of the thalamus (**Figure 1A**). **Figures 1B,D** show the QSM image of one representative patient. As shown, the QSM image provides a clear visualization on the anatomical structure of the CM (as indicated by an orange arrow) in a patient with Parkinson's disease. The anatomical boundaries of the medial, lateral, and posterior parts of the thalamus are also visible owing to different magnetic susceptibility values, as delineated in **Figure 1C**.

Figure 2 compares the contrast of CM on T1w, T2w, and QSM images at one representative section of a representative patient. The location of CM nucleus is difficult to be identified on the T1w or T2w images. However, QSM image clearly shows the substructures of the thalamus, for example, medial, lateral, and posterior parts of the thalamus. The CM nucleus is delineable from its surroundings on the QSM image. Clear delineation of CM and the surrounding tissues is attributed to the susceptibility difference existed between iron-rich nucleus and the adjacent myelinated white fiber axons. The QSM image exhibits a diamagnetic susceptibility within the CM and a relatively paramagnetic susceptibility of its surrounding thalamic tissues. The T1w, T2w, and QSM images at one representative section containing CM nucleus on each patient are presented in the **Supplementary Figure S2**.

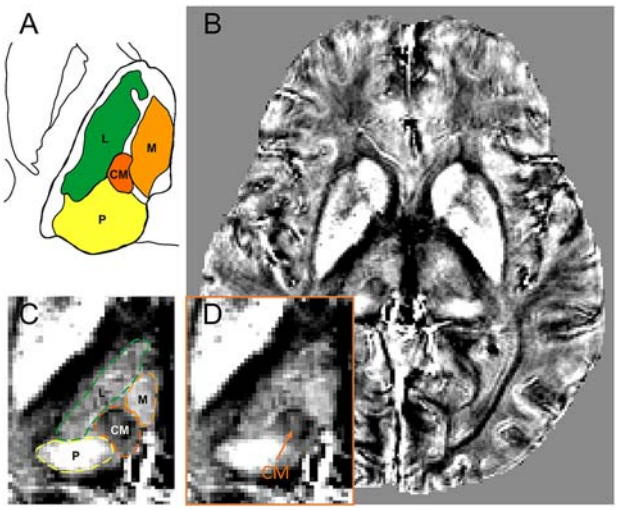

FIGURE 1 | The visualization of CM within the thalamus on quantitative susceptibility mapping (QSM) image. **(A)** A schematic drawing of the CM and its surrounding thalamic structures, referenced to the overlay of the Schaltenbrand and Wahren atlas (Schaltenbrand et al., 1977). **(B)** An axial view of a slice of QSM image with thalamic substructures on a representative patient. **(C)** Enlarged view of thalamic substructures with the anatomical boundaries of CM and its surrounding thalamic parts (medial, lateral, and posterior) delineated. **(D)** Enlarged view of thalamic substructures. The anatomical location of CM nucleus is pointed by an orange arrow. Abbreviations: CM, centromedian nucleus. L, lateral part of thalamus; M, medial part of thalamus; P, posterior part of thalamus.

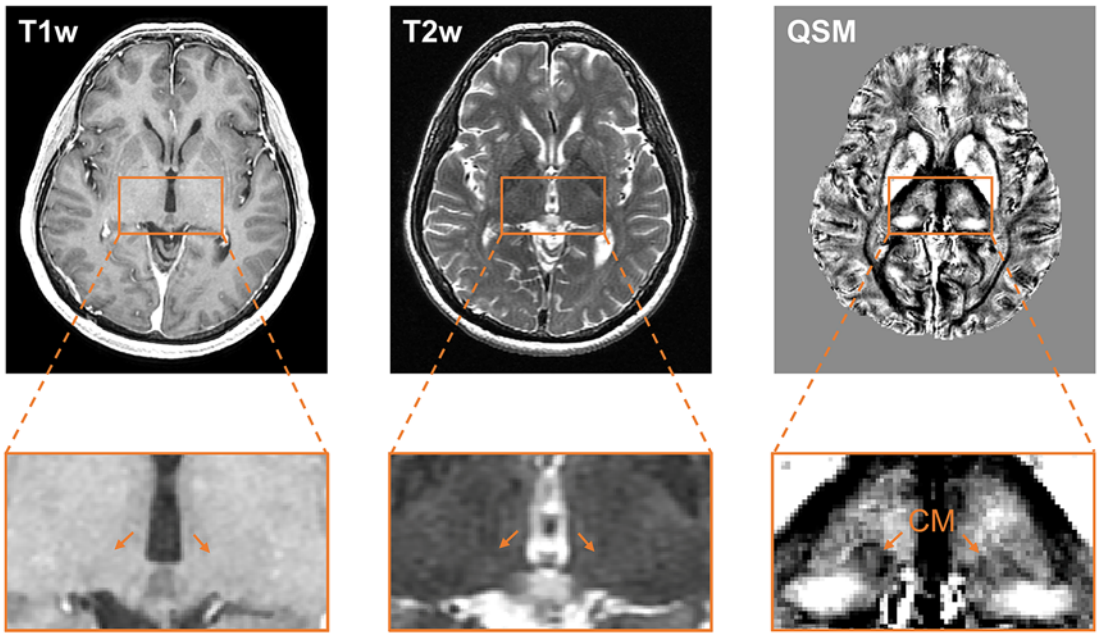

FIGURE 2 | Comparison of the visualization of the CM nucleus on T1w, T2w, and QSM images. Axial slice views (upper row) and enlarged views of the thalamus (lower row) on T1w, T2w, and QSM images at one representative section on a representative patient. Abbreviations: CM, centromedian nucleus; QSM, quantitative susceptibility mapping.

The CNRs of the CM nucleus to the posterior part of thalamus are 0.37 ± 0.35, 0.67 ± 0.43, and 3.43 ± 0.49, respectively, on T1w, T2w, and QSM images (**Figure 3**). The ANOVA reveals significant differences among T1w, T2w, and QSM images in terms of the CNR, $F_{(2)} = 177.14$, $p < 0.001$ (**Figure 3**). *Post hoc* tests (independent two-sample *t*-tests) indicate significant different CNRs between QSM and T1w ($t_{(11)} = 16.66$, $p < 0.001$), and between QSM and T2w ($t_{(11)} = 17.44$, $p < 0.001$). The mean CNRs for each type of patients are illustrated in the **Supplementary Table S1**, in which increased CNRs on QSM images are indicated in each of the three patient types. The mean volumes of the left and right CM nuclei are 160.95 ± 29.98 mm^3 and 169.73 ± 50.34 mm^3, respectively, as detected on the QSM images. No significant main effects of patient type on CNR value or CM volume, or interactions between patient type and CNR value, or between patient type and CM volume were found in our sample (*ps* > 0.142, **Supplementary Tables S1, S2**).

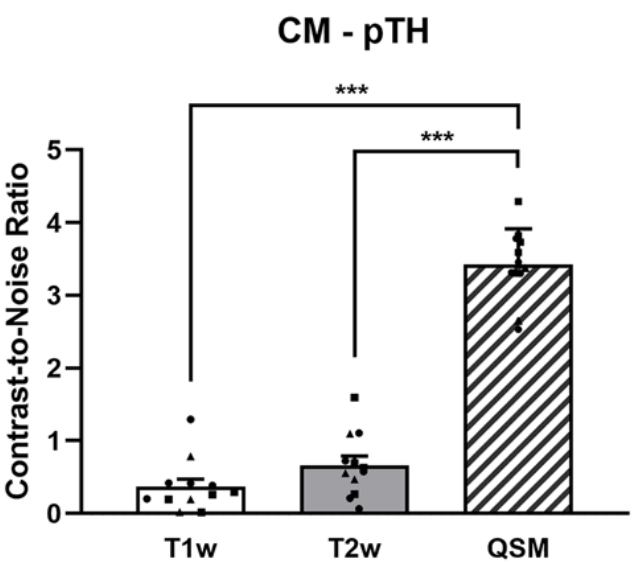

FIGURE 3 | The CNRs of the CM to the posterior part of thalamus on the T1w, T2w, and QSM images. The dots represent the individual values of the Parkinson's disease patients (square dots), the dystonia patients (circular dots), and the schizophrenia patients (triangle dots). ***Indicates $p < 0.001$. Abbreviations: CM, centromedian nucleus; pTH, posterior thalamus; QSM, quantitative susceptibility mapping.

DISCUSSION

The results demonstrate that with the QSM technique, the CM can be clearly delineated from the surrounding subthalamic nuclei. Compared with commonly used T1w and T2w images for DBS planning, QSM significantly improved the CNR of CM nucleus compared to its surrounding thalamic structures, suggesting that a QSM-based image is more suitable to target the patient-specific CM in DBS surgery directly.

Aside from the surgical targets routinely used in clinical treatment (e.g., subthalamic nucleus, nucleus accumbens), there are some other targets with potential effectiveness in treating

neurological and psychiatric diseases. The CM nucleus or centromedian–parafasicular nucleus complex, situated within the intralaminar nuclei of the thalamus, has abundant fiber connections with other thalamic nuclei, basal ganglia, and cerebral cortex (Ilyas et al., 2019). In several studies, the CM nucleus has been suggested as a potentially effective DBS target for the treatment of Parkinson's disease (Caparros-Lefebvre et al., 1999; Mazzone et al., 2006; Peppe et al., 2008; Stefani et al., 2009) and Tourette syndrome (Houeto et al., 2005; Savica et al., 2012; Testini et al., 2016; Marano et al., 2019). The clinical surgeries targeting at CM also show treatment effect for the generalized epilepsy (Fisher et al., 1992; Velasco et al., 2007; Valentín et al., 2013; Li and Cook, 2018) and intractable neuropathic pain (Young et al., 1995; Hollingworth et al., 2017) by means of DBS or thalamotomy. The DBS surgery targeting the CM nucleus currently uses indirect ways in which a two-dimensional stereotactic atlas of the thalamus is superimposed on a CT or MRI scan relative to coarse anatomical landmarks including anterior and posterior commissures (Stefani et al., 2009; Son et al., 2016; Testini et al., 2016). The indirect method of targeting the CM nucleus is due to the small volume of the CM, measuring smaller than 10 mm in most dimensions (Ilyas et al., 2019), and low image contrast between the CM nucleus and its surrounding thalamic structures on conventional MRI images. The challenge of precisely locating the nucleus would limit the clinical application and the efficacy of CM-DBS. Inter-patient variability may affect the accuracy of the placement DBS electrodes, and may sub-optimize treatment effect and increase the rate of surgical complications and adverse side effects (Chan et al., 2009). Direct imaging CM can be of great help for direct targeting of this intralaminar thalamic nucleus.

Recently developed QSM image reconstructed from the GRE-sequence image is an effective technique that takes advantage of differentiated iron concentration in different subcortical microstructures to identify their locations (Deistung et al., 2017). Thalamic nuclei have sufficient iron concentration and different nuclei are with different levels of iron deposits (Drayer et al., 1986; Morris et al., 1992). Thus, QSM can delineate one nucleus from its adjacent myelinated white matter axons, such as for imaging the CM in this study. The delineation of CM is attributed to the susceptibility difference existed in iron concentration compared to the adjacent myelin sheath fibers. Although CM nucleus is also visible on high-resolution T1w images, 2-D proton-attenuation-weighted images, or images acquired by optimized 3D MPRAGE protocol (Kanowski et al., 2010; Lemaire et al., 2010; Bender et al., 2011), those images usually would take at least 20 min (or even hours) to be acquired. GRE image of the whole brain can be acquired within less than 10 min, which is more realistic for routine clinical scans for DBS planning.

Based on our finding that QSM could provide direct visualization on CM nucleus, together with the recent findings that QSM could also provide superior anatomical delineation in subthalamic nucleus (Liu et al., 2013; Alkemade et al., 2017) and globus pallidus internus (Wei et al., 2019), the implementation of QSM imaging in clinical settings for relevant diseases should be given consideration by radiologists, neurosurgeons, MR manufacturers, and engineers. On the other hand, the QSM technique has plenty of room to improve on for clinical applications, including shortening acquisition time and reducing streaking artifacts to further improve the image quality (Wang et al., 2017).

The signal intensity on a QSM image depends on the tissue magnetic susceptibility (Wang and Liu, 2015). Due to the rich abundancy of iron in the blood, the blood vessel on a QSM image has a much higher intensity than gray matter, white matter, or cerebrospinal fluid (Haacke et al., 2015). The visual identification of the CM nucleus in the present sample is unaffected by the blood vessels nearby. Furthermore, strong QSM signal can be observed in the structures with bleeding or vascular dysmorphia (Liu et al., 2012, 2015; Chen et al., 2014). Although not being observed in the individuals of our sample, the delineation of the thalamic structures, including the CM nucleus, could be blurred in individuals with micro-bleeding or vascular dysmorphia at or around the regions of interest.

There are some limitations in the current study. The 3D GRE sequences is quite sensitive to patients' motion during the scan, and thus the application in patients with obvious tremor might be limited. The next limitation is that the scanning process for whole-brain QSM takes nearly 5–10 min. Although it is faster than the other methods that can also demonstrate the CM nucleus (Kanowski et al., 2010; Lemaire et al., 2010; Bender et al., 2011), more rapid QSM techniques are yet to be invented for DBS targeting in clinical application (Wei et al., 2019). Another limitation is that the segmentations were done manually in this study. In future studies, the QSM images could be normalized to MNI space and segmented based on available subcortical 3D atlases, e.g., using Lead-DBS toolbox[2]. Finally, the sample size of the present study is relatively small. However, even with small sample size, the superiority of QSM for depicting CM nucleus can still be observed. The negative results of CNR values and CM volumes between different types of patients may be attributed to the limited sample size. Future studies with large sample sizes are needed to reveal the profiles of CNR values and CM volumes in different types of patients, particularly in the patients where DBS has shown potential effectiveness (e.g., Parkinson's disease, Tourette syndrome, generalized epilepsy, and intractable neuropathic pain).

CONCLUSION

In summary, we have demonstrated that the QSM images provide a significantly clearer visualization of the CM nucleus than T1w and T2w images, suggesting that a QSM image is likely more suitable to aid directly determining patient-specific CM coordinates in the DBS and ablative surgeries. Future studies are highly needed to evaluate the QSM imaging CM nucleus on a large sample size, particularly in the

[2]www.lead-dbs.org

types of patients who might potentially benefit from DBS treatment, and confirm whether QSM technique can improve DBS targeting accuracy or effectiveness compared with indirect targeting methods.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW, DL, BS, CZ, and HW conceived and designed the study. WX and HW collected the data. JL, YL, LG, WX, and CL analyzed the data. JL, YL, LG, YW, CL, DL, BS, CZ, and HW interpreted the data and wrote the article.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Bilateral Posterior Subthalamic Area Deep Brain Stimulation for Essential Tremor: A Case Series

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Background: Deep brain stimulation (DBS) of the posterior subthalamic area (PSA) provides a potentially effective treatment for medication-refractory essential tremor (ET).

Objective: To study the clinical benefits and adverse-event profile of bilateral PSA-DBS for refractory ET.

Methods: Seven patients with refractory ET underwent bilateral PSA-DBS surgery under general anesthesia between September 2017 and May 2018. Clinical outcome assessments, using the Essential Tremor Rating Scale, were performed at 1-, 6-, and 12-month follow-up, except for the last assessment of one patient who was followed up to 9 months. Analysis was focused on changes in patients' motor symptoms and quality of life following surgery as well as documenting the adverse-event profile associated with the surgical PSA-DBS treatment.

Results: After surgery, patients' motor symptoms, including upper limb tremor and head tremor, were improved by 84.2% and their quality of life by 81.25% at 1-month follow-up. The clinical benefits to patients were maintained at 6-month and last follow-up. Adverse side effects included dysarthria (n = 4), balance disorder (n = 2), and paresthesia of the right limb (n = 1). No habituation effects were observed throughout the follow-up.

Conclusion: Bilateral PSA-DBS seems to offer an effective and safe alternative treatment for medically intractable ET, warranting further research into its clinical utility, adverse-event profile, and comparative effectiveness.

Keywords: essential tremor, deep brain stimulation, posterior subthalamic area, ventral intermediate nucleus of the thalamus, head tremor

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INTRODUCTION

Essential tremor (ET) is a relatively common movement disorder associated with marked physical and psychosocial disabilities (Louis and Ferreira, 2010). Deep brain stimulation (DBS) has emerged as a safe and effective treatment for medically refractory ET (Anderson and Kartha, 2013). The ventral intermediate nucleus of the thalamus (VIM) has been mainly used as the target

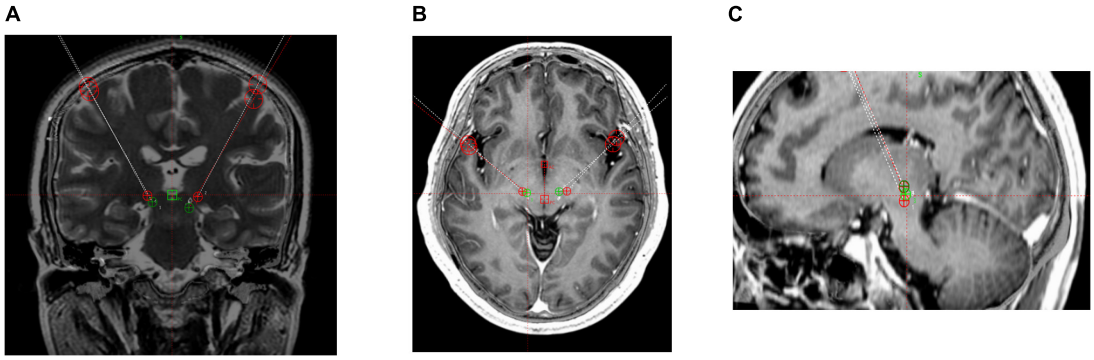

FIGURE 1 | 3 T magnetic resonance images. Target coordinates of the posterior subthalamic area (PSA) were 10 mm lateral, 7.7 mm anterior, and 3.4 mm superior. PSA (green) and ventral intermediate nucleus of the thalamus (red) contacts. **(A)** Coronal T2-weighted image. **(B)** Horizontal T1-weighted image. **(C)** Sagittal T1-weighted image.

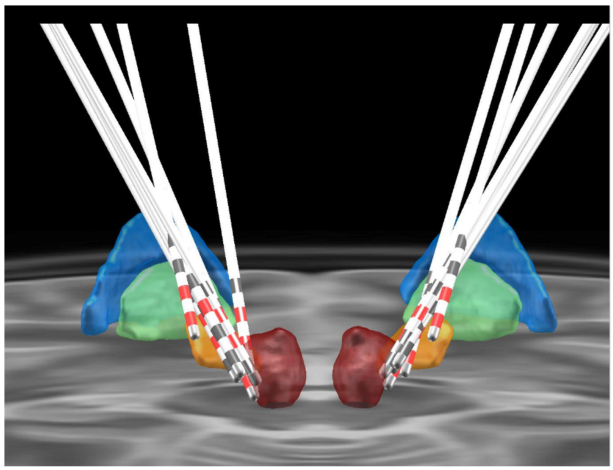

FIGURE 2 | Positioning of the electrodes for posterior subthalamic area-deep brain stimulation. The colored areas represent different anatomical structures (blue, globus pallidus externus; green, globus pallidus internus; orange, subthalamic nucleus; red, red nucleus).

in DBS treatment for ET, and its stimulation is particularly effective in reducing hand tremor (Flora et al., 2010). However, the effects of DBS on midline symptoms, such as head tremor, have been inconsistent across studies and are less predictable. It has been reported that bilateral VIM-DBS reduces head tremor and that bilateral stimulation is more effective than unilateral DBS (Obwegeser et al., 2000). However, bilateral VIM-DBS is associated with a higher risk of adverse side effects than unilateral VIM-DBS, including dysarthria, incoordination, and abnormal gait; DBS reprograming within the therapeutic window may not resolve these side effects (Mitchell et al., 2000). Moreover, 10–73% of patients who underwent VIM-DBS, particularly bilateral DBS, seems to develop observable tolerance and waning of benefits over the long-term treatment course (Benabid et al., 1996, 1998; Papavassiliou et al., 2004; Pilitsis et al., 2008; Shih et al., 2013). Given these limitations, several DBS studies have explored the utility of targets other than the VIM in treating ET.

Kitagawa et al. (2000) reported a case of ET treated with unilateral DBS of a target positioned 3 mm below the VIM. After treatment, the patient's postural tremor was substantially improved. Another target of interest is the posterior subthalamic area (PSA), which includes the zona incerta and prelemniscal radiation. Emerging evidence from PSA-DBS studies (Herzog et al., 2007; Patric et al., 2009; Blomstedt et al., 2010, 2011; Barbe et al., 2011, 2018; Fytagoridis et al., 2012; Ulrika et al., 2012) has indicated that stimulation of this target may be effective in reducing tremor, particularly when the tremor is difficult to control with VIM-DBS. Moreover, the adverse side effects of PSA-DBS seem to be mild and transient, without enduring side effects or stimulation tolerance (Pahwa et al., 2006; Fytagoridis and Blomstedt, 2010). To date, however, only a few studies have been conducted to assess the safety and effectiveness of PSA-DBS for ET, and even fewer studies have explored the clinical effects of bilateral PSA stimulation (Xie et al., 2012; Ghilardi et al., 2018). Therefore, we retrospectively assessed the clinical outcomes of a series of patients with medically refractory ET who underwent bilateral PSA-DBS. The study results should contribute to a better understanding of the clinical benefits and adverse-event profile of bilateral PSA-DBS in patients with refractory ET.

MATERIALS AND METHODS

In this retrospective case series, seven patients were identified from past medical records and followed up to the present. Each patient was clinically assessed and videotaped at regular intervals as part of standard care after they had received bilateral PSA-DBS surgery. Six patients were followed up for 12 months and one patient was followed up for 9 months. The average follow-up duration of the patient sample was 11.6 months. At the last follow-up, participating patients gave written informed consent for this study. The study was approved by the ethics committee

of Ruijin Hospital School of Medicine, Shanghai Jiao Tong University, and was performed in accordance with the Declaration of Helsinki.

Surgical Procedure

The surgical procedure included target localization and implantation of electrodes and pulse generators. Patients underwent 3.0-T magnetic resonance imaging (MRI) involving continuous scanning in the horizontal and coronal planes (slice thickness, 2 mm) and T2-weighted and post-gadolinium volumetric axial T1-weighted sequences. VIM targeting began with identifying the standard stereotactic coordinates relative to the posterior commissure (PC) on an anterior–posterior commissure (AC-PC)-aligned MRI; the position was 10.5–11.0 mm lateral to the wall of the third ventricle, 6.0–7.0 mm anterior, and 0 mm dorsal (Leksell Surgiplan, version 10.0, Elekta Instrument AB, Stockholm, Sweden). Subsequently, the PSA target was identified as being medial to the posterior tail of the subthalamic nucleus and lateral to the red nucleus on an AC-PC-aligned axial T2-weighted MRI at the level of the widest diameter of the red nucleus (**Figures 1**, **2**).

Our strategy was to target the VIM and PSA if both targets could be targeted. The trajectory was planned by using the PSA as the primary target. The coronal and sagittal angles were adjusted to attain a trajectory that traversed the VIM target. The planned trajectory was identified in coronal sections, beginning at the top of a gyrus and avoiding the ventricles, caudate nucleus, and blood vessels. The PSA was targeted in cases where the planned alignment was not achievable. In four patients, both the VIM and PSA were targeted. In the other three patients, both regions were not simultaneously targeted because we were unable to align them in one trajectory (Bot et al., 2017).

A stereotactic frame (Leksell) was installed under local anesthesia. The stereotactic pedestal was placed in parallel with the front and rear joint line (AC-PC). The head-computed tomography image was transmitted to the surgical planning system to determine the PSA target coordinates. Next, electrodes (3387, Medtronic or L102, PINS, Beijing Pins Medical Equipment Co., Ltd., Beijing, China) were implanted under general anesthesia. A pulse generator (37612 RC Medtronic or 102R PINS) was implanted under the clavicle. One week after DBS electrode implantation, the images of the patient's head and the preoperative MRI (using a Helix sequence) were

TABLE 1 | Patient characteristics (*N* = 7)*.

Sex (men/women)	6/1
Age (years)	
Age of onset (years)	39.00 ± 9.00 (19–46)
Age of surgery (years)	59.00 ± 21.00 (29–69)
Duration (years)	20.00 ± 11.00 (7–30)
Previous VIM-DBS surgery	1 (bilateral)
Follow-up duration (months)	9 (1/7) or 12 (6/7)

*VIM-DBS, ventral intermediate nucleus-deep brain stimulation. *Data values represent median ± interquartile range (min–max) unless indicated otherwise.*

TABLE 2 | Essential tremor rating scale scores before and after bilateral PSA-DBS (*N* = 7)*.

Item	Top score	Baseline	One month		Improvement	*p*-Value	Six months		Improvement	*p*-Value	Last follow-up#		Improvement	*p*-Value
			DBS ON	DBS OFF			DBS ON	DBS OFF			DBS ON	DBS OFF		
Tremor rate (items 1–9)	80	19.00 ± 10.00	3.00 ± 4.00	14.50 ± 13.00	84.21%	0.018	2.00 ± 3.00	14.50 ± 14.50	89.47%	0.018	2.00 ± 2.00	14.50 ± 14.50	89.47%	0.018
Head tremor (item 4)	4	1.00 ± 2.25	0.00. ± 0.00	1.00 ± 2.00	100.00%	0.048	0.00 ± 0.00	1.00 ± 2.00	100.00%	0.048	0.00 ± 0.00	1.00 ± 2.00	100.00%	0.048
Upper tremor (items 5, 6)	24	12.50 ± 3.00	3.00 ± 2.00	11.00 ± 3.50	76.00%	0.018	2.00 ± 2.00	11.00 ± 3.50	84.00%	0.018	1.00 ± 1.50	11.00 ± 4.50	92.00%	0.018
Rest	8	4.50 ± 5.00	0.00 ± 0.00	3.50 ± 4.50	100.00%	0.031	0.00 ± 0.00	3.50 ± 4.50	100.00%	0.031	0.00 ± 0.00	3.50 ± 4.50	100.00%	0.031
Posture	8	5.00 ± 1.50	1.00 ± 1.50	5.00 ± 1.50	80.00%	0.017	1.00 ± 1.50	4.50 ± 1.50	80.00%	0.018	0.00 ± 1.50	4.50 ± 1.50	100.00%	0.017
Action	8	5.50 ± 1.50	1.00 ± 2.50	4.50 ± 1.50	81.82%	0.018	1.00 ± 2.00	4.50 ± 1.50	81.82%	0.018	1.00 ± 2.00	4.50 ± 1.50	81.82%	0.018
Quality of life (items 15–21)	28	16.00 ± 9.00	3.00 ± 5.00	15.00 ± 9.00	81.25%	0.017	3.00 ± 4.00	14.00 ± 8.00	81.25%	0.017	2.00 ± 4.00	14.00 ± 9.00	87.50%	0.017
Speech (item 15)	4	0.00 ± 1.00.	0.00 ± 1.00	0.00 ± 1.00	–	0.317	0.00 ± 0.00	1.00 ± 1.00	–	0.083	0.00 ± 0.00	1.00 ± 1.00	–	0.083

*DBS, deep brain stimulation. Improvement refer to symptom change from baseline to follow-up with stimulation on. *Data values represent median ± interquartile range unless indicated otherwise. #Six patients were followed up to 12 months; 1 patient was followed up to 9 months.*

TABLE 3 | Essential tremor rating scale raw scores of each patient (DBS ON).

Patient	Head tremor (item 4)				Upper tremor (items 5, 6)			
	Baseline	One month	Six months	Last follow-up	Baseline	One month	Six months	Last follow-up
1	2	0	0	0	14.5	1	1	0
2	0	0	0	0	15	3	3	2
3	2	0	0	0	11	5	3	3
4	0	0	0	0	12	5.5	4	4
5	0	0	0	0	12	3	3	3
6	3	0	0	0	18.5	0	1	0
7	2	0	0	0	12.5	1	1	1

merged to determine the position of the electrodes before programing. In this study, we focused on assessing the clinical effects of PSA stimulation; only the electrodes located in the PSA were activated.

Clinical Examination

In each patient, DBS was activated 1 week after surgery. We examined the clinical effects of stimulation after the location of each electrode was confirmed. Electrodes that displayed the best stimulation effect were selected for chronic stimulation. As outlined in the prior section, we focused on the electrodes located in the PSA.

A movement disorder specialist performed the clinical outcome assessments, using the Essential Tremor Rating Scale (ETRS) (Fahn et al., 1988), before surgery and at 1-month, 6-month, and last (9- or 12-month) follow-up. Assessments focused on motor symptoms (items 1–9 of the ETRS), quality of life (items 15–21 of the ETRS), and complications, such as dysarthria, balance disorders, and hemiplegia. Additionally, the patients were videotaped with and without stimulation (stimulation was switched off during the preceding night) by another movement disorder specialist who was blinded to the patients' condition. This specialist also examined the videos.

TABLE 4 | Electrode position and final stimulation parameters.

Patient	Contact	Target	Voltage (V)	Frequency (Hz)	Pulse (μs)
1	C + 4–	L-PSA	1.75	125	60
	C + 0–	R-PSA	2.45	115	60
2	C + 8–9–	L-PSA	2.5	160	60
	C + 0–1–	R-PSA	2.5	160	60
3	C + 8–9–	L-PSA	3.0	145	60
	C + 1–	R-PSA	2.35	145	60
4	C + 6–	L-PSA	2.15	135	50
	C + 2–	R-PSA	2.0	135	50
5	C + 6–5–	L-PSA	3.35	135	60
	C + 1–0–	R-PSA	2.15	135	60
6	C + 6–5–	L-PSA	2.65	145	80
	C + 1–	R-PSA	2.35	145	60
7	C + 5–6–	L-PSA	2.35	145	60
	C + 1–2–	R-PSA	2.65	145	80

PSA, posterior subthalamic area; R, right; L, left.

Statistical Analysis

We performed a Kolmogorov–Smirnov test and the results indicated that nearly all variables were normally distributed and therefore suitable for parametric tests. However, it is difficult if not impossible to extrapolate data from a case series of seven patients to the overall population. Therefore, we utilized (non-parametric) Wilcoxon signed rank tests to make comparisons between the ETRS scores acquired under the different conditions. *P*-values less than 0.05 (two-sided) were considered statistically significant. The analysis was performed using SPSS 23 (IBM Corp, Armonk, NY, United States). Continuous variables are described as medians and interquartile ranges for parametric and non-parametric data distributions, respectively. The results are presented as the median ± interquartile range.

RESULTS

Patients

The seven patients (six male, one female; mean age: 56.1 ± 14.3 years, **Table 1**) had undergone bilateral PSA-DBS at the Neurosurgical Center of Shanghai Ruijin Hospital between 2017 and 2018. At the time of surgery, all patients showed bilateral upper extremity postural tremor. Three out of the seven patients also displayed head tremor. Each patient was diagnosed with ET by using the diagnostic criteria of the Movement Disorder Society (Bhatia et al., 2018), including a history of therapeutic failure of at least one first-line medication. After clinical examination, the patients underwent bilateral PSA-DBS surgery by a medical team of movement disorder specialists and functional neurosurgeons.

ETRS Data

The patients' ETRS scores before and after bilateral PSA-DBS surgery are presented in **Tables 2**, **3**. At 1-month follow-up, the patients' motor symptoms were improved, on average, by 84.2%, head tremor by 100.0%, upper limb tremor by 76.0%, and quality of life by 81.25%. These clinical benefits were significant and maintained at 6-month and last (9- or 12-month) follow-up (**Table 2**). No significant differences existed between the mean ETRS scores obtained at 6-month and last follow-up.

Electrode Position and Parameters

One week after surgery, the DBS parameters were set to the following values: pulse voltage = 1.5–2 V, frequency = 145 Hz, and duration = 60 μs, using monopolar stimulation. Subsequently, the stimulation parameters were adjusted according to the patients' symptoms and extent of adverse side effects in an effort to achieve the clinically best outcomes (**Table 4**). Ultimately, the stimulation parameters were set to 1.75–3.35 V, 115–160 Hz, and 50–80 μs (the Pins device pulse began at 30 μs).

Adverse Side Effects

Four out of the seven patients displayed mild dysarthria associated with the stimulation. Two patients in the sample developed a mild balance disorder. Both adverse side effects were resolved during the off-state condition at 6-month follow-up and did not reappear thereafter. One patient in the sample developed postoperative paralysis in the right arm due to edema in the trajectory of the left lead; this adverse event was similarly resolved at 6-month follow-up (**Figure 3**).

DISCUSSION

In this study, we explored the clinical benefits and adverse event-profile of bilateral PSA-DBS in several patients with medication-refractory ET. The results showed that bilateral PSA-DBS was associated with a significant improvement in patients' motor symptoms, particularly upper limb tremor and quality of life. These clinical benefits were evident at 1-month follow-up and maintained at 6-month and final (9- or 12-month) follow-up. At final follow-up, patients' motor symptoms were reduced by almost 90% compared with the severity of their symptoms before DBS treatment. Interestingly, bilateral PSA-DBS was also associated with a marked improvement in head tremor. The latter finding compares favorably with the 30–57% improvement in

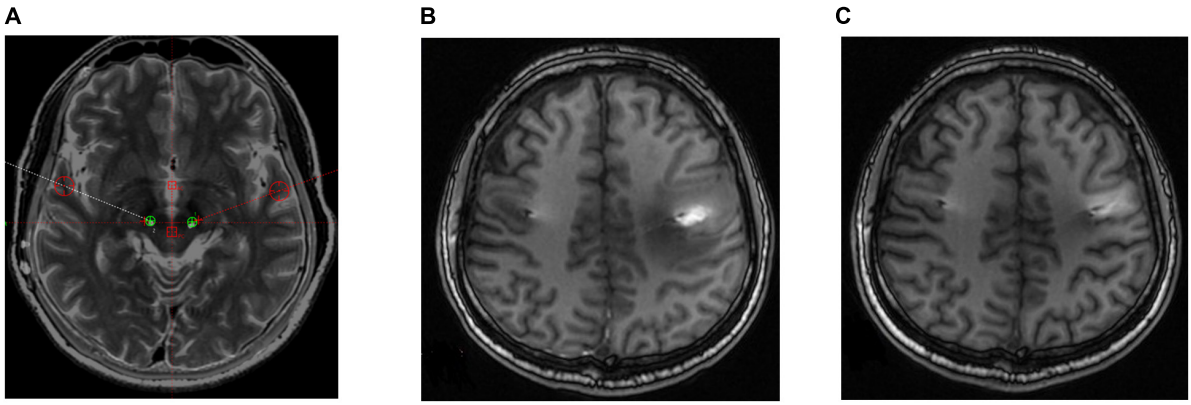

FIGURE 3 | Postoperative brain magnetic resonance (MR) images in a patient who developed right paralysis due to encephaledema. **(A)** Position of electrodes. **(B)** MR image taken 1 week postoperatively. **(C)** MR image taken 8 weeks postoperatively.

TABLE 5 | Stimulation parameters at 6-month and last follow-up[#].

Patient	Six months				Last follow-up			
		Voltage (V)	Frequency (Hz)	Pulse width (μs)		Voltage (V)	Frequency (Hz)	Pulse width (μs)
Patient 1	C + 4−5−	2.25	125	60	C + 4−	1.75	125	60
	C + 0−1−	2.25	115	60	C + 0−	2.45	115	60
Patient 2	C + 8−9−	2.5	160	60	C + 8−9−	2.5	160	60
	C + 0−1−	2.5	160	60	C + 0−1−	2.5	160	60
Patient 3	C + 8−	2.9	160	70	C + 8−9−	3.0	135	60
	C + 1−	2.3	160	60	C + 1−	2.35	135	60
Patient 4	C + 6−	2.15	135	50	C + 6−	2.15	135	50
	C + 2−	2.1	135	50	C + 2−	2.0	135	50
Patient 5	C + 6−5−	3.35	135	60	C + 6−5−	3.35	135	60
	C + 1−0−	2.15	135	60	C + 1−0−	2.15	135	60
Patient 6	C + 6−5−	2.25	145	80	C + 6−5−	2.65	145	80
	C + 1−	1.75	145	60	C + 1−	2.35	145	60
Patient 7	C + 5−6−	2.15	145	60	C + 5−6−	2.35	145	60
	1−2 +	2.65	145	80	1−2 +	2.65	145	80

[#]*Six patients were followed up to 12 months; 1 patient was followed up to 9 months.*

head tremor seen after unilateral VIM-DBS and with the 51–86% improvement observed following bilateral VIM-DBS (Obwegeser et al., 2000; Ondo et al., 2001; Putzke et al., 2005; Whiting et al., 2018). The present results indicate that bilateral PSA-DBS could provide a valuable alternative treatment for medically intractable ET, warranting further research into its clinical utility and comparative effectiveness.

Moreover, bilateral PSA-DBS was associated with mild and tolerable side effects in this study. Although dysarthria (n = 4) and balance disorder (n = 2) emerged in the initial stages of treatment, all adverse side effects were transient and subsequently resolved or reduced by DBS reprograming without affecting the therapeutic effects (**Table 5**). Indeed, previous studies have similarly shown that decreasing the pulse width or frequency or other parameter adjustments offer a powerful means to eliminate or reduce adverse side effects while maintaining the clinical benefits of DBS treatment to patients (Ramirez-Zamora et al., 2016; Choe et al., 2018; Moldovan et al., 2018). Thus, bilateral PSA-DBS could provide not only an effective but also a relatively safe treatment for refractory ET.

It was concerning, however, that one of the patients developed paralysis in the right arm due to edema in the trajectory of the left DBS lead. This adverse event was linked to the close proximity between the electrode trajectory and motor cortex. To adjust this, we used a large coronal and sagittal angle so that the electrodes crossed posterior to the central gyrus and encompassed both the PSA and VIM in one trajectory. Subsequently, the patient's paralysis was resolved at 6-month follow-up.

The results of this case series are promising but should be considered as tentative and preliminary given the study limitations. The study included only a small patient sample, did not include a comparison group, and had significant potential for bias and confounding. Accordingly, the results may be categorized as class IV evidence. In addition, the patient sample was clinically heterogenous and the DBS device used was not identical in all patients. Thus, additional research is required to support or refute the present findings before any firm conclusions can be drawn.

CONCLUSION

This study indicated that bilateral PSA-DBS could offer an effective and safe alternative treatment for at least some cases of medically intractable ET. The results seem to us sufficiently promising to warrant the initiation of larger and well-controlled studies to assess its clinical utility, adverse-event profile, and comparative effectiveness.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DL, YW, BS, and CZ performed the concept and design. XS and LH performed the data acquisition. XS, LH, and YW performed the analysis and interpretation of data. DL and YW performed the statistical review and critique. XS, LH, CZ, DL, YW, YP, TW, JD, and HL drafted the article. XS, DL, and YW approved the final submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Three-Year Gait and Axial Outcomes of Bilateral STN and GPi Parkinson's Disease Deep Brain Stimulation

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Objective: To examine the short- and long-term clinical outcomes of the bilateral subthalamic nucleus (STN) and globus pallidus internus (GPi) deep brain stimulation (DBS) on gait and axial symptoms in Parkinson's disease (PD) patients. Available data have been inconsistent and mostly short-term regarding the effect of both brain targets on gait and axial symptoms. We aimed to identify potential target specific differences at 3-year follow-up from a large single-center experience.

Methods: We retrospectively reviewed short-term (6-month follow-up) and long-term (36-month follow-up) changes in the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and III total scores of 72 PD patients (53 with bilateral STN-DBS and 19 with bilateral GPi-DBS). An interdisciplinary team made target-specific decisions for each DBS patient. We analyzed changes in gait and axial subscores derived from UPDRS II and III.

Results: In both the STN- and GPi-DBS cohorts, we observed no significant differences in gait and axial UPDRS derived subscores in the off-med/on stimulation state at long-term follow-up when compared to baseline. On-med axial scores remained similar in the short-term but worsened in both groups (STN, 2.23 ± 3.43, $p < 0.001$; GPi, 2.53 ± 2.37, $p < 0.01$) in the long-term possibly due to disease progression. At long-term follow-up, the UPDRS III off-med/on stimulation scores worsened but were persistently improved from baseline in both groups (-9.07 ± 13.9, $p < 0.001$).

Conclusions: The study showed that long-term both STN- and GPi-DBS had a similar effect on gait and axial symptoms in UPDRS derived subscores at 36-month follow-up despite potential baseline differences in criteria for selection of each target. More sophisticated measures of gait and balance beyond the categorical UPDRS score will be needed for future studies.

Keywords: deep brain stimulation, globus pallidus internus (GPi), subthalamic nucleus (STN), long-term effect, gait disability, axial symptoms, Parkinson's diasese

INTRODUCTION

Debilitating and progressive axial features, including gait disturbances, postural instability, and postural abnormalities are frequently observed during Parkinson's disease (PD) progression (Nutt et al., 2011). These symptoms have been associated with reduced mobility, loss of independence, and recurrent falls in some cases with subsequent injuries (Fasano et al., 2015). Collectively, the literature has suggested that at a decade or more after diagnosis, the axial symptoms predominate in motor performance and contribute to a disproportionate decline in the therapeutic response to standard dopaminergic treatment, although some symptoms can be improved with adequate doses of dopamine replacement therapy or physiotherapy (Krack et al., 2003; St. George et al., 2010; Castrioto et al., 2011; Eisinger et al., 2019). Although deep brain stimulation (DBS) is an established procedure for treating many of the motor symptoms and fluctuations in PD, the reports on the effects of neuromodulation on axial disability have been inconsistent and difficult to predict, particularly in the long term.

Axial motor symptoms can be improved in some patients, remain unchanged in others, or even worsen in a subset of patients after DBS (Xie et al., 2012; Pötter-Nerger and Volkmann, 2013; Collomb-Clerc and Welter, 2015; Di Giulio et al., 2019). Several factors can affect axial symptoms, including patient characteristics, DBS target, the precise positioning of the electrode within the nucleus and also the stimulation parameters (Tisch et al., 2007; Fasano et al., 2015; Ramirez-Zamora and Ostrem, 2018). The subthalamic nucleus (STN) and globus pallidus internus (GPi) are two common DBS targets utilized for the management of motor fluctuations in PD patients (Ramirez-Zamora and Ostrem, 2018). Previous studies have suggested that GPi-DBS might be associated with a milder long-term (more than 2 years) decline of axial signs, such as balance, freezing of gait (Ferraye et al., 2008), and postural instability (St. George et al., 2010; Fasano et al., 2015), while STN-DBS might provide greater improvement of axial motor symptoms in the short term (∼1 year; St. George et al., 2010). Most of the DBS efficacy data from 1 to 2 years follow-up of STN-and GPi-DBS for PD were derived from controlled studies, however only a few data focused on the axial symptoms and gait impairment (Xie et al., 2012; Aviles-Olmos et al., 2014; Kim et al., 2019). The long-term efficacy of bilateral DBS (particularly GPi-DBS) has been less well established.

In this study, we conducted a retrospective analysis of a large data set of PD patients managed with DBS in order to determine the short-term and long-term outcome of axial symptoms and gait function following bilateral STN- and GPi-DBS performed in a single center.

MATERIALS AND METHODS

Patients

The study was approved by the University of Florida (UF) Institutional Review Board (IRB). Informed consent was provided according to the IRB-approved UF INFORM protocol. The UF INFORM database is a widely-used large movement disorders database with demographic, clinical, and surgical data (Oyama et al., 2012). Patient information was anonymized and de-identified prior to analysis. Patients were eligible for enrollment if they had received a diagnosis of idiopathic PD from a movement disorders-trained neurologist and underwent bilateral DBS implantation surgery at the University of Florida from 2002 to 2015. The selection of target—either the GPi or STN—was reached by a standard of care interdisciplinary screening and discussion (Higuchi et al., 2016). Inclusion criteria were: (1) bilateral placement of DBS; (2) fulfill the UK PD Society Brain Bank Clinical diagnosis criteria (Hughes et al., 1992); and (3) patients must have received both on-med and off-med scores in the preoperative assessment, 6-month (considered between 3–9 months) and 36-month postoperative (considered between 33–39 months). Exclusion criteria were: (1) patients have more than two leads in one side or they do not have the same target on both sides; (2) patients experienced two operations on one side (revised or replaced the DBS lead).

Surgical Procedure and Electrode Location

Preoperative imaging was used to determine possible stereotactic coordinates of the GPi or STN target before surgery for each specific patient. A safe trajectory was chosen by the neurosurgeon. The target nuclei were structurally identified by manually fitting a digitized and modified Schaltenbrand-Bailey atlas to each individual's MRI through the identification of white and gray matter (Sudhyadhom et al., 2012). Microelectrode recordings and monopolar macro stimulation testing during surgery led to adjustments of the direct and indirect functional targets. All patients received Medtronic (Minneapolis, MN, USA) 3387 implants. The anatomical location of the DBS electrode was measured using a postoperative computed tomography (CT) scan. The measured electrodeposition was calculated and transformed into the normalized anterior commissure-posterior commissure (AC-PC) atlas space using the MRI and CT however the CT was obtained 4 weeks post-surgery to allow for edema and air to resolve (see **Supplementary Materials**). Neurostimulators were placed approximately 4 weeks later and activated during the first clinical visit for DBS programming. All surgeries were staged—that is, the first lead and second lead were implanted on different dates as this was the standard of care at the institution (see **Table 1**).

Assessments

The patient assessments were conducted before surgery (baseline) and then at 6 months (6 M) and 36 months (36 M) after surgery. The baseline information included age, gender, age of onset, and age at DBS implantation. The clinical assessment included the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and Part III. At baseline and during follow up, we obtained motor data from UPDRS-III in the on-medication and off-medication conditions with on-DBS in follow-up assessments. The off-medication condition was defined as being off dopaminergic medications for 12 h. The on-medication condition was defined as being the best statement after taking regular dopaminergic medications. We defined the gait score using UPDRS-II scores as the sum of the fall score (item 13),

TABLE 1 | Main baseline clinical characteristics of the patients with PD involved in the long-term study*.

	GPi (*n* = 19) Mean ± SD (Range)	STN (*n* = 53) Mean ± SD (Range)	*P*-value
Gender, M/F	13/6	39/14	0.666
Age of onset (years)	46.37 ± 7.00 (37–59)	48.61 ± 10.47 (30–66)	0.392
Age at surgery (years)	60.47 ± 7.61 (47–74)	58.55 ± 10.34 (35–76)	0.461
Duration between baseline score and first surgery (months)	4.98 ± 2.83 (0–11)	5.05 ± 3.18 (0–14)	0.892
Duration between first and second surgery (months)	12.63 ± 11.74 (5–47)	9.30 ± 10.68 (0–63)	0.260
Follow-up from baseline to the 36-month timepoint (months)	53.68 ± 11.37 (43–85)	50.21 ± 11.55 (32–97)	0.262
Duration of PD at baseline (years)	22.63 ± 6.69 (12–47)	20.98 ± 5.16 (9–35)	0.297
UPDRS-II**	19.53 ± 5.38 (10–31)	17.20 ± 6.35 (5–34)	0.160
UPDRS-III***			
Off-medication	42.79 ± 9.13 (28–68)	42.40 ± 13.91 (11–81)	0.909
On-medication	24.89 ± 11.86 (8–58)	24.91 ± 10.26 (9–53)	0.997
Dopaminergic responsiveness (%)	41.68 ± 22.04 (3.03–85.19)	39.01 ± 22.44 (−45.45 to 74.19)	0.823
Axial score dopaminergic responsiveness (%)	43.08 ± 30.98 (0–100)	46.97 ± 38.38 (−100 to 100)	0.783
Hoehn & Yahr			
Off-medication	2.89 ± 0.64 (2–4)	2.82 ± 0.90 (1.5–5)	0.260
On-medication	2.55 ± 0.62 (2–4)	2.30 ± 0.46 (1.5–4)	0.614
LEDD (mg)	1,238.11 ± 660.55	1,128.91 ± 402.03	0.505

*Plus-minus values are means ± SD. Baseline variables were compared between the two groups with the use of a two-group t-test, Mann–Whitney U-test, and chi-square test. **Scores on the Unified Parkinson's Disease Rating Scale part II (UPDRS-II) range from 0 to 42, with higher scores indicating more severe disease. ***Scores on the Unified Parkinson's Disease Rating Scale III (UPDRS-III) range from 0 to 108, with higher scores indicating more severe disease. GPi, globus pallidus internus; STN, subthalamic nucleus; SD, standard deviation; M, male; F, female; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, L-dopa equivalent daily dose.*

freezing of gait score (item 14), and walking score (item 15; Katz et al., 2015). We also defined an axial score using UPDRS-III scores corresponding to the sum of the stand from chair score (item 27), posture score (item 28), stability score (item 29), and postural stability score (item 30; Thevathasan et al., 2011; Bonenfant et al., 2017). the L-dopa equivalent daily dose (LEDD) was calculated using the method of Claire L et al (Tomlinson et al., 2010). Dopaminergic responsiveness was calculated with the following formula: [score (off-medication) − score (on-medication)] * 100/score (off-medication).

The primary analysis was the difference between the GPi group and the STN group in the mean change from baseline to 36 months in the gait and axial scores (off-med/on-stim and on-med/on-stim), UPDRS-II total scores, and UPDRS-III total scores (off-med/on-stim and on-med/on-stim). Additional *post hoc* analyses were conducted to assess the progression of symptoms between baseline and last follow-up at 36 months and between 6 months and 36 months in each target separately. DBS programming was by standard of care maximized by 6 months after surgery and we aimed to evaluate early differences in each target utilizing similar measures. In addition, we assessed the difference in the Hoehn & Yahr (H & Y) stage and UPDRS-III total score.

Statistical Analysis

Univariate descriptive analyses were used for reporting sample-level demographic and clinical characteristics. The independent samples two-tailed *t*-test for normal distribution data or Mann–Whitney *U*-test for non-normal data were used to compare the age of onset, age at surgery, duration of follow-up, duration of PD, UPDRS-II score, UPDRS-III score, and Hoehn & Yahr between groups. A chi-square test was used to compare gender between groups. The Mann–Whitney *U*-test was used to compare the differences between groups in the mean change of gait score, axial score, UPDRS-II total score, and UPDRS-III total score from baseline to 36 months (Verschuur et al., 2019). The one-way repeated measures ANOVA was applied to test for an effect of DBS target and follow-up time for each score. A Bonferroni test was used for *post hoc* analyses. Two-sided *P*-values of < 0.05 were considered significant. The statistical analyses were performed using the IBM SPSS, version 23.

RESULTS

Study Population

Seventy-two patients with complete data (19 with GPi-DBS and 53 with STN-DBS) were enrolled. Across all patients, the median time between the first and second surgery was 7 months (range, 0–62). The 36-month follow-up time point occurred at a mean (Mean ± SD) of 46.07 ± 11.19 and 35.39 ± 3.34 months after the first surgery and contralateral surgery, respectively. The main demographic and clinical characteristics are summarized in **Table 1**. No significant differences were observed in the baseline measures.

Primary Outcome Measures

Table 2 shows the mean change from baseline to 6 months and baseline to 36 months in the STN (**Figure 1**) and GPi (**Figure 2**) groups for primary and secondary assessments. In both the STN- and GPi-DBS cohorts, we observed no differences in off-med/on stim axial and gait subscores at short-term or long-term follow-up compared to baseline. Whereas the on-med/on-stim axial score remained comparable between targets in the short-term, symptoms worsened (STN, $p < 0.001$; GPi, $p < 0.01$) at long-term follow up likely due to disease progression. Specifically, at 36 months compared to baseline the mean score of UPDRS II gait subscore increased by 1.11 ± 3.41 points in the GPi group and 0.80 ± 3.35 points in the STN group (STN vs. GPi, $p = 0.642$), the off-med/on-stim axial score worsened

TABLE 2 | Mean change from baseline to 36-month in STN and GPi groups*.

	Mean score		Mean change from baseline to 6 M			Mean change from baseline to 36 M			Mean change from 6 M to 36 M		
	GPi	**STN**	**GPi**	**STN**	***P*** **	**GPi**	**STN**	***P*** **	**GPi**	**STN**	***P*** **
UPDRS-III Axial score (off-med/on-stim)											
Baseline	**6.00 ± 2.73**	**5.32 ± 3.52**									
6 M	5.33 ± 2.66	3.88 ± 2.61	−0.61 ± 1.65	−1.46 ± 3.56	0.679						
36 M	7.32 ± 3.00	5.42 ± 3.57				1.32 ± 2.85	0.09 ± 4.18	0.192	2.00 ± 2.74	1.44 ± 2.44	0.423
UPDRS-III Axial score (on-med/on-stim)											
Baseline	**3.53 ± 2.80**	**2.57 ± 2.12**									
6 M	4.17 ± 2.70	2.86 ± 2.19	0.82 ± 1.62	0.36 ± 2.01	0.312						
36 M	6.05 ± 2.55	4.79 ± 3.77				2.53 ± 2.37	2.23 ± 3.43	0.361	1.82 ± 2.32	1.90 ± 2.71	0.805
UPDRS-II Gait score											
Baseline	4.37 ± 2.83	3.45 ± 2.50									
6 M	3.42 ± 2.19	2.78 ± 2.19	−0.95 ± 3.19	−0.67 ± 2.71	0.905						
36 M	5.47 ± 2.37	4.25 ± 2.82				1.11 ± 3.41	0.80 ± 3.35	0.642	2.05 ± 2.12	1.45 ± 2.14	0.302
UPDRS-II Total											
Baseline	19.53 ± 5.38	17.20 ± 6.35									
6 M	17.32 ± 4.60	13.16 ± 5.55	−2.21 ± 6.72	−4.04 ± 7.82	0.318						
36 M	21.42 ± 5.35	17.43 ± 6.77				1.89 ± 7.86	0.24 ± 7.73	0.592	4.11 ± 5.60	4.09 ± 5.70	0.928
UPDRS-III Total (off-med/on-stim)											
Baseline	**42.79 ± 9.13**	**42.40 ± 13.91**									
6 M	36.78 ± 9.92	27.36 ± 8.08	−6.06 ± 10.25	−14.96 ± 13.17	0.013						
36 M	40.95 ± 8.58	33.32 ± 10.05				−1.84 ± 10.26	−9.07 ± 13.95	0.045	4.22 ± 11.18	5.64 ± 8.15	0.597
UPDRS-III Total (on-med/on-stim)											
Baseline	24.89 ± 11.86	24.91 ± 10.26									
6 M	29.23 ± 9.90	21.78 ± 7.82	5.76 ± 8.24	−2.46 ± 10.30	0.002						
36 M	30.84 ± 8.23	27.40 ± 11.26				5.94 ± 10.98	2.49 ± 12.66	0.106	1.41 ± 8.94	5.46 ± 9.30	0.240
UPDRS-III Total dopaminergic responsiveness (%)											
Baseline	41.68 ± 22.04	39.01 ± 22.44									
6 M	19.06 ± 18.39	20.70 ± 21.41	−23.01 ± 27.17	−18.76 ± 26.17	0.531						
36 M	24.29 ± 13.76	19.08 ± 20.20				−17.39 ± 20.34	−19.93 ± 30.63	0.596	5.45 ± 18.70	−1.45 ± 28.63	0.378
LEDD (mg)											
Baseline	1,238.11 ± 660.55	1,128.91 ± 402.03									
6 M	1,333.42 ± 670.64	798.72 ± 478.04	95.32 ± 602.97	−330.19 ± 557.33	0.007						
36 M	1,463.47 ± 899.11	921.34 ± 533.61				225.37 ± 735.00	−207.57 ± 669.22	0.021	130.05 ± 406.92	122.62 ± 422.71	0.947

**Plus-minus values are means ± SD. **The P-values were calculated with the use of the Mann–Whitney U-test. GPi, globus pallidus internus; STN, subthalamic nucleus; M, month; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, L-dopa equivalent daily dose; SD, standard deviation.*

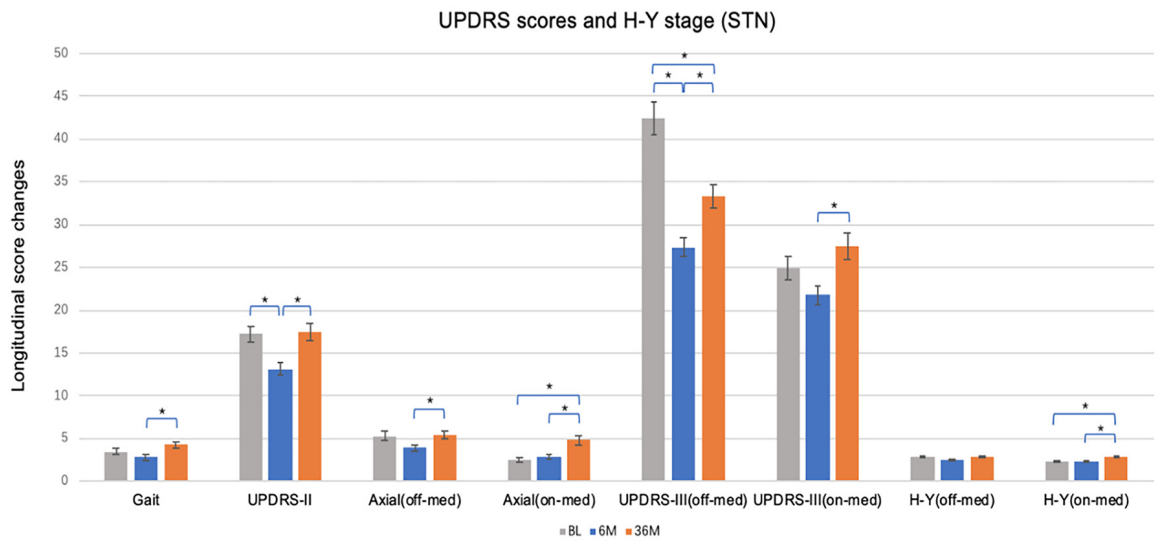

FIGURE 1 | Short and long-term effects of bilateral brain stimulation of the subthalamic nucleus on gait score, Unified Parkinson's Disease Rating Scale (UPDRS)-II, axial score, UPDRS-III and Hoehn & Yahr (H & Y) stage. STN, subthalamic nucleus; BL, baseline; 6 M, 6 months visit; 36 M, 36 months visit. Bars represent the mean and whiskers represent the standard error. *$p < 0.05$.

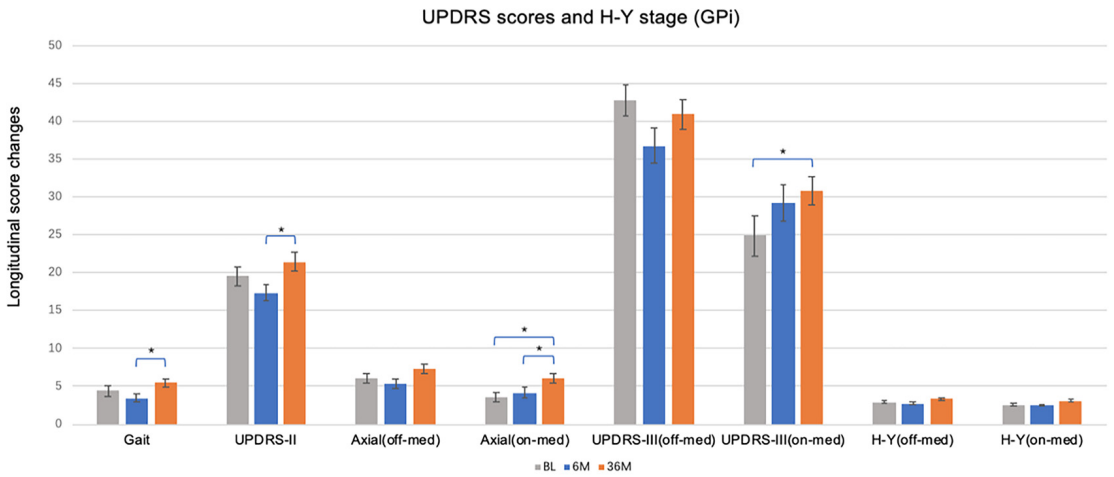

FIGURE 2 | Short and long-term effects of bilateral brain stimulation of the globus pallidus internus on gait score, UPDRS-II, axial score, UPDRS-III and H & Y stage. GPi, globus pallidus internus; BL, baseline; 6 M, 6 months visit; 36 M, 3 months visit. Bars represent the mean and whiskers represent the standard error. *$p < 0.05$.

by 1.32 ± 2.85 in the GPi group and 0.09 ± 4.18 in the STN group (STN vs. GPi, $p = 0.192$), and the on-med/on-stim axial score worsened by 2.53 ± 2.37 ($p < 0.01$) in the GPi group and 2.23 ± 3.43 ($p < 0.001$) in the STN group (STN vs. GPi, $p = 0.361$).

Additional Analyses

At 6 months, STN patients experienced improvement in UPDRS II (−4.04 ± 7.82, $p < 0.01$) and III (−14.96 ± 13.17, $p < 0.001$) off-med/on-stim scores (**Figure 1**), with greater improvement in motor scores in both of the UPDRS III off-med and on-med scores compared to GPi patients (all $p < 0.05$). At long-term follow-up UPDRS III off-med/on-stim scores remained improved from baseline (−9.07 ± 13.9, $p < 0.001$) in patients managed with STN-DBS. The scores worsened compared to the initial benefit observed at 6 months ($p < 0.001$). In contrast, the UPDRS III on-med/on-stim scores did not significantly change at 6 months (−2.46 ± 10.30, $p = 0.106$) or 36 months (2.49 ± 12.66, $p = 0.597$) follow-up compared to baseline. Notable in this data, however, was the smaller sample size of the GPi and the potential differences in decision making favoring a GPi target.

When comparing change over time, there were no changes in UPDRS II or III off-med/on-stim during the duration of the study in patients treated with GPi-DBS (**Figure 2**). These observations may reflect the need for dopaminergic therapies for non-motor symptoms along with compensatory programming strategies to manage specific symptoms and to reduce adverse effects. Slight worsening in UPDRS III on-med/on stim score was noted in the GPi-DBS group as a whole at long-term follow-up (5.94 ± 10.98, $p < 0.01$). The off-med H&Y score did not change in the STN or GPi group at 6 months or 36 months compared to baseline, however, the on-med H&Y score did worsen at 36 months (0.53 ± 0.87, $p < 0.001$) in the STN group only.

DISCUSSION

We retrospectively assessed the short- and long-term changes in axial and gait symptoms in PD patients treated with bilateral GPi-DBS and STN-DBS. Our results revealed that at 36 months of follow-up, the effect of neuromodulation on axial and gait symptoms was comparable between the two targets. Previous studies reported that both GPi- and STN-DBS are effective in improving levodopa-responsive PD symptoms, however, effect on gait and axial symptoms have erratic and inconsistent responses to levodopa (Fasano et al., 2015). Nonetheless, in our cohort, only the on-med axial score worsened with follow-up.

To our knowledge, there are few reports primarily designed to address differences in axial and gait outcomes between bilateral GPi- and STN-DBS patients utilizing long-term data. Furthermore, prior published findings were derived from heterogeneous studies and populations. Rodriguez-Oroz et al. (2005) reported that there was a predominant deterioration of axial characteristics at 4 years follow-up, and the results were less striking for patients in the GPi group. The Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) study showed that on some subscores GPi-DBS was less efficacious than STN-DBS in improving the axial symptoms at 1-year follow-up (Odekerken et al., 2013). Another randomized study showed (CSP study of 299 patients that GPi-DBS is superior to STN-DBS in improving gait symptoms in non-PIGD patients at 24-month follow-up (Katz et al., 2015). A recent meta-analysis of long-term results also revealed that a GPi group experienced improvement in the PIGD symptoms beyond 2 years, while the symptoms returned to preoperative levels in the STN-DBS group (St. George et al., 2010). Balance impairment, including falls, may more often occur after STN-DBS than GPi-DBS (Hariz et al., 2008). Although these reports have been inconclusive, it has been proposed that GPi-DBS might be a better target for severe gait difficulties (Celiker et al., 2019). Overall current data has been limited by a lack of objective gait assessments and clear separation among the different gait components and associated comorbidities.

These seemingly contradictory findings are not altogether surprising given that gait and axial symptoms are complex behaviors consisting of many sensorimotor subsystems that may not be fully characterized by the gait and axial items listed on the UPDRS. Although posture and gait are affected by bradykinesia, rigidity, and to a lesser extent tremor, other sensorimotor systems underlying posture and gait, such as dependent flexibility (Chong et al., 2000), sensory integration (Bronte-Stewart et al., 2002), and postural synergies (Horak et al., 2017), do not show the same responsiveness to levodopa. Therefore, each subsystem underlying control of posture and gait may be related to different neural circuits with varying sensitivities to levodopa or to DBS (Rocchi et al., 2002; Shivitz et al., 2006; Lyoo et al., 2007; Johnson et al., 2015). As STN and GPi project to different motor pathways within the CNS, stimulation at these sites may contribute differently to axial control (St. George et al., 2010). These different therapeutic outcomes of axial and trunk motor domains may reflect differential functional sub-loops of pathological motor network processing. This may be due to descending effects on the pedunculopontine nucleus or other non-dopaminergic centers in the mesencephalic locomotor area (Alam et al., 2011; Johnson et al., 2015).

In our cohort, the axial and gait scores increased at 36-month follow-up, especially in the on-med/on-stim axial score with a statistically significant change, and this differed from previous reports from other groups (Davis et al., 2006; Brosius et al., 2015; Collomb-Clerc and Welter, 2015; Kim et al., 2019). The gait score, which is composed of falls, freezing of gait and walking items, did not increase significantly at 36-month follow up. This is may have been due to the intrinsic limitations of our scales, lack of randomization, diaries and objective/specific markers of gait function, and assessment of freezing of gait and advanced disease. Disease duration was longer in our cohort compared with previous studies (22.63 ± 6.69 in the GPi group and 20.98 ± 5.16 in the STN group). In randomized controlled trials, for comparison the patients enrolled had a disease duration of approximately 10–12 years. Importantly, axial symptoms are known to be more prominent in patients with longer disease duration and severity. In the study by Rodriguez-Oroz et al. (2005), patients enrolled with 15 years of disease duration, 3–4 years after surgery, gait and postural scores worsened compared to baseline, especially in patients with STN-DBS. Other reports also noted increasing gait and balance difficulties at 2 years with STN-DBS (Celiker et al., 2019). Although DBS could consistently improve levodopa sensitive FOG (Brosius et al., 2015), there are cases of persistent or even worsening FOG after surgery (Davis et al., 2006; Collomb-Clerc and Welter, 2015).

The analysis of our secondary outcomes revealed differences between targets. Namely, the STN may be more effective than the GPi in reducing UPDRS-III total score, in the short-term, but in the long-term worsening of UPDRS scores appears to be less in patients treated with GPi-DBS. These findings are similar to previous reports (Holloway et al., 2010; Odekerken et al., 2016). Additionally, motor evaluation in the off state can be affected by the "long-duration response" of levodopa and its dose-dependent effect (Morgan and Sethi, 2005). Despite this finding might have been due in part to the use of higher doses of dopaminergic medications in the GPi-DBS group. The flexibility to use more dopamine and to adjust medications in the long-term may be an advantage to the GPi target, though this was not

explored in the current study. There may be other factors, such as group size and predominant clinical features, that may account for these observed differences and not be controlled in this study (Rodriguez-Oroz et al., 2005).

Our study had several limitations. First, the analysis of the clinical data was retrospective. Second, a potential limitation of these data is that our samples were not well-matched, although baseline comparisons show these two groups to be similar, particularly with respect to our primary outcome (gait and axial scores). Moreover, the clinical features of all study subjects were systemically evaluated pre and postoperatively by well-trained neurologists after the same pre-operative evaluation protocol. STN- and GPi-DBS surgeries were performed by one neurosurgeon based on the same institutional guidelines. Notwithstanding these limitations, we found that PD patients treated with both GPi- and STN-DBS showed minimal change from baseline in gait and balance subscores and total UPDRS-II and UPDRS-III scores during the 36-month follow-up. A large problem with the data in this study was that the sample was not randomized and at our center more patients underwent bilateral STN DBS than GPi DBS. Future studies will be necessary to better delineate the relationship between lead location, axial scores. The use of objective gait markers and gait and falls monitors would greatly help to address many questions and also to document balance dysfunction which can impair outcomes despite a promising change in the UPDRS score. Finally, a study of sufficient sample size at a center performing bilateral STN and GPi DBS in a completely randomized fashion with long term follow-up of symptoms beyond the UPDRS scores will be necessary to be better understand the issues.

CONCLUSION

In this cohort, we observed that both STN- and GPi-DBS had similar effects on gait and axial symptoms at long term follow up. Any benefits of STN-DBS in the short-term waned. Disease progression likely accounts for much of the axial and gait dysfunction however better metrics beyond the UPDRS for balance and other function will be necessary to understand long term functional impacts. In conclusion, GPi or STN are both viable DBS targets for the treatment of motor symptoms, and both cohorts will worsen over time in the UPDRS measured metrics of axial and gait symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available upon request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Florida (UF) Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM, RE, and AR-Z were the major contributors in writing the manuscript. MO, KF, CH, and AR-Z contributed to the diagnosis and treatment of patients. WH, TT, MO, and PC contributed to checking the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Tailoring Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease Using Evoked Resonant Neural Activity

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INTRODUCTION

Deep brain stimulation (DBS) applied to the subthalamic nucleus (STN) can be a highly effective therapy for Parkinson's disease (PD); however, there are significant issues which limit its effectiveness, reliability, and tolerability. Inaccurate electrode implantation is common, which can reduce efficacy and cause side-effects due to the undesired activation of neighboring brain regions (Okun et al., 2005; Paek et al., 2013; Rolston et al., 2016). Consequently, in most centers patients are typically kept awake during implantation surgery so that clinical assessments can help determine whether the positioning of electrodes is acceptable (Chakrabarti et al., 2014). The programming of stimulation is also often suboptimally performed, and there are many examples of patients being suddenly liberated from poor movement when chronically applied settings are changed (Okun et al., 2005; Sommer et al., 2015). Programming also confers a high burden to patients and neurologists, especially in the era of directional electrodes, often requiring multiple sessions over several months to identify the most effective DBS settings (Cagnan et al., 2019). Moreover, once programmed, DBS is then applied invariantly without "adapting" to the real-time fluctuating needs of the patient (Little et al., 2013; Priori et al., 2013).

A realistic solution to these issues is to use neuronal signals recorded from DBS electrodes to guide accurate electrode implantation (ideally with patients under general anesthesia), to automate programming, and to act as a feedback signal for continuous "adaptive" control. To achieve these aims, such a neuronal biomarker would likely need to localize to the STN (preferably the dorsal motor region where DBS is usually most effective; Herzog et al., 2004), reflect patient state and therapeutic effects with a reasonable time resolution, and, crucially, be reliably detectable in all patients and conditions, including under general anesthesia.

Potential biomarkers that may fulfill these criteria for STN DBS in PD include measures from spontaneous neural activity, such as beta oscillations (Little and Brown, 2012; Priori et al., 2013). However, beta band (13–30 Hz) activity is typically of small magnitude (microvolts) and can be variable across patients (Giannicola et al., 2010), making it challenging to reliably record with high fidelity, particularly using implantable, miniaturized systems (Neumann et al., 2016). Evoked responses elicited by DBS pulses offer alternative biomarkers (Ashby et al., 2001; Baker et al., 2002; Walker et al., 2012; Gmel et al., 2015; Kent et al., 2015; Romeo et al., 2019), including the recently identified phenomenon of evoked resonant neural activity (ERNA) (Sinclair et al., 2018).

ERNA

ERNA is not a spontaneous signal like those detected in local field potentials, but rather is evoked by each DBS pulse applied in the vicinity of the STN. ERNA has a characteristic decaying oscillation waveform with the first peak typically seen around 4 ms after the DBS pulse (**Figures 1A–C**). ERNA has been found to be modulated by consecutive DBS pulses applied at therapeutic rates (e.g., 130 Hz) (Sinclair et al., 2018, 2019). As the duration of ERNA can extend well-beyond the time interval between pulses (7.7 ms for 130 Hz DBS), to appreciate multiple peaks of the decaying oscillation, a "window" needs to be created during otherwise continuous DBS, e.g., by periodically omitting an occasional pulse (**Figure 1A**). Occasionally omitting a pulse (e.g., once per second) is presumed to have a negligible impact on therapy. Alternatively, as stimulation is required to elicit ERNA, during periods off DBS therapy, an occasional burst of pulses (e.g., 10 pulses delivered at 130 Hz) can be used to "probe" for ERNA (**Figure 1B**). Such patterning of stimulation is not difficult to achieve from an engineering perspective, especially using devices designed to cycle stimulation on and off.

A multitude of parameters can be extracted from the ERNA waveform, including amplitude [e.g., root mean square (RMS) amplitude, or peak-peak amplitude] and frequency (e.g., latency between peaks). A key benefit of ERNA is its large amplitude, with the difference between the first peak and trough typically

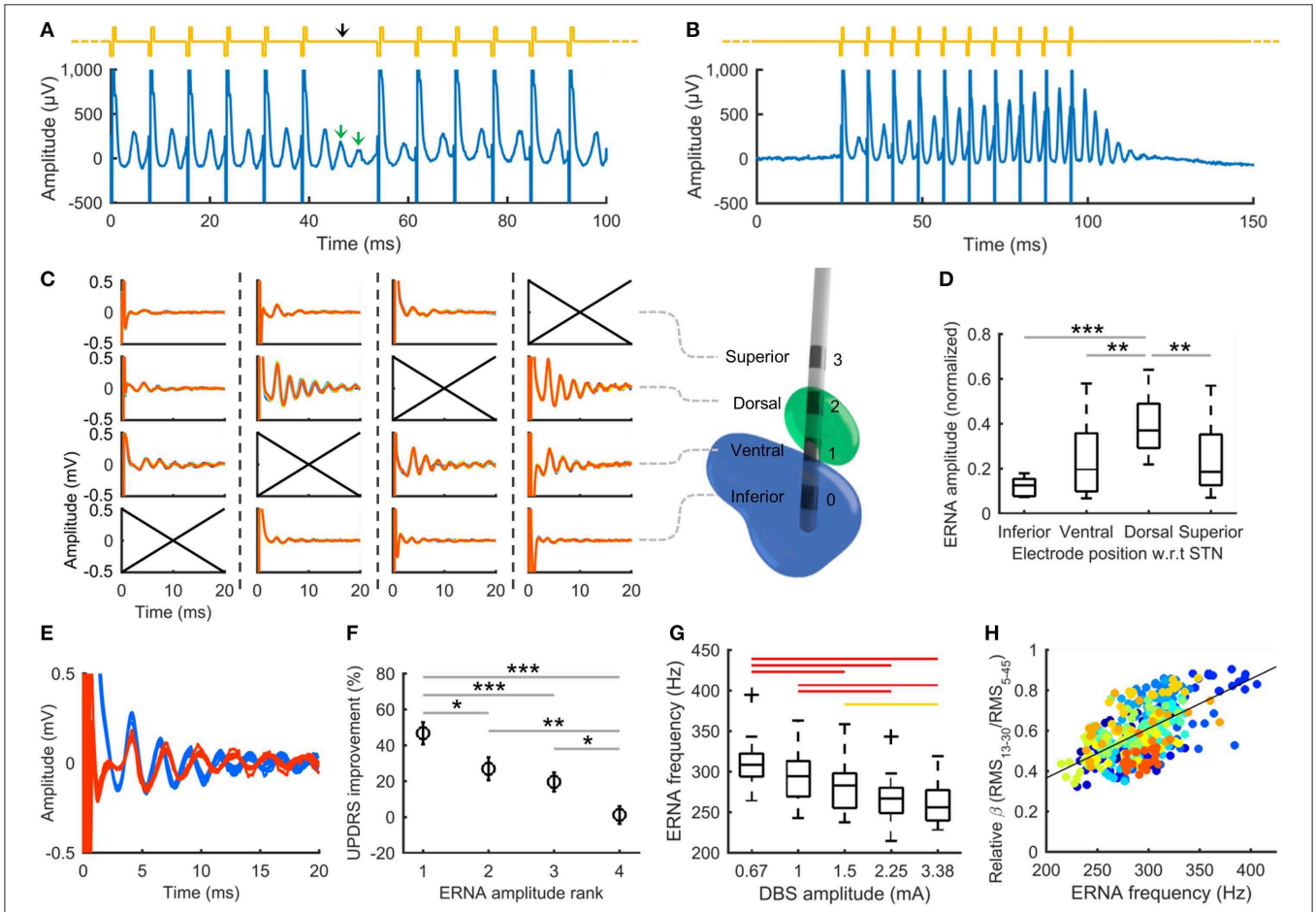

FIGURE 1 | DBS evoked resonant neural activity (ERNA). **(A)** Periodically omitting one pulse in otherwise continuous 130 Hz DBS allows several ERNA peaks to be observed. Yellow trace: stimulation applied; black arrow: omitted pulse. **(B)** Short bursts of pulses (e.g., 10 pulses at 130 Hz) can be used as a "probe" to measure ERNA during periods off DBS therapy. **(C)** Applying burst probe stimulation in the vicinity of the STN elicits ERNA that varies with electrode position. Columns show the ERNA recorded at each electrode for different stimulating electrodes (indicated by crossed axes) in a single example STN from a person with PD. A 3D reconstruction illustrates the electrode positions (green: STN, blue: substantia nigra). **(D)** Normalized ERNA amplitude varies with electrode position with respect to (w.r.t) the STN in people with PD (20 hemispheres tested) (box: 25th−75th percentiles; line: median; whiskers: range). $^{***}p \leq 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. **(E)** ERNA recorded in a person with PD at electrode implantation (blue) and under general anesthesia 560 days postop (red). **(F)** Mean Unified Parkinson's Disease Rating Scale (UPDRS) improvement from stimulation after ranking electrodes within each hemisphere according to ERNA amplitude (rank 1: largest ERNA; bars: standard error). Results from 10 PD patients tested post-surgery (20 hemispheres). **(G)** ERNA frequency decreases with increasing DBS amplitude (19 hemispheres tested). Red bars: $p \leq 0.001$; yellow bars: $p < 0.05$. **(H)** ERNA frequency correlates with relative beta band (13–30 Hz) amplitude across the stimulation levels shown in **(G)** ($\rho = 0.58$, $p < 0.001$). Colors represent different hemispheres tested. **(A,B,G,H)** reproduced from Sinclair et al. (2019), used with permission. **(C–F)** reproduced from Sinclair et al. (2018), used with permission.

being hundreds of microvolts, orders of magnitude larger than spontaneous local field potentials. This large amplitude and the inherent time-locking of responses to stimuli, makes ERNA readily recordable using fully-implantable hardware, e.g., such evoked signals have long been employed for use in cochlear implants (Shallop et al., 1999).

ERNA has also been confirmed to be of neural origin and not an inadvertent artifact from stimulation (Sinclair et al., 2019a). Variation in ERNA amplitude with electrode position relative to the STN (**Figures 1C,D**) and its absence in recordings obtained from neighboring brain region (e.g., ventral intermediate nucleus, posterior subthalamic area) using the same system (Sinclair et al., 2018), provides clear evidence that it is not produced by the stimulation and recording hardware. The ERNA waveform is also not inverted by reversing the polarity of stimulus pulses, indicating that it has a neural basis (Sinclair et al., 2019a). Furthermore, the existence of ERNA has been corroborated by other, independent, research groups (e.g., at the University of Alabama at Birmingham and at Duke University; Ramirez-Zamora et al., 2020). The neural mechanisms that allow generation of the ERNA signal have yet to be established. One hypothesis is that ERNA could reflect the resonant state of neuronal networks that support the emergence of oscillatory activity in local field potentials. It is notable that ERNA and high frequency oscillations occupy a similar frequency band in STN recordings (Sinclair et al., 2019). Modeling studies have also indicated that ERNA could arise from interactions between the STN and the pallidum, due to quasi-periodic pallidal inhibition following DBS pulses (Ramirez-Zamora et al., 2020).

POTENTIAL CLINICAL APPLICATIONS OF ERNA

ERNA may have utility to improve STN DBS in the following applications.

Electrode Implantation Guidance

ERNA is reliably recordable during STN DBS implantation—our group has done so in over 175 STN's. Crucially, ERNA appears to localize to the STN and is absent from recordings from white matter tracts adjacent to the STN (e.g., the posterior subthalamic area) (Sinclair et al., 2018). ERNA amplitude also varies within the STN, being greatest in the dorsal subregion (**Figures 1C,D**). ERNA recordings during surgery would therefore seem to offer a distinct potential advantage to standard microelectrode recordings—which do not reliably localize the ideal STN target (Soares et al., 2019). A further substantial benefit of ERNA is that it is recordable under general anesthesia, using standard agents such as propofol, sevoflurane, and isoflurane (Sinclair et al., 2018, 2019b) (**Figure 1E**), which could enable accurate localization of the STN during asleep implantation surgery.

DBS Programming

The localization of ERNA to the dorsal STN subregion raises the possibility that ERNA could serve as a biomarker to select beneficial electrode configurations to use for chronic DBS therapy. Indeed, in a recently completed, double-blinded, experimental study in 14 PD patients (28 STN's) performed in the off medication state (Sinclair et al., 2018; Xu et al., 2019), we found that electrodes with larger ERNA amplitudes produced greater clinical benefit from DBS (**Figure 1F**), and simply selecting the electrode with the greatest ERNA RMS amplitude over 4–20 ms yielded a hemibody motor benefit from DBS that approximated the maximal available benefit from each electrode array. The identification of beneficial electrode configurations may also be further enhanced by factoring in other ERNA features, such as frequency and decay rate. It can also be speculated that the localization of ERNA will result in variation around the different segments of steering electrodes, which may assist identification of segments to use for chronic therapy.

Our group is also investigating whether ERNA may contain information to help identify beneficial DBS frequencies to apply in individual patients. It is notable that ERNA frequency modulates with therapeutic DBS, with median frequencies across patients reducing from around 310 Hz to plateau around 260 Hz (**Figure 1G**)—two times the stimulation frequency applied (130 Hz), a rate that is considered to be effective in most patients. The exact frequency that ERNA decreases to varies across individuals, ranging from about 230–320 Hz, suggesting there are patient specific frequencies associated with therapeutic benefit. Thus, the clinical effectiveness of applying DBS at a subharmonic of the ERNA plateau frequency could be assessed as a potential method for "fitting" a DBS frequency tailored to the individual.

Adaptive DBS

The finding that ERNA frequency modulates with DBS also raises the possibility that this parameter could be used as a feedback signal for adaptive DBS control. Currently, we have only limited evidence that such modulation of ERNA frequency relates to the therapeutic efficacy of DBS on Parkinsonism. For example, we have performed limited intraoperative clinical assessments during DBS whilst recording ERNA and found that relief of upper limb akinesia and rigidity coincides with DBS levels where ERNA frequency plateaus (Sinclair et al., 2019). Moreover, ERNA frequency was found to correlate with the amplitude of beta band activity (**Figure 1H**), which can be considered a reasonable surrogate marker of akinesia and rigidity (Kühn et al., 2008, 2009). ERNA amplitude was also found to be modulated by DBS, suggesting it may have a role as a feedback signal; however, care needs to be taken to distinguish therapeutic effects from changes due to altering the stimulus intensity, such as variation in the volume of activation and saturation of neural firing (Sinclair et al., 2019).

DISCUSSION

ERNA is an exciting new prospect for a feedback signal that could be used to address shortcomings in the clinical application of STN DBS therapy for Parkinson's disease. It has key features of a large amplitude, localization to dorsal STN, is modulated by therapeutically-effective DBS, and is reliably measurable across patients, including under general anesthesia. However, while these attributes suggest it has promise for a variety of clinical

applications, further work is required to validate and realize the potential of ERNA. For instance, additional evidence is required to establish how ERNA parameters reflect patient state and pathology, the clinical relevance of their modulation, and their effectiveness as feedback signals for adaptive control. Moreover, while findings indicate that ERNA localizes to dorsal STN, further work is also required to assess the location sensitivity and specificity of ERNA, and to more precisely determine the STN region and circuits responsible for its generation. Regardless of whether the source of ERNA coincides with the "sweet spot" for STN DBS therapy for PD (Horn et al., 2017), accurate determination of the origin of ERNA will further enable its use as a robust landmark for guiding electrode implantation surgery and programming. Whether evoked potentials may assist in identifying other DBS targets, such as the pallidum, is also worth assessing.

There have been a number of recent innovations in DBS technology aimed at addressing the shortcomings of existing devices and techniques. These advances include the use of intraoperative imaging techniques to guide implantation surgery under general anesthesia (Starr et al., 2010; Burchiel et al., 2013; Ho et al., 2018; Yin et al., 2019), the introduction of directional electrodes (Contarino et al., 2014), the proof-of-concept of adaptive DBS (Rosin et al., 2011; Little et al., 2013; Arlotti et al., 2016; Swann et al., 2018), and development of implantable pulse generators with sensing capabilities to realize closed-loop control (Stanslaski et al., 2012; Neumann et al., 2016). The attributes of ERNA suggest that it could potentially augment and/or complement the application of these technologies. For instance, imaging-guided electrode implantation has been shown to have comparable outcomes to conventional awake surgery (Ho et al., 2018; Yin et al., 2019); however, using imaging alone places greater emphasis on anatomy, which may not fully reflect each individual's physiology. As such, an electrophysiological signal that is readily measurable under general anesthesia and localized to the neural target could be used in conjunction with intraoperative imaging to better identify beneficial electrode locations.

Furthermore, directional electrodes provide the ability to "steer" stimulation toward target neural structures and away from those that elicit side-effects, at the expense of increased programming complexity due to the larger number of possible electrode configurations. Spontaneous beta band activity has been shown to be potentially helpful at selecting directional segments to use for chronic therapy (Tinkhauser et al., 2018). While the variation in ERNA around directional electrode arrays needs further assessment, the localization of ERNA to dorsal STN suggests it could be used to guide programming in the same manner as beta. Beta band activity has also been proposed as a method to guide electrode implantation; however, it's intraoperative use can be limited by micro-lesioning effects caused by electrode insertion (Chen et al., 2006). In addition to providing a larger and more robust signal, ERNA may also provide complementary information to beta, as they occupy different frequency bands. The frequency of ERNA is around 200–500 Hz, which is consistent with the frequency of spontaneous high frequency oscillations that have been found to couple with beta activity and to be modulated by movement, medication, and DBS (Foffani et al., 2003; López-Azcárate et al., 2010; Özkurt et al., 2011; Sinclair et al., 2019). Thus, systems that use ERNA and beta activity, and/or other spontaneous or evoked measures, may ultimately prove to be most effective for automated programming and adaptive DBS applications.

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WT, NS, KB, and HM contributed to the conception, drafting and revision of the manuscript, and read and approved the submitted version.

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Conflict of Interest: The authors are named inventors on patents relating to ERNA, which are assigned to DBS Technologies Pty Ltd. WT, NS, KB, and HM hold shares and/or options in DBS Technologies Pty Ltd.

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Proceedings of the Seventh Annual Deep Brain Stimulation Think Tank: Advances in Neurophysiology, Adaptive DBS, Virtual Reality, Neuroethics and Technology

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The Seventh Annual Deep Brain Stimulation (DBS) Think Tank held on September 8th of 2019 addressed the most current: (1) use and utility of complex neurophysiological signals for development of adaptive neurostimulation to improve clinical outcomes; (2) Advancements in recent neuromodulation techniques to treat neuropsychiatric disorders; (3) New developments in optogenetics and DBS; (4) The use of augmented Virtual reality (VR) and neuromodulation; (5) commercially available technologies; and (6) ethical issues arising in and from research and use of DBS. These advances serve as both "markers of progress" and challenges and opportunities for ongoing address, engagement, and deliberation as we move to improve the functional capabilities and translational value of DBS. It is in this light that these proceedings are presented to inform the field and initiate ongoing discourse. As consistent with the intent, and spirit of this, and prior DBS Think Tanks, the overarching goal is to continue to develop multidisciplinary collaborations to rapidly advance the field and ultimately improve patient outcomes.

Keywords: deep brain stimulation, stereoelectroencephalography, depression, Parkinson's disease, tremor, optogenetics, local field potentials, neuroethics

INTRODUCTION

Since 2012, the annual Deep Brain Stimulation (DBS) think tanks have convened subject matter experts in neuromodulation research and clinical practice to exchange ideas, discuss developing technologies, address and plan for current and future challenges and opportunities in the field (Gunduz et al., 2015; Deeb et al., 2016; Rossi et al., 2016; Ramirez-Zamora et al., 2018, 2019). The Seventh Annual DBS Think Tank took place on September 8, 2019 (a virtual meeting held *via* Zoom Video Communications inc due to travel concerns and impediments caused by Hurricane Dorian). The meeting focused on advances in: (1) commercially available technologies; (2) the use of advanced technologies to improve clinical outcomes; (3) research in neuromodulatory approaches to treating neuropsychiatric disorders; (4) the use and utility of complex neurophysiological signals for advancing delivery of neurostimulation; and (5) ethical issues arising in and from research and use of DBS.

APPLYING ADVANCED NEUROPHYSIOLOGICAL SIGNALS TO ADVANCE DBS TREATMENT

Adaptive Deep Brain Stimulation in Parkinson's Disease

Adaptive deep brain stimulation (aDBS) for movement disorders has been demonstrated to be effective during in-clinic, short term testing. Early studies suggested that beta activity may be a reasonable biomarker for PD clinical state (Kühn et al., 2006; Little et al., 2012a,b). aDBS uses unique neurophysiological signals to direct the delivery of stimulation to control motor symptoms (**Supplementary Figure S1**). The first human trials of aDBS used a subcortical beta signal and a fixed threshold with short time scales (Little et al., 2013, 2016a,b). This protocol targeted prolonged beta bursts and, through stimulation, shortened their duration (Tinkhauser et al., 2017a,b). The initial studies found that aDBS was more effective than conventional (cDBS) using blinded Unified Parkinson's Disease Rating Scale (UPDRS) ratings (both unilaterally and bilaterally). Moreover, aDBS reduced speech side effects (acutely) and was appropriately responsive to levodopa medication (Little et al., 2016b). This approach has subsequently been shown to possibly prevent dyskinesia (Rosa et al., 2015; Arlotti et al., 2018).

The initial limitations of early studies were the post-operative microlesion effect and the brevity of stimulation. One post-operative study did however successfully stimulate for 8 h across medication cycles (Arlotti et al., 2018). Other studies have attempted to implement aDBS in the chronic phase, at battery change or in chronically implanted systems, and have shown aDBS to be as effective as cDBS, despite significantly reduced current delivery (Piña-Fuentes et al., 2017, 2019a; Velisar et al., 2019). Additional signals are being investigated, and dyskinesia has been associated with a narrowband gamma oscillation in the motor cortex between 60 and 90 Hz, with a similar but weaker oscillation in the subthalamic nucleus (STN) and strong phase coherence between the two (Swann et al., 2016). Successful control of hyperkinetic movements using an adaptive DBS design has been conducted with encouraging results (Swann et al., 2018b).

Notable was the use of a dual-threshold system and kinematic evaluation in a chronic fully implanted beta aDBS system. This approach was shown to be feasible and of practical utility in clinical settings (Velisar et al., 2019; **Supplementary Figure S2**). Direct kinematic assessments may be important for advancing aDBS and for preventing deleterious effects (although it remains to be determined if and to what extent small kinematic differences will impact clinical outcomes; Johnson et al., 2016). To date, there have been eight trials of aDBS in PD, and all trials have

shown aDBS to be at least equivalent to cDBS in achieving relevant clinical outcomes. Ascertainment of whether this approach will be equivalently more effective in out-of-clinic (i.e., real-world) environments will require larger trials using fully implanted devices with embedded sensing capabilities. The use of aDBS for treating other conditions, including tremor and dystonia, has only begun to be tested, and initial findings suggest that this approach could be promising for treating these conditions. As well, the use of patterned stimulation using the neural activity phase rather than just local field potentials (LFP) amplitude is being considered (Cagnan et al., 2014, 2017; Piña-Fuentes et al., 2019b). It is unclear if aDBS would provide a clear advantage in reducing the burden and complexities of prolonged programming visits as additional time might be required to set up appropriate stimulation. This is an important but as yet unanswered question that remains the focus of future research. Overall, these studies provide a building body of support for the use and value of aDBS in treating a number of movement disorders.

Sensing and Adaptive Loop Stimulation Using the Summit RC+S Platform: Early Experience

Chronically implantable neuromodulating devices that both sense brain activity and deliver stimulation (i.e., "bidirectional" interfaces) have generated excitement in the neurosurgical and neurology communities. Potential uses of bidirectional interfaces include the identification of electrophysiologic signatures of specific signs or symptoms of brain disorders, and the development of aDBS (Modolo et al., 2012; Swann et al., 2018b). However, the first-generation devices (that have been available since 2013) had limitations in signal quality, management of stimulation artifact, and the capability for continuous collection of brain data in home environments (Swann et al., 2018a). Toward closing these gaps, we have gained experience with a newly available second-generation device, Summit RC+S (Medtronic) in five patients with PD (Stanslaski et al., 2018). In our recent protocol, the Summit RC+S DBS was attached to a quadripolar depth lead (STN or Globus Pallidus Interna (GPi); for both stimulation and sensing), and a quadripolar paddle lead in the subdural space over the primary motor cortex (for sensing only). While this system was more customizable than previously used devices, the relative complexity of RC+S system necessitated a team approach to include software engineers to customize programs using the device application-programming interface (API). Summit RC+S provided substantial improvements over first-generation devices with respect to signal to noise characteristics, long term continuous data streaming, and interference from stimulation or other artifacts. These features permitted hundreds of hours of recording of electrophysiologic data that could be obtained in the home environment. Additionally, RC+S-obtained data can be synchronized offline to pair with external wearable sensors (such as smartwatches) to further characterize physiologic states. Our initial results showed canonical levodopa-related changes in subthalamic and cortical field potentials that have previously been demonstrated only using externalized leads in brief in-clinic recording periods. The use of LFP electrophysiologic signatures and classifiers made it possible to distinguish clinical states with high accuracy in out-of-clinic (i.e., home) environments (**Supplementary Figure S3**). We view this as a critical step in advancing aDBS toward a more useful therapy. Moreover, the capability for invasive neural recording over long periods of time in naturalistic environments will afford a novel method for acquiring basic neuroscientific data that can be used to guide subsequent bio-engineering and clinically relevant research directions and developments.

Combining Directional DBS and Physiology Toward an Adaptive Loop Approach

aDBS and directional DBS (dDBS) are two recent technological innovations that have fostered new strategies to refine the DBS programming process (Modolo et al., 2012; Kühn and Volkmann, 2017). aDBS is a technique in which DBS output incorporates real-time sensing data *via* a feedback mechanism in order to guide stimulation delivery. dDBS refers to DBS leads with segmented electrodes that enable the generation of a spatially selective electric field directed toward a brain region of interest. These methods contrast with cDBS, which utilizes a ring-shaped electrode that can only generate electric fields symmetric about the long axis of the lead. Both aDBS and dDBS have been important to developing DBS optimization strategies that focus both on temporal domains (utilizing aDBS), and spatial domains (using dDBS). Studies of dDBS have reported that although DBS programming time can significantly increase with this new approach, there is also potential expansion of the therapeutic window (Contarino et al., 2014; Pollo et al., 2014; Steigerwald et al., 2016; Dembek et al., 2017; Rebelo et al., 2018; Ten Brinke et al., 2018).

LFP recordings from basal ganglia in PD patients using dDBS technology have indicated that beta signal strength is not homogenously distributed around segmented leads (Fernández-García et al., 2017; Tinkhauser et al., 2018). Selective stimulation of these regions with high beta power was associated with greater therapeutic benefit (Tinkhauser et al., 2018) and could serve as a physiology-based tool to optimize DBS contact selection. As technology continues to improve, combining dDBS with aDBS may afford improved clinical outcomes due to a wider therapeutic window, a more flexible selection of stimulation and recording contacts, and improved DBS programming time through the utilization of automated aDBS techniques.

DBS Local Evoked Potentials: The ERNA

STN DBS for treatment of PD requires precise lead placement but marked variability between lead location among patients might cause difficulties optimizing stimulation parameters. The burden of programming has been increasing with the advent of current steering electrodes, and this technology has also increased the available parameter space. The use of a neuronal biomarker to guide electrode implantation could be beneficial for performing surgery, particularly if the patient is asleep. Such

a biomarker could guide stimulation in at least two domains: parameter settings and adaptive control. The biomarker should localize to the STN, reflect the clinical state of the patient, modulate with DBS, possess reasonably fast correlation, and be reliably detectable.

Currently, beta oscillations are a commonly used biomarker metric (Wingeier et al., 2006; Little et al., 2013; Tinkhauser et al., 2018). However, these oscillations are small (<15 μV), and can be difficult to detect in and across certain conditions. In this light, we propose a new biomarker, evoked resonant neural activity (ERNA), which is significantly larger than the beta band (>100 μV) and can be reliably recorded across all conditions (Sinclair et al., 2018, 2019). ERNA is evoked and recorded from within the STN itself and is generated by a train of square biphasic pulses. After cessation of the pulses, the evoked response persists with a decaying oscillation. Both the amplitude and frequency seem to be components of the biomarker. Unlike beta oscillations, ERNA is an active signal created by stimulation, and cannot be recorded from resting-state activity. ERNA localizes to the STN (**Supplementary Figure S4A**) and is present under general anesthesia (**Supplementary Figure S4D**), suggesting a role to guide electrode implantation with patients asleep without intraoperative imaging (Sinclair et al., 2018). ERNA amplitude varies even within the STN, being maximal in the dorsal subregion where DBS is reported to achieve the greatest benefit (Horn et al., 2017; Sinclair et al., 2018; **Supplementary Figure S4B**) and electrodes that record larger ERNA amplitudes have been found to produce greater clinical benefit (**Supplementary Figure S4C**). These findings raise the possibility that the ERNA amplitude could help guide electrode contact selection. Moreover, the frequency of ERNA modulates during DBS (**Supplementary Figure S4E**), reducing on average from around 310 Hz pre-therapy to around 260 Hz when therapy reaches clinically effective levels (Sinclair et al., 2019). It is intriguing that the latter value is around twice the commonly employed applied STN DBS frequency of 130 Hz, though it is crucial to note that the plateau frequency that ERNA reaches with therapeutic DBS differs between individuals. Future work will assess whether the plateau frequency that ERNA reaches with therapeutic DBS could inform on the ideal DBS frequency to apply in individuals. During DBS, modulation of ERNA frequency correlates with the amplitude of beta oscillations (a useful surrogate of the clinical state of the patient; **Supplementary Figure S4F**; Sinclair et al., 2019). During programming, the ERNA could facilitate optimization of more precise settings, especially given that there is a larger amplitude in the dorsal motor region of the STN (Sinclair et al., 2018). This raises the possibility that ERNA frequency could be investigated as a biomarker to trigger adaptive STN DBS in PD.

Multimodal Evoked Potential Elicited by DBS: New Candidate Biomarkers to Guide Novel Therapies

Optimal DBS therapy is challenged by complex new technologies and heterogeneous diseases, leading to two important questions. Which biomarkers are the most suitable, and where should one record? Multimodal recordings of stimulus-evoked activity elicited by DBS paired-pulse studies leverage electroencephalography (EEG), electrocorticography (ECoG), and DBS LFP data. Data from these recordings can be used to help answer these questions. Our group recorded EEG potentials from STN (i.e., in PD) and thalamic (i.e., in essential tremor) neurons during therapeutic stimulation. Stimulation generated a polyphasic event-related potential in the ipsilateral sensorimotor cortex, with peaks at discrete latencies beginning less than 1 ms after stimulus onset (Walker et al., 2012a,b). There are marked differences in evoked potential (EP) morphology between effective and ineffective stimulation, with high-frequency activity occurring after ineffective stimulation. Avoiding capsular side effects (elicited by stimulating the surrounding internal capsule) can also be important when recording.

We also evaluated ECoG responses recorded from the primary motor cortex, following paired-pulse stimulation. As the interstimulus interval between the conditioning stimulus (CS) and the testing stimulus (TS) diminished, the latency increased and amplitude decreased, and the evoked response disappeared entirely as the interval fell below 1 ms. These effects highlight the relative and absolute refractory periods of neurons. DBS LFP recordings stimulate from the two inferior contacts and record from the two superior contacts of the depth lead. They show a response with a latency of 350 μs, as well as ERNA (Sinclair et al., 2018). As the CS and TS approach become more proximate, there is evidence of relative and absolute refractory periods as the latency increases and amplitude decreases, with the evoked response and ERNA disappearing as the two stimuli converge. With trains of stimulation, the ERNA shows remarkable facilitation at 500 Hz and at the clinically relevant frequencies of 100–250 Hz.

When co-recorded, EEG, ECoG, and DBS LFPs show latencies of 1 ms, 1 ms, and 350 μs, respectively, with each modality showing an increasing amplitude of the response by an order of magnitude when measured from scalp to subcortical recordings. All modalities show relative and absolute refractory periods consistent with the activation of neural structures. These responses were consistently observed across all modalities. In a recent report, our group presented evidence that DBS-evoked responses, including those at extremely short latencies, have a neural origin beneath or very near the ECoG strip over the ipsilateral premotor and motor cortex (Awad et al., 2020). It is proposed that the most likely underlying mechanism responsible is non-synaptic, retrograde activation of cortical neurons whose axons project to the subcortical stimulation site. Other factors might impact the spatiotemporal patterns of cortical activation by DBS and additional computation and basic science experiments should focus on a comprehensive, systems-level and physiological understanding of DBS. Relevant discussion at the time of the meeting questioned the use of this technique in clinical practice. At the present time, no clinical decisions are made by the University of Alabama team using this research protocol. Parameters are selected based on the

most effective clinical response intraoperatively using a bipolar configuration with standard STN pulse width and frequencies.

Neuronal Sources of Evoked Potentials

SNT DBS produces EPs both locally (i.e., in STN; sEP) and in the cortex (cEP). EPs can be regarded as a possible biomarker of neural responses to stimulation, but the origin of EP activity is not wholly clear. To address this issue, we used computational models to better understand the neural elements involved in—and contributing to—EPs.

The cEP included short-latency positive (P1), intermediate latency negative (N1), and long-latency positive (P2) responses in the rat (Kumaravelu et al., 2018) and human models (Walker et al., 2012a). Using a computational model of the thalamocortical (TC) network (Traub et al., 2005) to decipher the origin of cEPs (Kumaravelu et al., 2018), DBS was simulated by activating layer 5 pyramidal axons (antidromically) and applying inhibitory postsynaptic current to the thalamus (orthodromically), thereby mimicking hyper direct and indirect pathway activation, respectively. Model-based cEPs matched well with cEPs obtained from both rats and humans. P1 and N1 responses were due to the direct and recurrent activation of L5 pyramidal neurons, respectively, while P2 responses arose from polysynaptic activation of L2/3 pyramidal neurons following a cortico-thalamocortical loop. Antidromic activation alone can faithfully reproduce cEPs. Understanding anatomical pathways of cortical modulation can be used to optimize therapeutic targets, and cEPs may aid in electrode placement, selection of stimulation parameters, and/or in adaptive (closed)-loop control.

Unlike thalamic DBS EPps (Kent et al., 2015), sEPs were polyphasic and highly stereotyped (Grill et al., 2015; Sinclair et al., 2018). Implementing a 3-dimensional biophysical model of the STN-GPe subcircuit enabled the determination of the origin of sEPs. Model-generated sEPs for 45 Hz and 130 Hz DBS were similar to sEPs from humans with PD, indicating the involvement of STN-GPe interactions and hyper direct axons. The early positive phase resulted from antidromic STN excitation, while the early negative phase reflected strong inhibition by local pallidal terminals. The high-frequency oscillations occurring after the DBS pulse were caused by quasi-periodic pallidal inhibition. As with cEPs, sEPs reveal functional connectivity, and may also be useful as a guide for lead placement or as signals for adaptive-loop control.

ADVANCEMENTS IN RECENT TECHNIQUES IN NEUROMODULATION: EMERGING BRAIN TARGETS, USE OF MULTIPLE LEADS AND STEREOELECTROENCEPHALOGRAPHY (SEEG)

Emerging DBS Targets in Non-motor Disorders

As the number of refereed publications reflects, the field and use of DBS have increased from the late 1990s to the present, as evidenced by less than 100 published papers to over 1,000 papers published per year (Lee et al., 2019). To characterize this growth and to describe the state of the field, a comprehensive overview was presented through data obtained using ClinicalTrials.gov. At the time of this Think Tank, there were 422 registered DBS trials. In recent years, there have been about 40 new studies entered per year. The purpose of these studies has varied from large classical trials for new indications to investigations focused on more novel uses and protocols of DBS (e.g., mindfulness during DBS to improve patient comfort). The majority of studies have been observational or early phase studies, with less than 10% being interventional phase III-IV trials. Approximately 60% of studies addressed the use of DBS for movement disorders, with other areas of interest including psychiatric conditions (e.g., obsessive-compulsive disorder, depression, etc.), cognitive disorders (Alzheimer's disease, non-Alzheimer's dementia, etc.), pain (e.g., headache, neuropathic pain), epilepsy, and others (e.g., tinnitus, lower urinary tract symptoms, etc.).

At present, 28 cerebral targets are utilized in DBS according to this registry. These targets (inclusive of multiple sites being used to treat the same disorder) included: PD [nucleus basalis of Meynert, STN, GPi, ventral intermediate thalamic nucleus, pedunculopontine nucleus (PPN)], depression (subgenual cingulate gyrus, habenula, medial forebrain bundle, inferior thalamic peduncle, ventral capsule/ventral striatum, nucleus accumbens and anterior limb of the internal capsule;), and obsessive-compulsive disorder (medial thalamus, inferior thalamic peduncle, ventral capsule/ventral striatum, nucleus accumbens, anterior limb of the internal capsule, bed nucleus of the stria terminalis and the STN; Budman et al., 2018; Lee et al., 2019). Nearby targets for the same disorder often may be no more than a few millimeters apart. As the number of disorders and brain targets under investigation continues to expand, improved neurosurgical targeting accuracy and current steering will be required to better define these targets and to delineate nuclei vs. pathway stimulation. As neurosurgical targeting becomes increasingly precise (and "personalized"), direct comparisons using crossover study designs will better inform the field. Advances in research and technology in the field of DBS might allow not only treatment of new disorders but also improve our understanding of the pathophysiological mechanisms of neuropsychiatric conditions and exploration of novel DBS targets using invasive and non-invasive approaches.

Emerging DBS Targets in Motor Disorders

PPN DBS continues to be investigated for its role in the freezing of gait in PD. Interest is driven largely by the PPN's documented relationship to the mesencephalic locomotor region. Variability in PPN DBS outcomes has been attributed to electrode targeting, patient phenotype, outcome measure, and duration of benefit (Thevathasan et al., 2018). As regards electrode targeting, a recent study summarized PPN anatomy and targeting terminology and noted domains of uncertainty that require further investigation and elaboration (Hamani et al., 2016). Outcome measures

have previously included the UPDRS as well as the use of questionnaires that specifically assess gait and freezing. While these are certainly valid, viable and of value, we opine that employing objective measures will likely facilitate the most useful and reproducible approaches. However, procedures used and data gained in gait laboratories may not represent real-world environments, and this variability of such environmental circumstances may be a critical factor for inducing freezing of gait. Indeed, many patients do not freeze (or display improvement of freezing) when in laboratory settings. Hence, reproducibility under laboratory conditions (i.e., efficacy) may not be a reliable measure—or predictor—of real-world effectiveness.

As well, it is important to note that the current state of knowledge on PPN DBS is derived from relatively small-scale studies, and there remains much room for continued (and broadened) investigation. For example, a single case of cyclical PPN DBS (DBS turned off overnight) provided extended benefit beyond that produced by non-cyclical PPN DBS (Stefani et al., 2013). Other approaches, including dual stimulation or dual-frequency stimulation of the STN and substantia nigra pars reticulata (SNr) for resistant axial motor impairment as well as spinal cord stimulation (Weiss et al., 2013; Samotus et al., 2018; Valldeoriola et al., 2019) and adaptive loop DBS has also been undertaken. Additional small uncontrolled studies are exploring other targets for refractory tremors including the caudal Zona incerta and the centromedian and parafascicular nuclei of the thalamus. Combined PPN and caudal zona incerta stimulation, stimulation of the Centromedian and Parafascicular nuclei of the thalamus, and extradural motor cortex stimulation are other targets currently being investigated for the management of refractory axial symptoms in PD (Anderson et al., 2017). While outcomes are promising, these (and additional) approaches will require further study.

Using Multiple DBS Targets

Electrodes with multiple contacts may be used to simultaneously reach many targets oriented along a dorsal-ventral axis. Exemplary cases have included stimulation of the STN and thalamus for mixed PD and ET-like action tremor (Baumann et al., 2012), as well as the aforementioned STN and SNr stimulation for gait and balance. Different electrode designs, such as the Boston Scientific 8-contact device (spanning 1.5 cm) may provide greater flexibility for simultaneously targeting multiple sites for DBS. This device could enable the option to stimulate the SNr, STN, posterior subthalamic region, and thalamus with a single trajectory.

A small double-blind, crossover study is currently in progress to test stimulation at many of these sites. Additionally, it is known that both GPi and globus Pallidus externa (Gpe) DBS may be beneficial for patients with PD (Vitek et al., 2004). Therefore, it may be of value to synergistically target the GPi and GPe, and double stimulation may be more beneficial than stimulation directed to either target alone. Further, a trial is currently underway that employs simultaneous targeting of GPi and the nucleus basalis of Meynert to affect motor and cognitive symptoms in PD (NCT02589925). Novel electrode designs may also prompt further innovation in multiple targeting approaches. The trend in the field has been slowly moving toward the use of multiple DBS targets. These can now be accessed with a single DBS device, and we believe that such developments will afford greater possibility, accuracy, and effectiveness for targeting multiple signs, symptoms, and dimensions of a variety of neuropsychiatric (and other) disorders.

A Randomized Controlled Trial of Personalized Adaptive-Loop DBS to Ameliorate Treatment-Resistant Depression

Major depression is a leading cause of disability worldwide. As well, not all patients respond to pharmacological standard of care interventions. Thus, we believe that those patients resistant to current standards of care might benefit from the use of novel neurotechnologies like DBS. However, randomized control trials of using continuous DBS of pre-selected brain locations to treat major depression, while relatively efficacious, did not yield statistically significant results (Kisely et al., 2018). Difficulties in treating depression with DBS may be related to the complex and heterogeneous nature of this disorder. A personalized aDBS approach that takes into account inter-individual differences could address these challenges. We have designed a 3-stage randomized controlled trial for intervention against treatment-resistant depression (i.e., the PRESIDIO trial) that will test the feasibility, safety and initial efficacy of personalized adaptive-loop DBS with the NeuroPace Responsive Neurostimulation (RNS) System (NCT04004169). Enrollment will include 12 adults with severe treatment-resistant depression who have been unresponsive to four trials of antidepressant medication and psychotherapy.

During the first stage of the study, subjects will undergo temporary implantation of electrodes and will be tested for biomarkers and conduct stimulation endpoints in order to guide target selection. In the second stage, the NeuroPace RNS System will be implanted with lead placement guided by results achieved during stage 1. Subsequently, the short-term and long-term efficacy of personalized adaptive-loop DBS treatment will be examined. The primary outcome measure will be a change in the Montgomery-Asberg Depression Scale (MADRS) score after 6 weeks of treatment stimulation compared with 6 weeks of sham stimulation. Safety will be monitored and recorded throughout the trial. This trial will provide a first-time opportunity to obtain direct recordings of neural networks involved in—and focal to the treatment of—treatment-resistant depression. This trial may enable the identification of quantitative markers of depression and afford an understanding of their dynamics.

Stereoelectroencephalography for DBS Targeting in Pediatric Patients

The targets of DBS treatment of pediatric secondary dystonia vary across patients. The current standard of care to confirm DBS targets in secondary dystonia involves intra-operative microelectrode recordings, which entail waking the patient

during surgery, and therefore necessitates anesthesia without intubation. However, there are children who are unable to tolerate this standard technique because of hyperkinetic dystonic movements and/or airway issues. To overcome this challenge, we have developed a novel 3-stage neuromodulation approach to determine clinically effective DBS targets (Sanger et al., 2018). At stage 1, patients are implanted with stereoelectroencephalography (SEEG) electrodes (Adtech mm16c) in ∼10 potential targets for 5 days of testing and observation. This testing involves single-unit recordings, confirmation of locations with peripherally- and intracortical-EPs, identification of the therapeutic window (efficacy and side effects), and the effect(s) of stimulation on specific tasks. These data can then be used to determine whether to proceed with the second stage (i.e., implantation of DBS leads) and third stage (i.e., implantation of the pulse generator). Typically, approximately 50% of patients with secondary dystonia who undergo DBS show clinically relevant improvement. In comparison, 88% of subjects showed improvements on dystonia scales (Burke-Fahn-Marsden Dystonia Rating Scale, an average improvement of 10 points), and no subjects had worsening of signs and symptoms when utilizing this neuromodulation approach. Overall, this approach was well-tolerated, but there was a significant microlesion effect that seemed to resolve within a week, and this effect may limit the number of thalamic leads to six. Moving forward it will be important to focus on smaller electrodes that may induce smaller microlesions and a simplified conversion to permanent leads.

Use of SEEG for Early Evaluation of Novel Targets and Indications

Classical DBS targets have primarily been based on decades of clinical experience using therapeutic lesions. Advancements in neuroimaging, recording electrodes and overall insight to the node and network function in the brain (both in health and disease) have prompted consideration and exploration of new targets for DBS to treat an expanding number of pathologies. However, new targets and indications lack the validation necessary to move from promising preclinical studies to rigorous clinical trials. One possible means to address and close this gap between preclinical studies and clinical trials is SEEG. As discussed above, SEEG involves the temporary (<3 weeks) implantation of multiple depth electrodes with an array of contacts in different deep brain regions. SEEG electrodes are similar in size and impedance to traditional DBS electrodes, can be implanted into many regions simultaneously, and can utilize externalized stimulators to test novel waveforms and adaptive-loop paradigms. This technique has been used in epileptic patients since the 1960s to record the onset and early spread of seizures (Youngerman et al., 2019). This history of being a well-tolerated and safe technique affords SEEG a particular advantage when considering its use in other protocols and paradigms. Still, it is important to note that the use of SEEG in epilepsy patients may not provide direct comparative value for the use of this technique with DBS.

Yet this too provides a window of opportunity to assess the efficacy, effectiveness and relative research and clinical value of SEEG in tandem with DBS. Toward such ends, the SEEG may be used: (1) for research in patients without epilepsy; (2) with implantation of other (additional) electrodes for studying effects in recording and stimulating brain regions of patients with other (non-epileptic) disorders; (3) for clinical purposes; and (4) to modify the trajectory of clinical electrodes. Evidently, there are ethical issues that must be considered when deciding upon an implantation intent and strategy (e.g., institutional review board (IRB) approval, informed consent, FDA exemption, and scientific rationale rigor). Some examples of recent use of SEEG with DBS include treatment of tinnitus; developing brain-computer interfacing of the primary motor cortex; DBS of the dorsal hippocampal commissure for treatment of mesial temporal lobe epilepsy; DBS of the hypothalamus for treating hypertension; theta burst stimulation/of the fornix region for treatment of post-traumatic memory loss; and DBS of the rostral cingulum bundle for treatment of bipolar disorder. Thus, with proper approval, SEEG can provide a powerful tool to evaluate short-term stimulation of novel DBS targets, and in such ways, may be instrumental to the discovery of new methods and applications of DBS.

NEW DEVELOPMENTS IN OPTOGENETICS AND DBS

Thalamocortical (TC) Physiology in Autism

To understand how different gene mutations lead to a common behavioral phenotype, it is necessary to gain insight into the ways that diverse genetic etiologies converge at the level of neuronal circuit physiology, and how changes in these circuits are involved in behavior. Previous studies have identified prefrontal circuits that are operative in symptoms and signs of autism spectrum disorder (ASD; Cheon et al., 2011; Kalmbach et al., 2015; Demetriou et al., 2018; Brumback et al., 2018; Maximo and Kana, 2019). The integrity of the reciprocal circuit, from the thalamus to the prefrontal cortex (PFC), is required for many prefrontal-dependent behaviors (Parnaudeau et al., 2018). However, the ability to target these reciprocal prefrontal-TC circuits for neuromodulation is hampered by the lack of understanding of thalamic cell types (Rikhye et al., 2018). Apropos of this paucity of understanding, our current work focuses on single-cell electrophysiology of specific mediodorsal (MD) thalamic neurons that provide ascending input to the PFC, with emphasis upon the ways that these neurons are affected in a model of the autism-associated Fragile-X syndrome (FXS). Using a mouse model, retrograde tracers were stereotactically injected into the medial PFC to fluorescently label neurons in the thalamus that project to PFC. Using acute brain slices, whole-cell patch-clamp recordings were taken from visually-identified TC neurons in MD. It was observed that MD→mPFC neurons divide into two populations based on the presence or absence of a prominent conductance mediated by hyperpolarization and cyclic nucleotide-gated (HCN) channels ("voltage sag"). It was hypothesized that these two populations ("High Sag" and "Low Sag") may be globally affected in autism models, or alternatively, that one population would be selectively impacted. To test this, recordings from these two populations of MD→mPFC neurons

were taken in acute brain slices from FXS mice and control littermates. It was observed that in FXS mice, High Sag neurons were hypoexcitable; whereas Low Sag neurons were relatively unaffected. This mirrors findings of abnormal excitability in High Sag mPFC→MD neurons as previously described by our group and others. Ongoing studies aimed at obtaining *in vivo* recordings of LFPs and optogenetic manipulations will evaluate how differences in High and Low Sag neuron physiology influence TC oscillations and behavior. It is hoped that localizing symptoms and signs to specific circuits will help to create circuit-level therapies regardless of the genetic cause of the disorder.

Neural Circuit Mechanisms of Memory Retrieval: Toward Mechanistic Insights and Therapeutic Targets

A current approach to understanding memory involves activating populations of cerebral neurons in order to examine how specific circuits and networks interact with the hippocampus to form, store and retrieve information. Our studies are aimed at identifying frontal brain areas and networks that could contribute to top-down (i.e., cortico-hippocampal) vs. bottom-up (i.e., Hippocampo-cortical) memory processing. Such top-down networks are indicative of storage pathways that are relatively independent of acquisition pathways, and these pathways could prove to be viable targets for DBS-based therapy for Alzheimer's disease and/or Post-Traumatic Stress Disorder.

This technique involves injecting a retrograde virus to the hippocampus to identify direct inputs, including a direct prefrontal- -hippocampal pathway. Using tracer technology, it was demonstrated that these inputs were monosynaptic, and electrophysiological patch recordings revealed a prevalence of direct short-latency excitatory transmissions (Rajasethupathy et al., 2015). Optical activation of the prefrontal inputs to the hippocampus suggested the existence of prefrontal cortical mechanisms that could drive goal-directed memory retrieval in the hippocampus. Further experiments using *in vivo* calcium imaging of the hippocampus, paired with optogenetic activation of prefrontal inputs elucidated that behavioral training fortified hub neurons in the hippocampus that exist within an otherwise uncorrelated neural ensemble. These hub neurons were preferentially targeted by top-down prefrontal inputs and appear to act as conduits to recruit other domains of the memory network. These results suggested that plasticity in the prefrontal cortico- hippocampal network may contribute to PFC engagement of (the most recently active) memory encoding cells to enable future rapid retrieval of important memories. These insights into PFC-hippocampal memory networks may be important to the development of next-generation neuromodulatory approaches to learning and memory acquisition, preservation, and retrieval.

Optogenetic STN DBS

The mechanisms underlying the therapeutic effects of STN DBS for PD are still poorly understood. The anatomical heterogeneity of brain tissue is such that DBS can modulate the activity of multiple neuronal elements in the STN, as well as in surrounding regions. Optogenetic techniques that enable cell-type-specific activation allows assessment of the behavioral effects of selective stimulation of STN local neurons and hyper direct pathway axons (Gradinaru et al., 2009). Selective activation of STN excitatory neurons is not effective for treating Parkinsonian symptoms in the unilateral 6-OHDA lesioned rat model of PD (Gradinaru et al., 2009). However, this conclusion may have been influenced by the slow response kinetics of channelrhodopsin-2 (ChR2) precluding generation of the regular high rate activity required for symptom relief (McConnell et al., 2012, 2016), and it remained unclear whether STN local cells contributed to the therapeutic effects of DBS.

Therefore, we re-examined the role of STN local cells in mediating the symptom-relieving effects of STN DBS using a much faster opsin: Chronos (Klapoetke et al., 2014). Optogenetic stimulation of Chronos-expressing STN cells at 130 Hz reduced pathological circling behavior, in contrast to results obtained using the much slower ChR2 opsin. Furthermore, optogenetic DBS of STN with Chronos was strongly dependent upon stimulation rates: high-frequency DBS (75, 100, 130 pps) relieved ipsilateral turning; while low rates (5 and 20 pps) were ineffective. In addition, optogenetic STN DBS at 130 pps corrected the bias to use the unimpaired forepaw in forelimb stepping; while the low rate (20 pps) DBS was not effective. These results indicated that direct optogenetic stimulation of STN neurons was effective in treating the symptoms of parkinsonism in the 6-OHDA lesion rat, provided that a sufficiently fast opsin was used. These findings highlight that the kinetic properties of opsins can strongly influence the effects of optogenetic activation/inhibition, and therefore must be considered when employing optogenetics to study neural stimulation.

HOLOGRAPHIC DEEP BRAIN STIMULATION; THE COMBINATORY USE OF MIXED, AUGMENTED, AND VIRTUAL REALITY AND DBS

Virtual reality (VR) and augmented reality (AR) are increasingly being utilized for research and clinical applications. Technologies such as the Oculus VR system, the Microsoft Hololens, and other VR and AR systems enable enhanced visualization of neuroanatomy within a 3-dimensional (3-D) environment. Currently, most neuroanatomy has been presented in 2-dimensional (2-D) images utilizing generic axonal pathways that have been derived from textbook illustrations. This approach has not been sufficiently accurate to understand the complexity of axonal pathways and the effect of stimulation as applicable to deep brain neuromodulatory approaches. The Microsoft Hololens was first demonstrated in 2013. The Hololens enabled researchers to render 3-D visualization and allowed multiple users to interact with a model while maintaining interaction with each other[1].

The first step in developing an accurate 3-D model of an axonal pathway atlas for DBS is to reconstruct tractographically-

[1]https://case.edu/hololens/

based pathways in basal ganglia. Layers of cortical surface rendering and vasculature can be added to the holographic 3-D model to increase the interactivity within and between users (Petersen et al., 2019; **Supplementary Figure S5**). These components allow neurosurgeons to better understand the different pathways within, between, and across brain structures. After the structures and axonal pathways are constructed, users can adjust the electrode trajectory to display different DBS lead insertions. Combining the trajectory and volume of tissue activation facilitates the visualization of structures and pathways that potentially would be activated by stimulation. This method can be used to enhance patient-specific surgical planning. Holographic visualization provides a new medium for creating axonal pathway models that we believe will certainly advance the scientific understanding and clinical utility—and value—of DBS.

Using VR for Patient Engagement

The recent technological advancement coupled with the increased presence of social media has afforded growing opportunities for engaging and interacting with neurosurgical patients. In some circumstances, we believe that it is important to initiate the engagement of patients prior to commencing clinical care. To maximize pre-clinical patient engagement, we have developed informative social media and/or online websites that use AR simulation to provide high fidelity examples of prior surgical cases (Steinberger et al., 2020). This process allows patients to view and acquire gain knowledge of surgical procedures prior to the consultation, which can fortify patients' level of familiarity and comfort with the procedures to be implemented. Of course, it is important to obtain patient consent if and when sharing information on social media. As well, when sharing information using simulation for social media engagement, caution should be exercised to avoid any patient identifiers.

The surgical team should explain how the AR simulation is created and how the surgical plan will be based upon the simulation. Surgical Center, an FDA approved surgical planning software, is currently being used for all AR simulations at the Mt. Sinai School of Medicine. The software includes 3-D modeling of the brain, a patient-specific navigation system, and a non-distracting heads-up display. Using these technologies, surgeons can develop a tailored consultation based on types of surgery within the nervous system. AR simulation is increasing patient satisfaction and retention. For example, after using AR for patient consultation, patient satisfaction with (i.e., -Press Ganey Scores), and confidence in the surgical team was shown to increase. A pilot study at Stanford studied the effect of neurosurgical VR services on patient satisfaction and revealed that overall more positive evaluations of surgical experiences (Collins et al., 2018). Currently, a research study is underway to assess the effect(s) of AR simulation on several metrics of neurosurgical patient satisfaction due to AR. While contributory to an increased appreciation for, and relative value of the potential uses and benefit of AR-based neurosurgical simulations, there is also a need for large-scale randomized trials to further explore patient engagement, experience and satisfaction when using this technology.

Using VR With Local Field Potential Acquisition

Beyond surgical planning and patient orientation, VR can be used to simulate real-world environments while simultaneously studying neural signals. One problem with current methods for measuring and/or modulating brain activity has been movement artifacts that may obscure the signal. In combination with wireless chronic recording and stimulation devices such as Neuropace RNS, the Medtronic Percept, and the Medtronic RC+S, VR has facilitated the development of simulated tasks that are naturalistic and therefore more ecologically valid in order to study the neural signals relevant to DBS therapies in awake behaving humans (Collins et al., 2018).

To accomplish this goal, Topalovic et al. (2019) have developed a wireless control and synchronization system for the Neuropace RNS system using a Raspberry Pi equipped with network synchronization. This is a lightweight portable system including the Neuropace programmer and accessory that can communicate with the neurostimulator. While working on the synchronization system, a challenge arose due to telemetry-induced artifacts in scalp EEG. Although the artifacts could be filtered from the signal, it was more beneficial to utilize a custom USB switch to turn off telemetry after the recordings start. This procedure prevented injecting artifacts into the neural recordings. Layered atop the synchronization system and VR was the latitude to add external biometrics using eye-tracking and inertia sensors to capture the comprehensive behavioral data simultaneously during neural recordings.

This system is not specific to the Neuropace RNS system, and it can be adjusted for use in another system by simply connecting the sensing program to a Raspberry Pi interface. This procedure allows for full integration. We have found this system to be capable of integrating VR and LFPs. Additionally, Aghajan et al recently published their work using VR/AR in combination with Neuropace RNS to study spatial memory (Aghajan et al., 2017). This platform enables novel methods to study intracranial EEG activities during freely moving tasks with naturalistic behavior under experimental control.

ADVANCES IN COMMERCIAL TECHNOLOGY AND FUTURE DIRECTIONS

Towards Adaptive Therapies in DBS

In recent years, DBS technology has evolved to improve patients' clinical outcomes and experience and interactions with the device. There are several mechanisms that can be employed to improve patient results, including calibration (optimizing parameters for specific patients and symptoms), lead localization, and the use of adaptive (closed-loop) technology. We opine that the improvement of aDBS applications will be particularly important—and necessary—to bridge this technology from research into clinical practice.

aDBS uses a marker to potentially trigger multiple stimulation parameters to improve the outcomes of stimulation. An example of this technology is provided by a Medtronic system, the Percept PC+S, that is capable of aDBS approaches for both

research and clinical applications. The device offers state-of-the-art stimulation capabilities and includes a sensing engine for recording during stimulation. The device was designed to offer flexible configurations and real-time recording with longer telemetry distances. The device is smaller than other units and has longer battery life. Utilizing the PC+S real-time sensing and controlling capabilities allows aDBS applications. However, iterative evidence of efficacy will be required to clear this system for clinical use.

Previous approaches in aDBS focused on disease indications (e.g., PD, essential tremor, dystonia, epilepsy, Tourette syndrome, etc.,) For each indication, the initial approach has been to identify a signal of interest and to create control parameters (i.e., how the sensing signal triggers the stimulation). Controller classes based on amplitude, triggered response, desynchronization patterns, and other settings can be used group or categorize applications. The goal of centering use on controller classes is to develop broad evidence of safety and utility in order to expedite broader access to these technologies without the limitations incurred by simply using narrow disease-based applications or signals of interest.

Directional DBS: Looking Back to Look Ahead

Previous DBS Think Tanks have identified key limitations with the technologies available at the time. Technologies under development were evaluated for their potential to serve unmet needs, and for each experimental approach, the most pertinent unknowns were identified. For example, the use of a segmented lead to provide "directional" or axially-asymmetric stimulation fields was one such development that was assessed in prior Think Tanks (Deeb et al., 2016; Ramirez-Zamora et al., 2018). In this regard, three important questions were posed: (1) would dDBS achieve a wider therapeutic window?; (2) how would stimulation through smaller, higher impedance electrodes affect power consumption?; and (3) how many segmented contacts would need to be activated, and would current fractionalization technology (e.g., multiple independent current controllers or temporal fractionalization through multi-stimulation sets/ interleaving) be required to achieve effective "steering" of electric fields?

The Abbott-sponsored study of directional vs. omnidirectional (conventional) stimulation (PROGRESS) provides the first high-quality evidence to address these clinically pertinent questions. This study prospectively enrolled 234 patients with STN DBS across 32 actively enrolling sites in Europe, the United States, and Australia. The primary outcome measure, therapeutic window, was evaluated in a randomized, double-blinded manner, 3 months after study enrollment. Secondary endpoints (patient and physician preference, on-meds UPRDS III) were evaluated in a sequential single-arm cross-over design: all patients received 3 months of omnidirectional stimulation followed by 3 months of directional stimulation. A performance target of 60% of patients with gain in therapeutic window on at least one side with dDBS was defined—in agreement with the European regulatory agency—as the superiority end-point. Primary endpoint data were available for 202 patients at the time of this year's (2019) Think Tank. Of those evaluated, 90.6% of patients achieved a wider therapeutic window with dDBS (with a mean 40% gain in therapeutic window), thereby surpassing the superiority endpoint. Additionally, 86.6% of patients achieved a superior therapeutic window with the activation of a single segment compared to omnidirectional stimulation.

Directional stimulation achieved similar benefits at significantly lower therapeutic current strength (39% lower compared to conventional stimulation), which can have a meaningful positive impact on IPG lifespan. The programming approach prescribed as part of the protocol: prioritizing single segment activation and small step size for amplitude increments during a monopolar review, may importantly contribute to these results.

Focusing on Improving DBS Outcomes

Boston Scientific has been developing technologies to improve DBS outcomes and accelerate programming. One of these products, developed with Great Lakes NeuroTechnologies, is Kinesia StimPoint: a tablet-based solution for augmented programming. This software presents a 2-D plot (stimulation location vs. amplitude) used to test, score, and view the clinical outcome of stimulation. Scores can be entered manually, or automatically using integrated accelerometer-based objective measures. This process updates the 2-D plot to reveal a stimulation response surface, and an algorithm suggests next settings. Boston Scientific is working to add support for directional leads to StimPoint. Programming may also be aided using patient imaging data paired with 3D stimulation models as in the Guide XT software, developed with BrainLab. When available, the combination of surgical, imaging, and stimulation response priors with real-time clinical response may further assist programmers.

Prior experimental and modeling studies have demonstrated that using hyperpolarizing or depolarizing pre-stimulation pulses affects stimulation outcome, especially between fibers of differing (bio)physical properties (Grill and Mortimer, 1996). Simulation of microelectrode stimulation also suggests selectivity between cells and fibers may be possible (Grill and McLntyre, 2001). DBS experiments suggest that changes in the stimulating pulse results in changes in response (Akbar et al., 2016). Boston Scientific has developed research programming software which unlocks additional stimulator capability, without the need to alter device firmware. In particular, the software can control the polarity, amplitude, and pulse-width of additional active stimulation pulses, adding a pre- and post-pulse to the existing stimulation pulse. These pulses can be distributed across the lead electrodes (e.g., a pre-pulse to E1, stimulation to E1 and E2, and a post pulse to E2). Boston Scientific stimulators support combined pulse configurations of up to 12 active phases, enabling clinical testing of pulse shapes previously explored in computational models (Foutz and McIntyre, 2010).

The INSHAPE DBS project, led by KU Leuven, has tested various non-commercial pulses in PD and ET patients in a randomized double-blind crossover design using the above system. For this study, a sensing component was added by

including EPs recorded with EEG, and further testing will be performed in an expanded cohort in the chronic condition. The project has investigated 12 different stimulation pulses, combining cathodic, anodic, and biphasic pulses with additional hyperpolarizing pre-pulses of a low, medium, and high amplitude with pulse widths of 120, 240, and 360 μs. Therapeutic window was measured between the minimum current to observe a therapeutic response and the maximum current before observing any side effect. From preliminary data in 4 patients, these investigators found that the different combinations of stimulation pulses had distinct effects in the therapeutic window and that this effect was patient-specific. Additional research will be required to refine this technique toward improving clinical outcomes.

NEUROETHICAL, LEGAL, AND SOCIO-CULTURAL ISSUES OF DBS

As this report, and proceedings from prior Think Tanks illustrate, DBS, like many domains of current and emerging neurotechnology, is advancing, in large part, because of increasingly sophisticated engineering, and expanding knowledge as well as an enhanced understanding of neural systems (Gunduz et al., 2015; Deeb et al., 2016; Rossi et al., 2016; Ramirez-Zamora et al., 2018, 2019). These advances are fostering growing consideration of DBS for studying and treating a broadening scope of neuropsychiatric disorders. Moreover, DBS research and clinical use are becoming ever more international, as several countries are dedicating considerable financial resources to large-scale neuroscientific and neurotechnological initiatives. The field is collaborative and competitive; and both collaboration and competition can evoke asymmetries in technological capability, focus and scope of research, and provision and access to interventions (Martin et al., 2016; Becker et al., 2017; Giordano, 2017). These asymmetries can—and likely will—occur both within nations (e.g., as reflective of differing economics, insurance coverage, etc.,), and between nations (i.e., in light of distinct cultures' economies, norms, and values, philosophies, ethics, and laws).

Thus, while some ethical issues can be similar or identical (e.g., risks of neurosurgery; inherent uncertainties of new technology), others may not (Martin et al., 2016; Becker et al., 2017). As we have noted, even fundamental ethical concepts (e.g., meanings, value, and questions about autonomy, as affected by DBS such as those described below) can be viewed and regarded through differing cultural lenses (Giordano, 2016). Laudably, several intra- and multi-national groups have committed resources to address the ethical-legal and social issues generated by DBS research and use (for example, the efforts of the United States' National Institutes of Health; and Asociación Mexicana de Neuroética, as reported in this article, as well as numerous others).

This is vital, given that the internationality of brain science enterprises would require any authentic neuroethics to be insightful, relevant, and responsive to issues arising in and from the development and applications of DBS—and other neurotechnologies—on the global stage (Rossi et al., 2014; Ramirez-Zamora et al., 2018). To effectively approach these challenges—and opportunities—it will be important to establish some international forum for the iterative exchange of ideas (of currently committed programs, and newly emerging projects in neuroethics), that remains apace with worldwide developments, capabilities, and limitations of neuro-engineering and the social sphere.

The IEEE Brain Initiative Neuroethics Program

Toward such ends, the Institute of Electrical and Electronics Engineers' (IEEE) Brain Initiative Neuroethics Subcommittee is engaged in a multi-year effort to identify current international trends in neuro-engineering; define uses in various contexts and practices; describe ethical-legal and social implications, issues, questions and problems; and develop guidelines for their responsible address. Bringing together subject matter experts in engineering, anthropology, philosophy, ethics and law (see www.braininitiative.org/alliance/ieee-brain), the project is creating an open-access, web-based (and print) platform that enables interactive discourse and ongoing updates as pertinent to developments in the field—and its spheres of application. Importantly, the project aims to develop: (1) consensus and dialectic among share- and stake-holders in the field; and (2) public visibility and awareness of the process. The project, which began in summer 2018 is aiming toward completion by mid/end-2021 (for more detailed information, see www.braininitiative.org/alliance/ieee-brain).

To be sure, the use of DBS, like any therapeutic approach, is aimed at providing maximum benefit for the good of those patients in need. As DBS gains in both technologic sophistication and relative popularity, we must be cognizant that the use of these technologies and techniques uphold patients' values and goals. These concerns call special attention to evaluating DBS and its outcomes, incorporating neuroethical assessment and guidance into research, and understanding the use of DBS in and across international contexts of use.

Control, Personality, and Neuroethical Issues in the Use of DBS for PD

Gisquet (2008) have claimed that DBS is a disruptive experience for some patients due to the associated loss of control of the illness and of one's life, and the possibility of undesired personality changes incurred by the use of this technology. These concerns generated considerable conceptual neuroethical discourse, however, most publications addressing this topic were not based on empirical data (Frederic Gilbert and Ineichen, 2018). Thus, efforts are underway to employ empirical methods to re-examine assertions that DBS results in diminished control and undesired personality changes. Initial studies focused on DBS for PD systematically solicited patients' major symptom-reduction and functional expectations and goals for DBS surgery. Changes in symptoms and patients' perception(s) of control were prospectively assessed at baseline, 3 months post-op, and 6 months post-op. It was found that overall, DBS significantly improved patients' symptoms and personal goals and that these outcomes were highly meaningful and valuable to them.

Interestingly, despite conversations with multiple team members regarding expectations, symptoms that typically do not respond well to DBS (i.e., non-motor symptoms) were among those most cited as symptom-relevant goals (Kubu et al., 2017). Patients' underlying motivations to pursue DBS were primarily related to larger life goals including relationships, avocational pursuits, and work. Additionally, patients' sense of global control of their life significantly increased after DBS, whereas their desire to control their device decreased as patients developed increasing trust in the treatment team and their expertise. Importantly, these initial studies revealed that existing clinical measures do not fully capture patients' goals and motivations. This is a critical issue for assessing patient-centered care, the effectiveness of DBS, and the clinical team's performance (Kubu and Ford, 2012; Kubu et al., 2017, 2018). Furthermore, patients' primary treatment goals changed after DBS, calling into question the idea of how these expectations may change over time, and what this infers for consent.

Current studies are exploring patients' and family members' perspectives and experiences of the preservation of their most valued personality characteristics at different stages of PD and over the course of DBS, using a cohort of patients with PD diagnosed less than 1 year prior, diagnosed within 5–7 years prior, and patients approved for DBS. Preliminary results reveal that standard personality measures do not comprehensively assess what matters most to patients. Furthermore, patients retrospectively reported an average decline in valued personality characteristics over the course of PD across all three cohorts. However, patients who are candidates for DBS were significantly more likely to anticipate future gains in valued personality characteristics (closer to their premorbid level), whereas patients who are not candidates for DBS anticipated continued losses of valued personality characteristics over time. Finally, DBS was associated with personality ratings closer to reported historical scores and an increase in global control. In sum, these data refute some of the claims that DBS causes undesired personality changes, provides empirical evidence of what clinical goals and outcomes are most important to patients and families, and these findings highlight the need to develop clinical measures that are more patient-centered and more accurately address and reflect individual patients' values.

Updates on the NIH BRAIN Initiative in Neuroethical Issues

As developments in technology and neuroscience introduce novel ethical challenges in research and clinical care, a more contemporary definition of the foci and functions of neuroethics—as a field and set of practices—is needed. Advances in neurotechnology research, development and use make it important to consider emerging questions and implications that such progress foster for research participants, family members, researchers, and the community-at-large. To address these questions and develop a roadmap for future inquiry in neuroethics, the National Institutes of Health (NIH) established an advisory committee under auspices of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. In recognizing the need and value of supporting neuroethical inquiry and address, the NIH has begun to fund research and training projects through a variety of funding mechanisms (e.g., R01s, F32s), and administrative supplements to embed ethicists into BRAIN Initiative-supported research.

As we use novel neurotechnology in clinical trials, several guidelines have been developed, with safety being the most important factor to consider. In this regard, researchers should ensure informed consent processes are attentive towards psychosocial risks (i.e., changes in self-identity, effects of research interventions on interpersonal relationships, and potential shifts in patient values), and should include detailed protocols that address end-of-trial and post-trial responsibilities relevant to physical and psychological risks that may be incurred at post-study follow-up. Additionally, researchers should include a clinician on study teams to enable a better understanding of the clinical implications of research undertaken.

Moreover, it will be important to foster public education to create dialogs to communicate results of research in ways that be broadly understood. Crucial to this pursuit is an awareness of media influence on public views. To maximize the relevance and generalizability of DBS research, it will be even more important to include the public in neuroethical discourse. Finally, but certainly not least, interdisciplinary collaborations should be developed to more ably integrate neuroethical assessment and guidance to ongoing research projects. We believe that each and all of these steps will encourage attentiveness to neuroethical dimensions of DBS research while supporting training opportunities for the next generation of neuroethics, researchers and clinicians.

Neuroethics in Global Context: The Use of DBS in Mexico

Research and clinical use of DBS are expanding beyond the developed world. This has prompted consideration if and to what extent DBS is cross-culturally valid, pertinent and valuable. As an exemplar, in Mexico, there are particular neuroethical, legal and socio-cultural issues (NELSCI) that might shape perceptions and evaluations of scientific and technological tools and techniques (Karen Herrera-Ferrá et al., 2019). These factors prompt consideration of proactive inclusiveness of diverse ethnocultural contexts and factors (e.g., needs, values, philosophies, beliefs and traditions) within and across countries, in order to better understand various views (i.e., culturally-framed cognition), specific local NELSCI, and attitudes that could direct the use -or non-use- of advanced neurotechnology, such as DBS. Comprehensive cultural competency could—and should—be developed and fortified to provide complementary reflections to enable more meaningful discourse, this will be important to identify and increase clinical goals and benefits, reduce burdens and harm(s), and in these ways, improve global efforts to promote and sustain ethically sound translational—and sensitively *transnational*—use of DBS.

Summary and Conclusions

The Seventh Annual DBS Think Tank addressed in the most current: (1) commercially available technologies; (2) use of

advanced technologies to improve clinical outcomes; (3) research in neuromodulatory approaches to treating neuropsychiatric disorders; (4) use and utility of complex neurophysiological signals for advancing delivery of neurostimulation; and (5) ethical issues arising in and from research and use of DBS. Every year, the attendees of the DBS Think Tank are asked to answer a questionnaire in which they position different neurotechnologies on the Hype Cycle curve (**Supplementary Figure S6**). Sixty participants responded, the vast majority working at academic institutions and universities. The weighted-mean experience in the field of neurotechnology of the participants is 10 years. In the last year, DBS for Parkinson's disease and essential tremors remain at the slope of enlightenment. Similarly, vagus nerve stimulator (VNS) uses in obesity, rheumatoid arthritis, heart failure, and stroke are at the technology trigger. Interestingly, low-intensity focused ultrasound moved from technology trigger to peak of inflated expectations, which corresponds with its expanding applications. On the other hand, cochlear implants dropped from the slope of enlightenment to the trough of disillusionment.

These advances serve as both "markers of progress" and challenges and opportunities for ongoing address, engagement, and deliberation as we move to improve the functional capabilities and translational value of DBS. It is in this light that these proceedings are presented to inform the field and initiate ongoing discourse. As consistent with the intent, and spirit of this, and prior DBS Think Tanks, the overarching goal is to continue to develop multidisciplinary collaborations to rapidly advance the field and ultimately improve patient outcomes. Our ongoing work remains dedicated to these efforts.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. Individual investigators will provide datasets at time of publication of specific research.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Individual academic institutions. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR-Z, JG, AG, JA, JC, SC, RE, JG, SL, BP, JW, PD, BP, SC, WG, HW, SL, RG, GT, WT, NS, AL, TF, AF, SS, GS, TS, JM, AB, PR, CM, LS, NS, CK, LS, KH-F, SG, BC, GS, CH, LA, WD, KF, and MO fulfilled the authorship criteria by substantial contributions to the conception of the work, providing data for the work, revisiting it critically for important intellectual content, approving the final version, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00054/full#supplementary-material.

FIGURE S1 | Adaptive Deep Brain Stimulation (aDBS) relies on identifying unique neurophysiological biomarkers using local field potentials (LFPs) at the cortical (using Ecog) or subcortical (through the DBS lead) level to trigger and deliver stimulation using an advanced sensing device (for additional details please refer to main text).

FIGURE S2 | Example of a neuronal closed loop-DBS trial: upper panel demonstrates fluctuation of subthalamic nucleus (STN) beta power within, above and below the dual thresholds; lower panel demonstrates the DBS voltage response. The insert highlights the decision events over a 1 s period, whether DBS voltage increased (red triangles), stayed the same (no symbols), or decreased (blue triangles). From Velisar et al. (2019) with permission.

FIGURE S3 | Real-time collection of local field potential to enable high accuracy differentiation of clinical states for adaptive neuromodulation (i.e., home environments).

FIGURE S4 | DBS evoked resonant neural activity (ERNA). **(A)** Applying stimulation in the vicinity of the STN elicits evoked responses with decaying oscillation morphology. Columns show the ERNA recorded at each electrode when stimulation was applied to different electrodes (indicated by crossed axes) in a person with PD. A 3D reconstruction illustrating electrode positions (green: STN, blue: substantia nigra). **(B)** Normalized ERNA amplitude varies with electrode position with respect to (w.r.t) the STN in people with PD (20 hemispheres tested; box: 25th–75th percentiles; line: median; whiskers: range). $^{***}p \leq 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. **(C)** Mean Unified Parkinson's Disease Rating Scale (UPDRS) improvement from stimulation after ranking electrodes within each hemisphere according to ERNA amplitude (rank 1: largest ERNA; bars: standard error). Results from 10 PD patients tested post-surgery (20 hemispheres). **(D)** ERNA recorded in a person with PD at electrode implantation (blue) and under general anesthesia 560 days postop (red). **(E)** ERNA frequency decreases with increasing DBS amplitude (19 hemispheres tested). Red bars: $p \leq 0.001$; yellow bars: $p < 0.05$. **(F)** ERNA frequency correlates with relative beta band (13–30 Hz) amplitude across the stimulation levels shown in (**E**; $\rho = 0.58$, $p < 0.001$). Colors represent different hemispheres tested. Panels **(A–D)** from Sinclair et al. (2018) with permission. Panels **(E,F)** from Sinclair et al. (2019) with permission.

FIGURE S5 | Illustration of Pathway Generation Process including: **(A)** histological data from the Morel atlas, **(B)** histological data fitted to the CIT 168 brain atlas, **(C)** preliminary pathway trajectories were generated using information from the MRI, histology, and previous literature, **(D)** mean trajectories were generated for each pathway, **(E)** preliminary streamline bundles were generated, **(F)** using the HoloLens system, these pathways were visualized, discussed, and manually edited *via* holographic interactions with the neuroanatomists and **(G)** finalized pathways. From Petersen et al. (2019) with permission.

FIGURE S6 | Hype Cycle schematic representation. This Figure represents the position of certain DBS-associated technologies at different stages of development on the Hype Cycle curve (Fenn, 1999).

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Electrophysiology and Structural Connectivity of the Posterior Hypothalamic Region: Much to Learn From a Rare Indication of Deep Brain Stimulation

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Cluster headache (CH) is among the most common and debilitating autonomic cephalalgias. We characterize clinical outcomes of deep brain stimulation (DBS) to the posterior hypothalamic region through a novel analysis of the electrophysiological topography and tractography-based structural connectivity. The left posterior hypothalamus was targeted ipsilateral to the refractory CH symptoms. Intraoperatively, field potentials were captured in 1 mm depth increments. Whole-brain probabilistic tractography was conducted to assess the structural connectivity of the estimated volume of activated tissue (VAT) associated with therapeutic response. Stimulation of the posterior hypothalamic region led to the resolution of CH symptoms, and this benefit has persisted for 1.5-years post-surgically. Active contacts were within the posterior hypothalamus and dorsoposterior border of the ventral anterior thalamus (VAp). Delta- (3 Hz) and alpha-band (8 Hz) powers increased and peaked with proximity to the posterior hypothalamus. In the posterior hypothalamus, the delta-band phase was coupled to beta-band amplitude, the latter of which has been shown to increase during CH attacks. Finally, we identified that the VAT encompassing these regions had a high proportion of streamlines of pain processing regions, including the insula, anterior cingulate gyrus, inferior parietal lobe, precentral gyrus, and the brainstem. Our unique case study of posterior hypothalamic region DBS supports durable efficacy and provides a platform using electrophysiological topography and structural connectivity, to improve mechanistic understanding of CH and this promising therapy.

Keywords: cluster headache, deep brain stimulation, posterior hypothalamus, local field potential, diffusion tractography

BACKGROUND

Cluster headache (CH) is a severe trigeminal autonomic cephalalgia and often considered among the most difficult types of headaches to manage. Varying approaches have been taken in attempts to treat CH, however, poor understanding of the underlying mechanism has led to limited improvement in management (Leone et al., 2001; Vyas et al., 2019). Approximately 10% of CH patients fail medical therapy and ultimately seek surgical intervention, such as deep brain stimulation (DBS; Lovely et al., 1998). Several neuroimaging studies including tractography, positron-emission tomography, and voxel-based morphometry have linked abnormalities in hypothalamic activity to pain processing centers likely involved in CH pathogenesis (May et al., 2000; Qiu et al., 2013). DBS targeting the posterior hypothalamic region has had some success in mitigating CH although with some variability in targeting strategies across groups (Leone et al., 2001; Broggi et al., 2007; Bartsch et al., 2008; Franzini et al., 2010; Leone et al., 2010; Clelland et al., 2014). We examine a rare case of posterior hypothalamus DBS for CH to better characterize the electrophysiological properties of the posterior hypothalamus and surrounding structures. Further, we use probabilistic tractography to estimate the structural connectivity of the targeted region.

MATERIALS AND METHODS

Clinical Data

This investigation is built upon the case of a 67-year-old, right-handed male with a long-standing history of medically refractory chronic CH in the setting of comorbid medically refractory essential tremor. The patient was primarily referred for essential tremor treatment with unilateral DBS of the ventral intermediate nucleus of the thalamus, however, before surgery, his CH was characterized by 10–120-min episodes of stabbing left-sided retro-orbital pain, ranging 8–10/10 in intensity, with 4–8 episodes per day. He failed all attempts at conservative therapy, including verapamil, prednisone, topiramate, gabapentin, indomethacin, fentanyl patches, high-flow oxygen therapy, and a sphenopalatine ganglion nerve block. An opioid dependence related to CH management was treated with buprenorphine and naloxone therapy. The patient thus consented to off-label posterior hypothalamic region DBS implantation, and this case study was approved by our institution's internal review board (IRB#33146). A robot-assisted frameless implantation was performed as described previously (Ho et al., 2019). The left posterior hypothalamus was first targeted indirectly (x, y, z = 2, −5, −3 mm from the mid-commissural point) as described by others (Franzini et al., 2003; Sani et al., 2009), and confirmed by intra- and post-operative thin-cut CT imaging merged to pre-operative MRI. Microelectrode recordings were performed at 1 mm intervals on approach to the target, per our standard clinical protocol. Upon reaching the target depth, the microelectrode was removed and replaced with a Medtronic DBS lead used solely for therapeutic stimulation (Model 3387, Medtronic Inc., Dublin, Ireland).

Electrophysiology Acquisition and Analysis

The methods of our signal acquisition and analysis pipeline have been previously described (Wu et al., 2018; Miller et al., 2019). MERs were captured at 50 kHz using Guideline 3000 MER system (Axon Instruments Inc., Foster City, CA, USA; gain, 10,000; band-pass filtered from 1 Hz to 10 kHz). In brief, 60-s recordings were captured at each depth and segmented into 5-s epochs. To extract units, the raw voltage was band-pass filtered from 3 kHz to 9 kHz and for each sample deflection above the threshold, 7 ms window from 2 ms before maximal deflection was obtained. Windowed data were decomposed using principal component analysis. Field potentials were extracted from the MER by band-pass filtering the 1 kHz downsampled data from 1 to 300 Hz. Normalized power spectral density estimates were calculated using MATLAB's "pwelch" (50% overlap, 1–50 Hz, 2 s Hanning window) function (MATLAB 2017b, The MathWorks Inc., Natick, MA, USA). Oscillations were visually apparent and revealed by peaks in the PSD at 2 Hz (delta), 5 Hz (theta), 8 Hz (alpha), 17 Hz (beta), and 32 Hz (gamma). For each oscillation, a complex analytic signal was constructed using a band-pass (delta 1–3 Hz, theta 4–7 Hz, alpha 8–12 Hz, beta 13–25 Hz, gamma 28–50 Hz) and then applying the Hilbert transform. The rhythm phase coupling to locally measured activity was estimated by calculating the log-broadband amplitude as a function of the rhythm phase in small phase intervals (Miller et al., 2012). Finally, cross-frequency phase-amplitude coupling (PAC) was measured using the Brainstorm (v3) toolbox in MATLAB. This implementation is based on the mean-vector length modulation index as previously described for calculating a "direct PAC" measure, where a value of 0 indicates a lack of phase-amplitude modulation (Canolty et al., 2006; Özkurt and Schnitzler, 2011; Tadel et al., 2011). All implementation details are freely and readily documented and can be verified in Brainstorm's open-source software code. For statistical analysis, a one-way analysis of variance was calculated on measured PSD between depth groups for each frequency band. Similarly, a one-way analysis of variance was calculated on measured direct PAC between depth groups for each phase-amplitude pair. Significance was determined at an alpha cutoff of 0.05 on p-values adjusted using the false discovery rate (FDR) method. All p-values reported are FDR-adjusted.

Imaging Acquisition

Preoperatively, a T1-weighted structural 3T MRI was obtained throughout the entire cranial volume. Diffusion-weighted images (2 mm isotropic, TR/TE = 8,000/103.7 ms, 30 directions uniformly distributed on the sphere, b = 1,000 s/mm^2, 300 s) were acquired from the patient. Thin-cut CT images were obtained intra (i.e., O-arm, Medtronic) and post-operatively to confirm lead placement location.

Reconstruction of Electrodes and Volume of Activated Tissue

Lead-DBS (v2) was used to localize and visualize a 3D model of the electrodes in the patient after linear registration of the CT into the patient's T1-weighted MRI scan (Horn et al., 2019). The co-registrations were checked by manual confirmation. The electrode trajectory was automatically reconstructed in 3D space using a search for artifacts caused by electrode leads by manually selecting the starting point of the artifact for each hemisphere. After the automatic pre-reconstruction, manual reconstruction ensued to maximize precision. The volume of activated tissue (VAT) for the bipolar stimulation modality was calculated using a finite element method based on the DBS programming parameters and the conductivity characteristics of the neural tissue activated, inferred from the contrast of the patient's T1-weighted MRI (Horn et al., 2017).

Diffusion Tractography

Preprocessing was performed on the diffusion-weighted images to prepare the images for tractography using Oxford FMRIB's FSL suite. The "top-up" tool was used to estimate and correct non-zero off-resonance fields caused by the susceptibility distribution of the subject's head. The "eddy" tool was used to correct for the eddy current caused by the rapid switching of the diffusion gradient. ROIs were generated using Freesurfer automatic segmentation to the Freesurfer subcortical atlas and the Desikan-Killiany cortical atlas (Ashburner and Friston, 2005). FSL's Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) and ProbtrackX was used to run probabilistic tractography, sampling the fiber orientation distribution in each voxel 5,000 times, accounting for crossing fibers. The seed regions for tractography were the VAT masks derived from the bipolar electrode programming parameters, with contacts 1 and 3 activated. Tractography resulted in an m × n connectivity matrix, where m refers to each voxel within the VAT, and n refers to the number of streamlines to the ROI. The voxels that did not have any streamlines to any ROI were removed. The number of streamlines from each VAT voxel was normalized by dividing the total number of streamlines between the voxels and all ROIs so that the normalized total number of streamlines is equal to 1. The proportion of streamlines from each seed voxel to each ROI were analyzed to determine significant projections. For visualization purposes, streamlines were generated using the same seeding parameters in MRtrix, and visualized in 3D using DSI Studio (Smith et al., 2013; Yeh et al., 2013).

RESULTS

Post-surgical Course

Two weeks postoperatively, the patient was seen for initial programming. Contacts were found to be in the midbrain (contact 0, C0), posterior hypothalamus (C1), and ventral anterior thalamus (VAp; C2 and C3; **Figure 1A**). Monopolar testing of the lead contacts revealed decreased headache on activation of contact 2 (C2). Follow-up testing found that bipolar stimulation of contacts 1–2 (0.5V, C1− C3+, 60 ms, 165 Hz) resulted in the most robust response with no discernable headache symptoms. At 18 months post-surgically, active contacts were unchanged but stimulation parameters were slightly modified due to modest recurrence of symptoms (1.2V, C1− C3+, 60 ms, 100 Hz). At this time, the patient endorsed a lack of headache symptoms and no adverse side effects (**Figure 1B**). The patient also experienced expectedly unrelated relief of his essential tremor with activation of his thalamic lead (data not shown).

Intraoperative Electrophysiology and Tractography

MER started 14 mm from the hypothalamic region target (x, y, z = 2, −5, −3 mm from the mid-commissural point) along the pre-planned trajectory and they were collected at 1 mm interval advancements (**Figure 1A**). The microelectrode was then removed and replaced with a DBS lead along the same trajectory. As a single trajectory was used for both MER and DBS lead placement, reconstruction of MER positions was extrapolated from the measured lead depth. Overall, theta- and alpha-band power increased with proximity to the hypothalamic region (alpha-band: $F_{(1,3)} = 103.1$, $p < 0.0001$, 1 mm vs. rest: $p < 0.0001$, 5 mm vs. 10 mm/other depths: $p < 0.0001$; **Figure 1B**). Comparing power across depths, alpha and beta-band power showed local maxima at depths of 1 mm and 5 mm (C1) from target while theta-power maxima were observed at depths of 5 mm (C1), and 10 mm (C3) from target (beta-band: $F_{(1,3)} = 43.6$, $p < 0.0001$, 5 mm vs. rest $p < 0.0001$; theta-band: $F_{(1,3)} = 33.4$, $p < 0.0001$, 5 mm vs. 1 mm/other depths: $p < 0.0001$, 10 mm vs. 1 mm/other depths: $p < 0.0001$; **Figure 1C**). Delta-band power had one clear peak at 5 mm (C1) from target (delta-band: $F_{(1,3)} = 130$, $p < 0.0001$, 5 mm vs. rest: $p < 0.0001$). Finally, notable delta-band phase and beta-band amplitude coupling was observed at 5 mm (C1) but not at any other depth (delta-beta PAC: $F_{(1,3)} = 14.5$, $p < 0.0001$, 5 mm vs. rest: $p < 0.0001$; **Figure 1D** and **Supplementary Figure S1**). Also, theta-band phase and gamma-band amplitude coupling was increased at 5 mm compared to 1 mm and other depths but not 10 mm (theta-gamma PAC: $F_{(1,3)} = 4.5$, $p = 0.004$, 5 mm vs. 1 mm/other depths: $p < 0.05$).

To explore the white matter fiber tracts of the VAT, tractography was performed from the VAT calculated for initial parameters at 2 weeks (bipolar, C1−C3+), and parameters at 1.5 years (**Figure 2A**). The initial 2-week programming parameters of bipolar stimulation at C1− and C3+ resulted in a VAT that had prominent streamlines (>5%) to the insula, rostral anterior cingulate cortex (rACC), inferior parietal lobe, precentral gyrus, and brain stem (**Figures 2B,C**). The VAT resulting from parameters at 1.5 years had nearly an identical streamline profile to that at 2-weeks postoperatively.

DISCUSSION

This investigation sheds light on the mechanisms of a successful DBS treatment of CH. Electrophysiological mapping along the posterior hypothalamus trajectory suggests a topological correspondence between field potential activity and the position

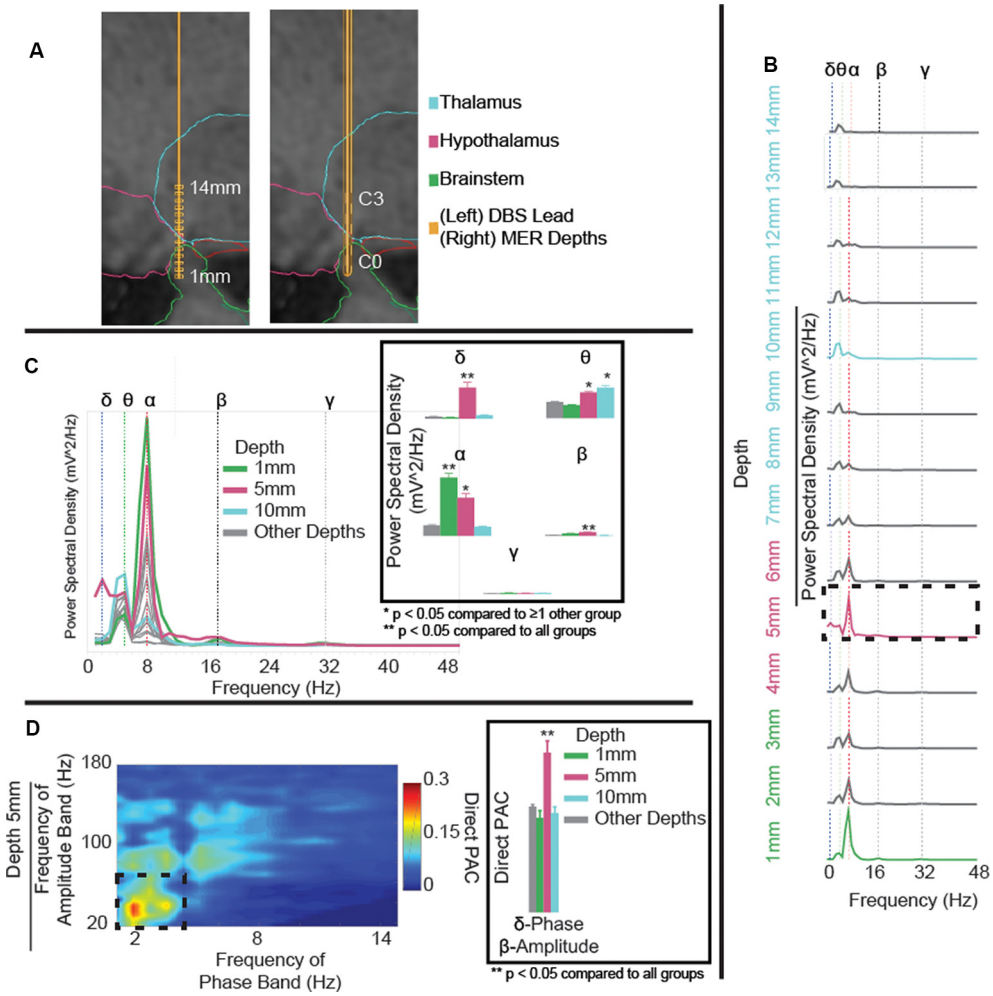

FIGURE 1 | (A) Microelectrode recording (MER) depths (left) and deep brain stimulation (DBS) lead position (right) in T1 sagittal slice with overlaid segmented regions. Reconstruction shows DBS contacts C0 in the brainstem, C1 in the posterior hypothalamus, and C2 and C3 in the ventral anterior thalamus (VAp). **(B)** Power spectral density (PSD) estimates for field potentials collected at each depth to target, coded to the approximate region of interest. Variations in power observed in delta- (blue-dotted line), theta- (green-dotted line), alpha- (red-dotted line), beta- (black-dotted line), and gamma-frequency bands (gray-dotted line). Delta- and alpha-band powers increase with proximity to the posterior hypothalamic region. **(C)** Aggregated PSD estimates for field potentials collected at each depth to target, coded to the approximate region of interest. Panel **(C)** highlighting significant ($p < 0.001$) delta power in the posterior hypothalamic region (5 mm), increased theta at 5 and 10 mm, and increased alpha at 1 and 5 mm from the target. **(D)** Cross-frequency phase-amplitude coupling (PAC), using the direct PAC measure. Panel **(D)** highlighting significant ($p < 0.001$) delta-band phase coupling to beta-band amplitude in the posterior hypothalamic region (5 mm), not present at any other depth (**Supplementary Figure S1**). $^{**}p < 0.05$ when compared to all other depth groups, $^{*}p < 0.05$ when compared to ≥ 1 other group.

of clinically therapeutic contacts. Specifically, delta- (3 Hz) and alpha-band (8 Hz) powers increase with proximity to this region with significant coupling between delta- and beta-band (17 Hz). Further, the VAT encompassing this region has a high proportion of streamlines to regions associated with pain processing (May et al., 2000; Qiu et al., 2013).

Targeting of regions including the posterior hypothalamus and selection of active contacts largely relies on results from prior treatment trials and trial and error during intraoperative and post-operative stimulation testing. Regional electrophysiology, namely readily recordable field potentials, and VAT tractography models provide a potential bridge to optimizing both preoperative planning and intraoperative targeting and in aiding in postsurgical programming (Chen et al., 2006; Thompson et al., 2014; Tinkhauser et al., 2018; Akram et al., 2017). In the case of the subthalamic nucleus in Parkinson's, field potential biomarkers have been reported to be predictive of contacts with greater therapeutic effect upon stimulation (Chen et al., 2006). In the case of the posterior hypothalamus in CH, electrophysiological mapping of the region has largely been limited to recordings in a small number of case series, largely focused on reporting single-unit firing rates (Bartsch et al., 2008; Cordella et al., 2007, 2010; Starr et al., 2007; Micieli et al., 2017; Sani et al., 2009).

To our knowledge, only two studies have reported on field potentials in the posterior hypothalamus. Nager et al. (2011) demonstrated event-related field potential differences to motivational (sexually-relevant and food) stimuli compared

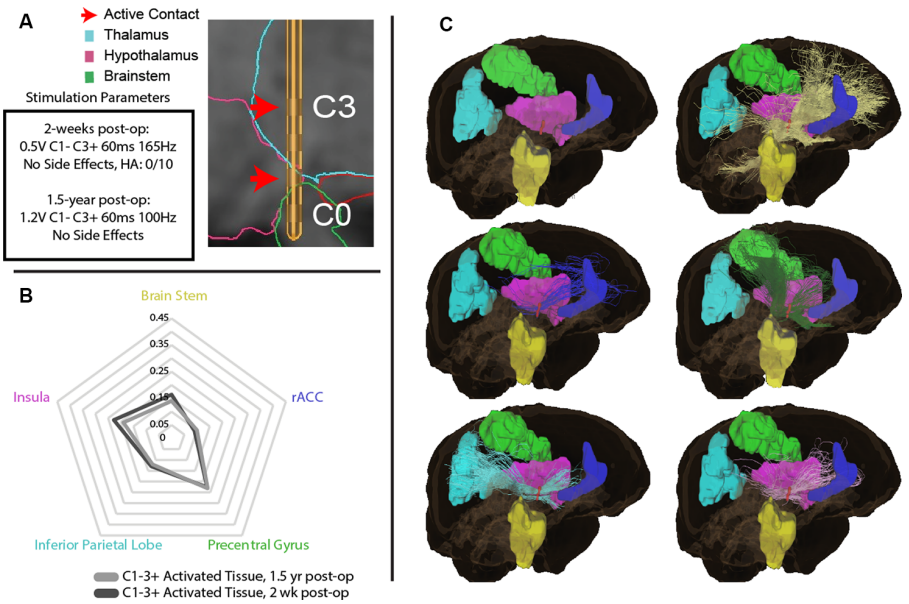

FIGURE 2 | (A) Initial parameters at 2-weeks post-operation and 1.5-year post-surgically with DBS lead depicting active contacts in green. **(B)** Regions of interest (ROIs) with greatest tractography-based proportion of streamlines (>5% of normalized streamlines) to the volume of activated tissue (VAT) with parameters at 2-weeks post-operation, and 1.5-years post-surgery. **(C)** Visual representation of ROIs with greatest tractography-based proportion of streamlines to the brain stem (yellow), rostral anterior cingulate cortex (rACC, blue), precentral gyrus (green), inferior parietal lobe (blue), insula (pink), and brain stem (yellow).

to common control items, however, they did not characterize frequency-band specific results (Nager et al., 2011). Brittain et al. (2009) demonstrated that during a CH attack, there was a significant increase in beta-band (20 Hz) field potential power, representing a possible pathologically-relevant biomarker. Here, we demonstrate field potential topography in and around the hypothalamic region with the increasing prominence of low frequency- (delta-, and alpha-) band power with proximity to this region. While recordings here were performed outside of a CH attack episode, we find prominent delta- and beta-band coupling in the hypothalamic region, highlighting the previously demonstrated pathologic association. This marker could be utilized in localizing an appropriate depth to target the region in future implantations. However, the spectral findings in this study are limited by a lack of control data to delineate their specificity as a pathologically-relevant biomarker. Further work is needed including capturing spectral changes during CH attacks and in non-CH patients to better characterize this activity and explore its utility during intraoperative targeting and post-surgical programming.

The pathological basis of CH is poorly understood but many studies have demonstrated aberrant activity in some pain processing regions. Although the results from this investigation are representative of a single case of CH, our analysis sheds light on the possible mechanisms of CH pathogenesis *via* the pain-matrix network and central autonomic matrix. Painful stimuli elicit activation upon the pain-matrix network of cortical structures, such as somatosensory, insular, and cingulate areas. Activation of this network has been demonstrated in multimodal investigations, suggesting that it functions as a salience detection system for pain (Legrain et al., 2011). Moreover, functional MRI studies have suggested two major groups of structures to be involved in CH—the pain-matrix network structures, and separately, the hypothalamus (May and Goadsby, 1999). In the case of the central autonomic network, dysfunctional autonomic regulation, with the hypothalamus as a key mediator, contributes to the pathological mechanism of CH with autonomic symptoms including lacrimation, ptosis, and conjunctival injection present during attacks (May, 2005). Our results provide further evidence of an association between these structures through prominent streamlines from the hypothalamic VAT that may modulate or be modulated by structures in the pain-matrix and central autonomic networks.

Notably in this study, the ACC, insula, and brainstem received a high proportion of streamlines to the VAT associated with clinical improvement. Within the pain-matrix network, the ACC and insula are thought to be centers for affective components of pain processing and perception and modulation of pain, respectively (Fuchs et al., 2014; Lu et al., 2016). Within the central autonomic network, the ACC, insula, and several brain stem regions are key nodes in the autonomic nervous system function (Sklerov et al., 2018). Streamlines to the precentral gyrus and the inferior parietal lobe were prominent with our parameters. These findings are consistent with previously reported structural and functional abnormalities in cluster headache patients, which have helped to shed light on their possible pathologic roles. In CH patients, the precentral gyrus was found to have decreased cortical thickness (Cosentino et al., 2015; Seifert et al., 2012). It has also been reported that CH patients possessed decreased gray matter volume in structures in the pain-matrix network, notably the precentral gyrus, insula, and inferior parietal lobe (Absinta et al., 2012). The inferior

parietal lobe has been reported to have increased resting-state functional connectivity to the posterior hypothalamus in CH patients that further increases during painful episodes (Qiu et al., 2013; Chou et al., 2017). Also, repetitive transcranial magnetic stimulation of the precentral gyrus has been used to successfully deliver therapeutic benefit to CH patients (Cosentino et al., 2015; Hodaj et al., 2015). DBS modulation of pain processing pathways is further supported by recent studies showing that responders to posterior hypothalamus stimulation have VAT along the trigeminohypothalamic pathway and associations between the posterior hypothalamus with other regions for autonomic regulation and pain (May et al., 2006; Akram et al., 2017). Put together, the findings from this investigation bring a new perspective with direct neural recording, imaging, and direct modulation results that helps to elucidate the mechanisms of DBS in the context of the treatment of CH. Future studies can probe the extent that these spectral and tractographic features predominate in CH attack vs. non-attack posterior hypothalamic region activity and how these features are modulated by DBS.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Stanford University School of Medicine Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CH, KM, DD, and BK contributed to the conception and design of the study. BK, SS, and DB performed the statistical analysis. All authors contributed to the drafting and revision of the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00164/full#supplementary-material.

FIGURE S1 | (A) Cross-frequency phase-amplitude coupling at each microelectrode depth recording revealing prominent delta-band phase coupling to beta-band amplitude in the posterior hypothalamic region (5 mm), not present at any other depth. **(B)** Non-zero direct PAC measure for each phase-amplitude pair by depth group highlighting significant delta-phase to beta-amplitude coupling in the hypothalamic region. $^{**}p < 0.05$ when compared to all other depth groups, $^{*}p < 0.05$ when compared to $\geq$1 other group.

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BRIEF RESEARCH REPORT
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Neurophysiological Correlates of Gait in the Human Basal Ganglia and the PPN Region in Parkinson's Disease

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This study aimed to characterize the neurophysiological correlates of gait in the human pedunculopontine nucleus (PPN) region and the globus pallidus internus (GPi) in Parkinson's disease (PD) cohort. Though much is known about the PPN region through animal studies, there are limited physiological recordings from ambulatory humans. The PPN has recently garnered interest as a potential deep brain stimulation (DBS) target for improving gait and freezing of gait (FoG) in PD. We used bidirectional neurostimulators to record from the human PPN region and GPi in a small cohort of severely affected PD subjects with FoG despite optimized dopaminergic medications. Five subjects, with confirmed on-dopaminergic medication FoG, were implanted with bilateral GPi and bilateral PPN region DBS electrodes. Electrophysiological recordings were obtained during various gait tasks for 5 months postoperatively in both the off- and on-medication conditions (obtained during the no stimulation condition). The results revealed suppression of low beta power in the GPi and a 1–8 Hz modulation in the PPN region which correlated with human gait. The PPN feature correlated with walking speed. GPi beta desynchronization and PPN low-frequency synchronization were observed as subjects progressed from rest to ambulatory tasks. Our findings add to our understanding of the neurophysiology underpinning gait and will likely contribute to the development of novel therapies for abnormal gait in PD.

Clinical Trial Registration: Clinicaltrials.gov identifier; NCT02318927.

Keywords: Parkinson's disease (PD), brainstem, deep brain stimulation (DBS), gait, DBS, deep brain stimulation

INTRODUCTION

The pedunculopontine nucleus (PPN) region has recently generated much interest as a deep brain stimulation (DBS) target for the treatment of freezing of gait (FoG) in Parkinson's disease (PD; Stefani et al., 2007, 2013; Moreau et al., 2009; Moro et al., 2010; Khan et al., 2012; Welter et al., 2015; Hamani et al., 2016). Surgically targeting the PPN region has proven challenging due to the lack of clear anatomical demarcations on traditional imaging. Outcomes from small clinical trials have shown mixed benefits (Zrinzo et al., 2008, 2011; Mestre et al., 2016). A better electrophysiological understanding of the PPN region will be critical to the development of future therapeutic strategies and especially to closed-loop neuromodulation which relies on the identification of a control signal. Several clues point to the PPN region as an important node in human gait-related activities. First, it has been shown that gait-related symptoms have been closely associated with diseases associated with prominent PPN degeneration (e.g., PD and progressive supranuclear palsy). Second, the PPN has been shown in animals to be a critical node in the gait cycle. Finally, altered gait has been reported in lesional studies of the PPN region, and gait deficits are improved by electrical stimulation in both rat and non-human primate PD models (Aziz et al., 1998; Breit et al., 2001, 2005; Jenkinson et al., 2006; Nandi et al., 2008; Karachi et al., 2010; Grabli et al., 2013).

The globus pallidus internus (GPi) and the subthalamic nucleus (STN) are common targets for DBS therapy and have been utilized to address dopamine responsive symptoms in PD (e.g., tremor, rigidity, bradykinesia), as well as medication-related motor fluctuations and dyskinesia. However, both targets have failed to adequately address gait-related issues (Heremans et al., 2013; Morita et al., 2014). One approach to address this important gap in treatment has been to augment GPi or STN DBS with PPN region DBS (Stefani et al., 2007; Moreau et al., 2009).

The current study aimed to record simultaneously from the human PPN region and the GPi to elucidate the electrophysiological correlates of human gait. The study was part of a Michael J. Fox Foundation challenge grant to improve neuromodulation approaches in patients with gait and freezing issues not responsive to dopamine replacement therapies. Also, patients included in the study were not required to possess a 30% improvement with dopaminergic medication. The data presented here is collected from electrodes implanted bilaterally in the PPN region and bilaterally in the posteroventral GPi from five ambulatory human participants with PD. Local field potentials (LFPs) were collected chronically during the no active stimulation condition through bidirectional DBS implants.

MATERIALS AND METHODS

Subjects

University of Florida Institutional Review Board and FDA IDE (G140181) approvals were granted for the recruitment of five human PD subjects (two females; age range: 50–74 years). A confirmed medical history of on and off dopaminergic medication FoG was required, despite exhaustive dosage optimization by a movement-disorder trained neurologist. Additionally, participation required more than two FoG episodes per month, a score of more than 1 on item #3 on the Freezing of Gait Questionnaire (FOG-Q; Giladi et al., 2000), and also a minimum of five FoG episodes under a provocation gait protocol. Study candidates were screened and evaluated at the Norman Fixel Institute for Neurological Diseases at the University of Florida by an interdisciplinary clinical-research DBS team. The public listing with the full inclusion and exclusion criteria can be found on ClinicalTrials.gov (NCT02548897). Seven potential candidates were screened, from which five subjects (aged 50–75, two females) were recruited and provided written informed consent before any study interventions (**Table 1**). Subject 3 deteriorated very quickly after surgery and could only complete tasks by utilizing a walker.

Device and Implantation Surgery

The implantation procedure was divided into three stages. Two leads were unilaterally implanted in the first stage, and in the second stage of the operation 2 to 4 weeks later the other two leads were implanted contralaterally. In one subject the two PPN leads were placed in one stage and the two GPi leads in a second stage which was performed 2 to 4 weeks later. The final stage of the operation occurred approximately 4 weeks after stages one and two and in this stage, the four DBS leads were connected to the implantable neurostimulators (INS) and secured in a sub-clavicular pocket. Each of the three stages was separated by a month to resolve brain edema, minimize brain shift, and to avoid prolonged time in the operating room. Each subject received two quadripolar Medtronic model 3,387 leads targeting the GPi, bilaterally, and two model-3,389 leads targeting the PPN, also bilaterally. Both GPi leads were connected to a Medtronic Activa PC+S (Medtronic PLC, Minneapolis, MN, USA) in a sub-clavicular pocket on the left side, and both PPN leads were connected to another Activa PC+S in a different sub-clavicular pocket on the right. Pairing the leads by nuclei instead of laterality was performed to facilitate the preferred differences in therapeutic frequencies for each brain target. Traditionally, the PPN has been stimulated at lower frequencies than the GPi and a single IPG cannot drive two leads with differing frequencies. Nuclei targeting was achieved through high-resolution MRI imaging performed before surgery. A stereotactic head CT was coregistered to T1 and FGATIR MRI images. Additionally, these images were fused to a patient-specific, 3-D deformable brain atlas (Sudhyadhom et al., 2012). During the implantation surgery, the subjects remained awake for microelectrode recordings performed using an FHC 4000 LP+ system (FHC, Bowdoin, ME, USA). A movement-disorder neurologist evaluated changes in neural firing derived from the microelectrode recordings to refine the physiological mapping of the nuclei borders of each target. Since the PPN region has not been shown to exhibit clear demarcations on MRI images and has not been demonstrated to have widely accepted and reproducible physiological markers during MER mapping, the PPN region targeting relied more on interpolation from surrounding structures and measurements than from 4th ventricular landmarks (Hamani et al., 2007; Zrinzo et al., 2008; Shimamoto et al., 2010; Morita et al., 2014). Post-operative CT

TABLE 1 | Subject demographics.

Subject ID	Years Since PD Diagnosis	L-DOPA OFF Freezer	L-DOPA ON Freezer	Mean UPDRS III (Screening/ 6 Month)		Mean UPDRS IV (Screening/ 6 Month)	
1	9	Yes	Yes	26	22	5	7
2	10	Yes	Yes	23	17	5	3
3	23	Yes	Yes	30	40	5	6
4	9	Yes	Yes	24	21	14	5
5	5	Yes	Yes	35	33	5	6

Legend: L—dopa-levodopa, UPDRS—Unified Parkinson's Disease Rating Scale, UPDRS III—motor and IV-fluctuations in therapy.

images co-registered with pre-operative MRI was used to confirm the post-operative position of the leads.

Postoperative Data

Monthly electrophysiological data collections commenced approximately 30 days after the last phase of the surgical procedures and were performed acutely in a gait laboratory equipped with a 10-camera motion capture system (Vicon Motion Systems, Oxford, UK) and three embedded force plates (Bertec, Newton, MA, USA). The Activa PC+S recorded from two electrodes in a symmetric bipolar configuration for common-mode rejection. The bipolar contacts were separated by a middle contact, which could be used for stimulation in a monopolar configuration (Afshar et al., 2012; Stanslaski et al., 2012; Bourget et al., 2015). Although the data presented here were collected in the absence of stimulation, we aimed to identify gait features that could guide in responsive stimulation. Neural data were sampled at 421.9 Hz. Concurrent EMG and inertial (accelerometer, gyroscope, and magnetometer) data were recorded with wireless sensors (Delsys, Inc., Natick, MA, USA) sampled at 1,925.93 Hz and 148.25 Hz, respectively. To synchronize the neural signals with the external sensor data, the PC+S delivered a low-frequency marker burst (∼5 Hz in the GPi and ∼8 Hz in the PPN). A nearby EMG sensor (on the neck or forehead) was able to detect the onset and termination of the low-frequency marker bursts. The data were also supplemented with 24 frames/s of video recordings. Short synchronization pulses were ported to the EMG amplifier that simultaneously flashed a LED captured by the video camera. Each modality was linked through marker bursts or EMG/LED pulses and the data were conjoined manually in MATLAB. The protocol was comprised of a battery of tasks, performed both on and off dopaminergic medication, to study gait and to elicit FoG, including stepping in place, changing cadence, narrow passages, dual-attention tasks, turning, and navigating obstacles (Snijders et al., 2008, 2010, 2012; Spildooren et al., 2010; Stegemõller et al., 2012). Subjects restricted dopaminergic medication for at least 12 h before the off medication data collections. Recurrent data collections over 5 months post-implant were conducted during the patients' monthly check-up/programming visits.

Signal Processing and Statistics

Signal processing was performed within MATLAB 2018a (MathWorks, Natick, MA, USA) with custom scripts. Power spectral densities (PSD) were calculated using a 40-order autoregressive model (Schalk et al., 2004; Stoica and Moses, 2004). The data was windowed at 250 ms and with a 50% overlap. Each spectral bin within a condition was tested for significance *via* the Mann–Whitney test with Bonferroni correction. Mean power distributions between two conditions were tested for significance with the Kruskal–Wallis test with Dunn's corrected test for multiple comparisons. Multiple linear regressions were done to compare the PPN feature band against gait measures for all subjects. Individual regressions were done for conditions and variables that reached significance at the group level. *F*-tests were used to test the regressions for significance. Spectral bins that were significant were labeled as "feature detection." We picked the channels with the strongest feature during the "feature extraction" step. This approach is commonly used by our laboratory and other laboratories performing similar experiments. In choosing contacts for analysis, we chose a method to avoid picking a single combination *a priori*, not knowing where the difference in modulation would be found. Since multiple contact combinations and hemispheres showed a difference, for subsequent analysis, the combination that showed the largest difference was used.

Clinical Scores and Assessment

Each monthly visit included biomechanical gait measures (e.g., gait speed, cadence, stride length) collected *via* the Vicon motion capture system and processed by the Applied Neuromechanics Laboratory at the University of Florida. The subjects were administered the FoG-Q, the Gait and Falls Questionnaire (GFQ; Giladi et al., 2000), the Activities/Balance Confidence Scale (ABC; Powell and Myers, 1995), the PD Quality of Life Questionnaire (PDQ; Peto et al., 1998), and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987). Assistive-walking-device information was also collected. These measures were assessed during screening and at baseline (before DBS implantation). Clinical scores and assessments were primarily used to evaluate the effectiveness of responsive PPN DBS and to track disease progression and the clinical outcomes (Molina et al., 2018). An independent movement disorders neurologist reviewed the videos recorded during data collections. The neurologist labeled freezing episodes, the type of freezing (such as during walking, start hesitation, or turning hesitation), the severity of the freeze, and the confidence in the label of a freezing event.

RESULTS

Due to the variation in PPN localization, two methods were used to assess the location of the recorded electrophysiology. **Figure 1A** shows T1 inverted (left panels) and T2 (right panels)

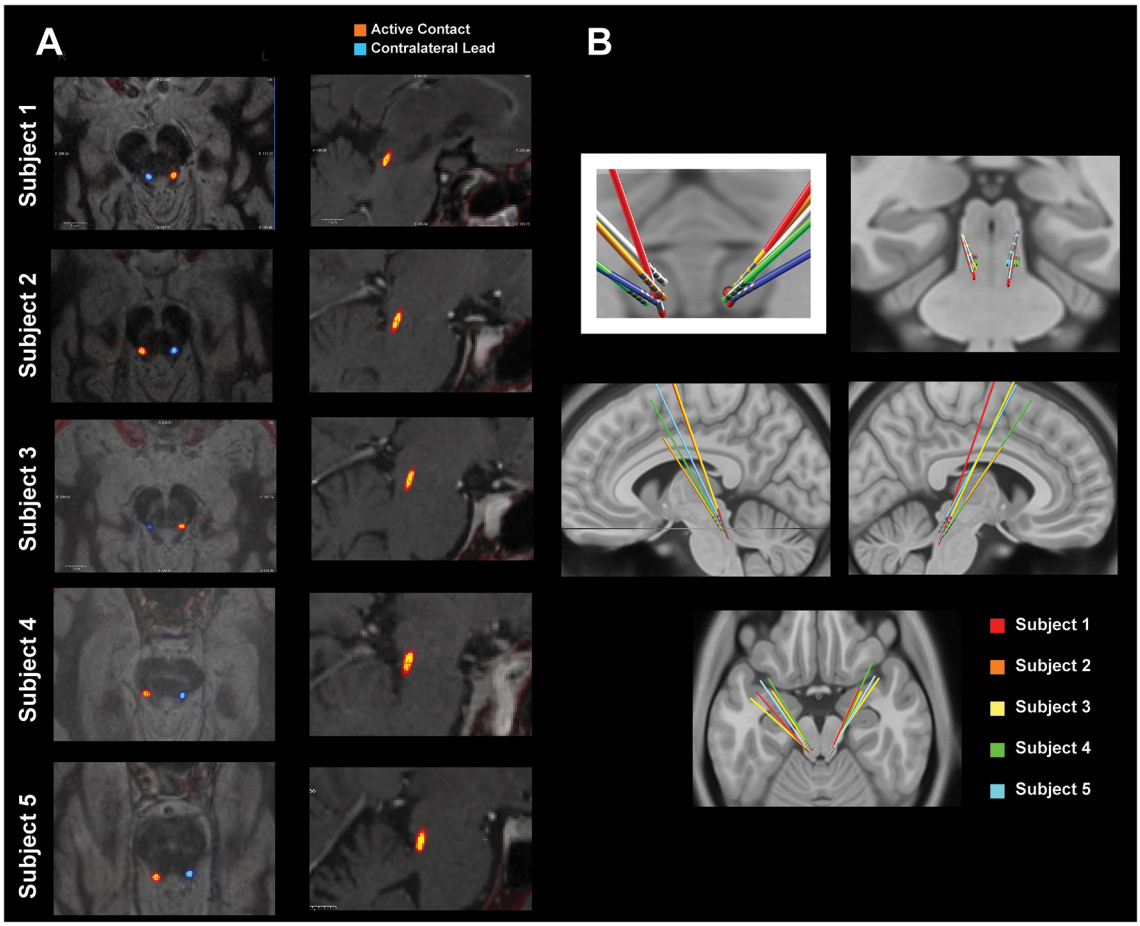

FIGURE 1 | Pedunculopontine nucleus (PPN) lead localization methods. **(A)** MRI-CT co-registered images of each subject. The "active contact" marks the center of the bipolar electrode configuration that yielded the feature most correlated with gait. The left panels show T1 inverted axial views of the active contact (orange) and the contralateral lead (blue). The right panels show T2 sagittal views of the active contact. **(B)** Leads normalized to MNI space using Lead-deep brain stimulation (DBS). All leads are shown with a red dot that roughly defines the location of the PPN.

MRI images of the active contact (middle) from the symmetric bipolar recordings shown in **Figures 2**,**3**. The rostral face of the PPN region resides in an area laterally and ventrally bound by the spinothalamic tract, the lateral lemniscus, and medial lemniscus, as well as dorsal-medially by the spinal cerebellar peduncle (SCP) decussation (Hamani et al., 2016). Visual inspection of imaging, shows that subjects 1–4 were generally within this area, while subject 5's leads were dorsal to the region. Additionally, anatomically the rostral part of the PPN region is in the plane of the mid-inferior colliculus. T2 images confirmed the active DBS contact to be at or below this plane for all five subjects. **Figure 1A** reveals the active contacts in the PPN region. **Figure 1B** shows a second confirmatory method that was used to determine DBS lead placement, using Lead-DBS to normalize the individual images to the MNI brain space. Collectively by both methods, the leads are shown to be in an estimated PPN region (Snijders et al., 2016). The leads show a consistent cluster. The additional analysis did not reveal a relationship between the spatial location of the active contact and the corresponding clinical score. The locations marked as "active contact" in **Figure 1A** depict the contact from which stimulation was provided for therapy. These contacts were chosen for therapy as the bipolar recordings from their two adjacent electrodes yielded the highest PPN neural correlate for gait in the absence of stimulation.

Figure 2A shows the PSD of GPi signals in one of the subjects tested under two different medication conditions while performing different tasks. Each task was performed for 3 min and aggregated across five consecutive months. In all the conditions, a peak in the low beta range (8–22 Hz) in at least one bipolar combination and one hemisphere is prominent. This beta peak modulates in response to the task and the medication state, and specifically, the peak decreases with medication intake (red vs. blue lines in **Figure 2A**). **Figure 2B** shows the mean power in the low beta frequency range for each subject. A decrease in low beta was observed in response to dopaminergic medication intake across four of the five subjects, with Subject 3 lacking a decrease in low beta. Baseline pre-operative clinical improvement response to medication was measured as a percent reduction in UPDRS

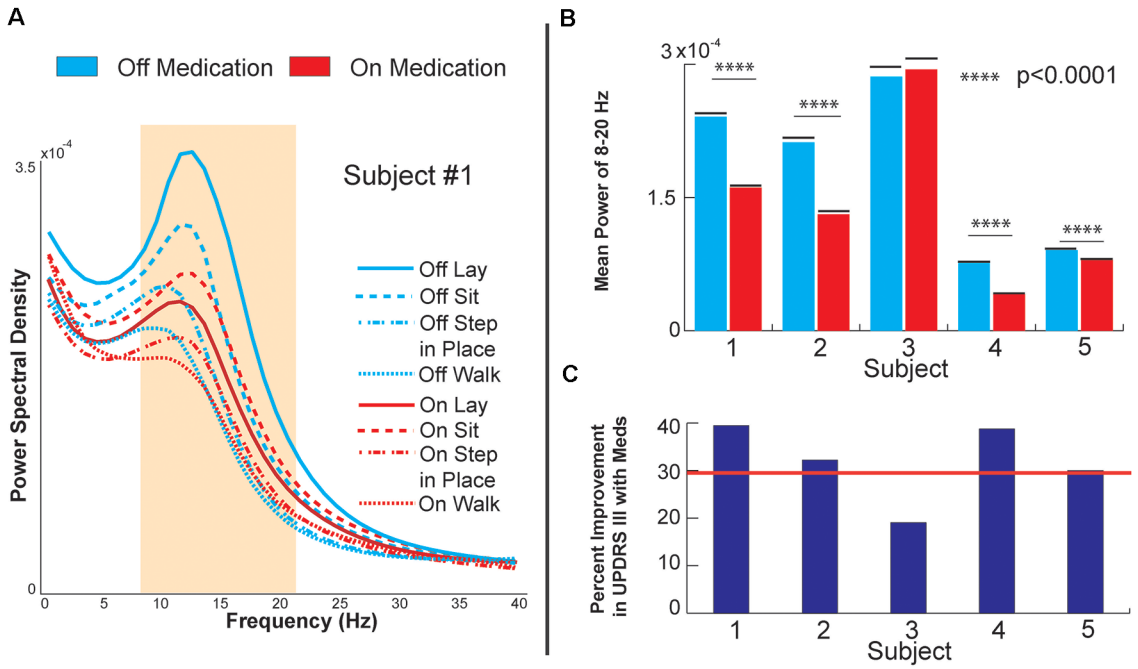

FIGURE 2 | Globus pallidus internus (GPi) response to medication. **(A)** Power spectral density of GPi signals from Subject 1, OFF, and ON levodopa medication during various baseline and gait tasks. **(B)** Bar plots of raw decrease in GPi beta power during sitting (8–20 Hz). **(C)** Bar plots of each subject's percent improvement in UPDRS III score from OFF medication to ON medication during sitting. The red line marks a 30% improvement, a commonly employed clinical benchmark for medication responsiveness.

III PD motor score off and then on medication in this study cohort. **Figure 2C** shows the percent improvement in UPDRS III scores in response to the medication at the pre-operative baseline. Except for Subject 3, the cohort met the usual clinical benchmark of a 30% improvement off to on dopaminergic medications. Subject 3 did not exhibit either medication-induced beta suppression in GPi or minimal improvement (<30%) in clinical scores with medication. **Figure 3** summarizes the spectral modulation in the GPi and the PPN during different walking tasks during the on medication condition. A full dataset of walking tasks during off medication per the protocol was not available and is therefore not shown. Each task was performed for 3 min and aggregated across five consecutive months. The power spectral density of a single subject is shown in **Figure 3A**. There was an increased PPN activity in the sub-8 Hz spectral range with axial and gait trials compared to sitting and standing. The data reveal differences in walking and rest for all subjects and differences between most other tasks. As subjects progressed through sitting, standing, stepping-in-place, and walking, the PPN 1–8 Hz feature modulated in response to the task, reaching maximum power during walking in four out of five patients. The significance bars denote tasks that were differentiable from gait across all recordings within 6 months with $p < 0.01$. The walking task was the most distinguishable from the other tasks in all subjects except for Subject 3, who had to perform the stepping-in-place and walking tasks using a walker due to rapid disease progression. The stimulation contact was chosen the be in the center of the two electrodes that yielded the most significant PPN 1–8 Hz feature. This feature was observed to be closer to the rostral part of the PPN region which was located near the level of the mid-inferior colliculus (see **Figure 1A**). **Figure 3B** (PPN) and **Figure 3C** (GPi) are boxplots of the features of interest. **Figure 3B** shows a decrease in the 1–8 Hz band with freezing of gait, albeit there were few episodes captured in the laboratory (3–12 episodes). **Figure 3C** summarizes the data from GPi and it reveals a decrease in beta power from rest to gait initiation. **Figure 3D** shows the temporal evolution of neural signatures with gait initiation and the spectrogram from the same subject as **Figure 3A** averaged across gait initiation trials in one session. This subject exhibited a beta peak while at rest, and this beta peak decreased with gait initiation, while the PPN modulated in response to walking in the 1–8 Hz spectral band. The outlined bands show the dissipation of the beta rhythm in the GPi while the PPN feature bands modulated at the onset of gait.

The 1–8 Hz feature band was tested against measured cadence, walking speed, and stride length in multiple linear regression, where power in the feature band was the dependent variable and cadence, walking speed, and stride length were the predictors. Four different multiple regressions were done, during off and on medications, and testing both the lead that yielded the most reliable modulation between conditions in **Figure 3** and the contralateral lead. The regressions using power from the reported lead reached significance (p-value 0.00027 and 0.016, off and on medication, respectively), while

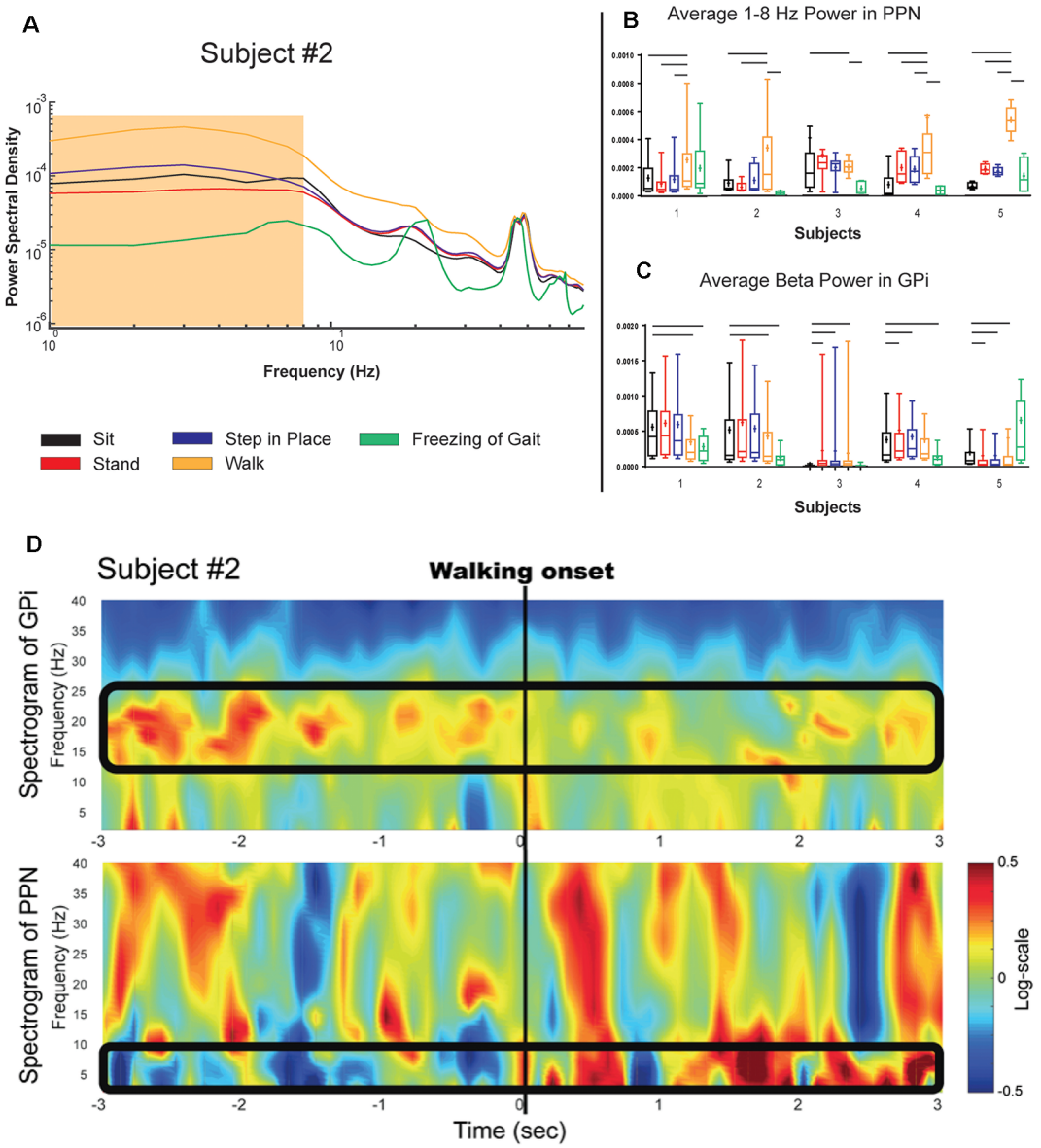

FIGURE 3 | PPN and GPi response to gait tasks in the on medication condition. **(A)** Logarithmic power spectral density of PPN signal power in a single subject during various balance and gait-related tasks. **(B,C)** Single-subject (log normalized to standing) demonstrating PPN low frequency and GPi beta modulation with gait onset shown as boxplots. Significance bars indicate that tasks that statistically could be differentiated from gait every month ($p < 0.001$). Panel **(D)** Shows the temporal evolution of neural signatures with gait initiation and the spectrogram from the same subject as **(A)** averaged across gait initiation trials in one session. This subject exhibited a beta peak while at rest, and this beta peak decreased with gait initiation, while the PPN modulated in response to walking in the 1–8 Hz spectral band. The outlined bands show the dissipation of the beta rhythm in the GPi while the PPN feature bands modulated at the onset of gait.

the regressions for the contralateral lead did not (0.066 and 0.15, off and on medication, respectively). The only feature to produce significance in the regressions in the available subjects was the PPN 1–8 Hz feature against walking speed (0.0076 and 0.0019, off and on medication, respectively). The individual regressions are shown in **Figure 4**. Complete gait metrics were available for three subjects (subjects 1, 2, and 5). Recording conditions or missing alignment artifacts precluded the inclusion of data from the other two subjects. Additionally, the location of the correlated feature was not the same bipolar contact for Subject 2 as shown in **Figure 1**, but it was observed on the same (ipsilateral) lead. Finally, changes in medication state were observed. The OFF-medication state resulted in higher r^2 values (0.591, 0.42, and 0.497, respectively) than the ON-mediation state (0.052, 0.058, and 0.26, respectively). The slopes were significant for all of the OFF-medication regressions, and only for the ON-medication data for subject 2.

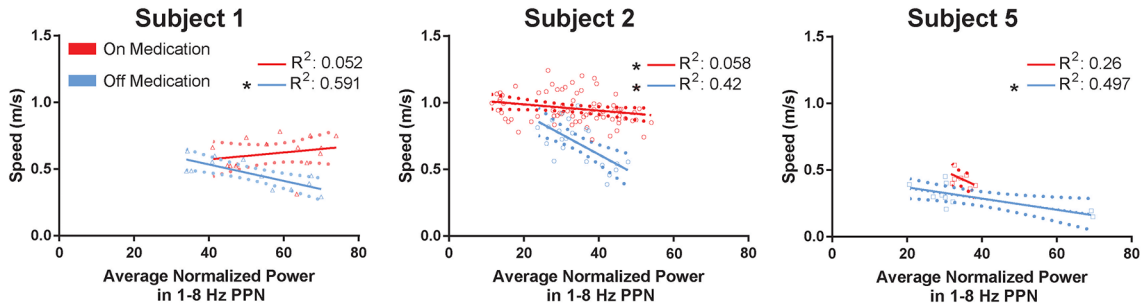

FIGURE 4 | PPN low-frequency feature compared against gait metrics. The mean walking speed of subjects 1, 2, and 5 are plotted against their averaged normalized power in the 1–8 Hz PPN feature band. Each regression is performed by subject and within the same medication condition, for a total of six regressions. Each point represents a trial. Error bars are shown as dotted parabolas following the trend line. *$p < 0.1$.

DISCUSSION

Herein we report human electrophysiological recordings from the GPi and the PPN regions during various gait tasks in five subjects. Our findings showed suppression of low beta power in the GPi in response to medication, and a 1–8 Hz modulation in four subjects in the PPN region correlating with human gait in the on medication state. Significant decreases in the GPi beta band with medication corresponded to marked improvements in clinical scores, which increased our confidence in the signal quality captured with the bidirectional neurostimulators. GPi beta also decreased during gait tasks. Meanwhile, the 1–8 Hz power in the PPN region increased with walking and seemed to correlate with walking speed, which was not the case for GPi beta activity. GPi beta desynchronization and PPN activation in 1–8 Hz was shown as subjects progressed from rest to ambulatory tasks. Finally, postoperative imaging and normalization tools suggested that the PPN region was reasonably targeted and the DBS leads were well clustered, although the precise targets for DBS in this region remain unknown. Additionally, the small size of the cohort and the clustering of the active contact in the region may have prevented a clear delineation in the contact location by the subjects' clinical response to the therapy (Goetz et al., 2019). The results from this study complement the current literature regarding low-frequency oscillations in the caudal region of the PPN and the relationship to human gait (Thevathasan et al., 2012).

The data further revealed a reproducible mean power change in the 1–8 Hz power band in response to gait initiation. Recent studies have reported a similar feature of low-frequency bands of interest in the PPN (Androulidakis et al., 2008; Thevathasan et al., 2012). However the data presented herein, collected over several months, did not reveal a distinct peak but rather changes in broad activity in the 1–8 Hz band. Variations in lead localization, the recording devices, and the experimental setup are a few of the many possible reasons for the difference between the feature reported herein and in other studies. Our group acknowledges that there is commonly uncertainty in the exact source of each LFP in human studies such as ours. This feature was observed to be closer to the rostral part of the PPN region which was located near the level of the mid-inferior colliculus. This 1–8 Hz power band will likely be important for guiding future studies and therapeutics.

An important observation from this study was the change in the correlation between walking speed and PPN activity in response to dopaminergic medication. Rodent and primate studies have suggested changes in neural activity in the on and off dopaminergic parkinsonian state (Mitchell et al., 1989; Futami et al., 1995; Breit et al., 2001, 2005; Matsumura and Kojima, 2002). It is reasonable that in the PD cases there is an important effect of medications and gait changes on efferent nuclei within the basal ganglia and brainstem. The current circuitry model broadly and nonspecifically suggests that gait is regulated by a large corticolimbic-ventral striatal-ventral pallidal-PPN-pontomedullary reticular nuclei-spinal cord network (Nutt et al., 2011). This network likely includes tonic inhibition of the mesencephalic locomotor region (MLR) through the GPi and the STN (Pahapill and Lozano, 2000; Hamani et al., 2007; Grillner et al., 2008; Alam et al., 2011). **Figure 4** shows an example of GPi beta that is present during rest and dissipates at gait onset. Our data suggest the possibility that efferent brainstem nuclei are modulated with beta desynchronization in the GPi. It was interesting that the 1–8 Hz activity appeared during walking. The curious observation was the decrease in 1–8 Hz activity as the walking speed increased which conflicts with some of the published literature. Since this was only a five patient study and the study was of "on freezers" we would need to interpret this finding cautiously and we could not reliably conclude that 1–8 Hz power reflects an impairment of fast walking. The data also suggest that the PPN region has a role not limited to gait but is likely involved in tasks requiring balance and lower limb activation (i.e., standing and stepping-in-place).

Finally, we report GPi beta suppression with dopaminergic medication and a correlation to improvement in pre-operative clinical on-off medication scores. Data from Subject 3 was insightful and demonstrated that GPi beta suppression was not a direct consequence of levodopa intake but was more likely an indicator of symptomatic improvement as reflected in UPDRS scores. Beta power in multiple basal ganglia regions has been previously shown to correlate with symptom severity and its suppression, either through dopaminergic therapy or

DBS and has been correlated with improvements in UPDRS scores (specifically bradykinesia, and rigidity; Brown et al., 2001; Levy et al., 2002; Kühn et al., 2006, 2009; Ray et al., 2008; Jenkinson and Brown, 2011). Excessive inhibitory (GABA-ergic) activity from the basal ganglia may dampen the activity of efferent nuclei such as in the brainstem PPN region. Furthermore, one may posit that a successful therapy may reestablish a healthier basal ganglia modulation, which in turn reduces rigidity and bradykinesia. A possible hypothesis for the lack of beta suppression in Subject 3 may be that under severe degeneration and lack of clinical response to dopamine, basal ganglia function cannot be restored, and beta power remains unchanged. This point will need further clarification as therapeutic strategies that target beta may be affected by disease progression.

Understanding the neural correlates of gait is crucial in defining future therapeutic strategies. The response to the beta band could dictate optimal dosage, administration times, or serve as a measure of disease progression. The roles GPi and the PPNregion each play in gait could also be harnessed to develop better therapies for walking disturbances.

We would also like to address potential artifacts in the dataset. The manufacturer, Medtronic, and their team of engineers recognize movements as a possible source of artifacts however these artifacts would produce large amplitude, broad bandwidth, narrow duration (concentrated) impulse responses in the spectrograms. Although **Figure 3** does have broadband activity, this does not fit the narrow duration of movement artifact. Each subject had two devices, one for GPi leads and one for PPN region leads. If the PC+S was susceptible to movement artifacts presenting in the low-frequency band, then it would likely have shown up in at least one of the GPi recordings. None of the GPi recordings revealed a significant difference in the 1–8 Hz as was observed in the PPN data.

There were several important limitations of this study. This population suffered from debilitating gait and postural instability, from levodopa refractory FoG, from lower limb orthopedic issues, and other diseases, unrelated to PD or DBS. Obtaining high-quality recordings in different conditions was challenging in this population. Performing a large number of unassisted continuous walking trials was non-trivial. Subjects performed walking in short trials of ∼8 m, followed by a spotter walking alongside the subject, and occasionally walking with an assistive device. Although recording conditions were not ideal, this study was able to collect neural data for the first time from ambulatory humans with a real-time recording from GPi and PPN regions. Furthermore, the few FoG episodes captured in only a few conditions and the required electrode configurations for recording also may have impacted the analysis. Second, we acknowledge the small sample size, although we would also argue that a small cohort facilitated greater depth of interaction with the subjects and also generated robust physiology datasets for analysis and interpretation. Moreover, this project was an early feasibility study of an invasive high-risk multi-lead procedure. We acknowledge that atypical parkinsonism could not be completely ruled out in these patients. However, without pathology or additional evidence of another disease, the clinical diagnosis for the cohort was idiopathic PD with "on" medication freezing. Finally, the localization of the human PPN region continues to be a formidable challenge. We presented individual data on localization using two methods and we purposely refer to this as a "region" rather than as a clearly demarcated target. However, the challenges presented in this study are not atypical and have been observed in the limited number of PPN DBS studies in the literature (Thevathasan et al., 2018).

To summarize, this study revealed the neural correlates of gait in human GPi and the PPN region in a population of patients with "on" dopaminergic gait and freezing issues. Real-time human electrophysiology revealed suppression of low beta power in the GPi in response to medication and gait tasks and a 1–8 Hz modulation in the PPN region that was correlated to ambulation.

DATA AVAILABILITY STATEMENT

The datasets from this study may be available upon request from the corresponding author with appropriate regulatory agreements.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by US Food and Drug Administration (FDA) IDE G140181 and University of Florida (UF) IRB-01 201400951. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM collected data, analyzed data, and wrote the first draft of manuscript. CJH designed research, collected data, and edited manuscript. KS collected data, analyzed data, and edited the manuscript. AS, EO, and JR collected data and edited the manuscript. DM-R analyzed data and the manuscript. CWH edited the manuscript. KF performed surgeries. MO designed research and edited the manuscript. AG designed research, supervised research, and edited the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Secondary Worsening Following DYT1 Dystonia Deep Brain Stimulation: A Multi-country Cohort

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Objective: To reveal clinical characteristics of suboptimal responses to deep brain stimulation (DBS) in a multi-country DYT1 dystonia cohort.

Methods: In this multi-country multi-center retrospective study, we analyzed the clinical data of DYT1 patients who experienced suboptimal responses to DBS defined as <30% improvement in dystonia scales at the last follow-up compared with baseline. We used a literature-driven historical cohort of 112 DYT1 patients for comparison.

Results: Approximately 8% of our study cohort (11 out of 132) experienced suboptimal responses to DBS. Compared with the historical cohort, the multi-country cohort with suboptimal responses had a significantly younger age at onset (mean, 7.0 vs. 8.4 years; $p = 0.025$) and younger age at DBS (mean, 12.0 vs. 18.6 years; $p = 0.019$). Additionally, cranial involvement was more common in the multi-country cohort (before DBS, 64% vs. 45%, $p = 0.074$; before or after DBS, 91% vs. 47%, $p = 0.001$). Mean motor improvement at the last follow-up from baseline were 0% and 66% for the multi-country and historical cohorts, respectively. All 11 patients of the multi-country cohort had generalization of dystonia within 2.5 years after disease onset. All patients experienced dystonia improvement of >30% postoperatively; however, secondary worsening of dystonia commenced between 6 months and 3 years following DBS. The improvement at the last follow-up was less than 30% despite optimally-placed leads, a trial of multiple programming settings, and additional DBS surgeries in all patients. The on-/off-stimulation comparison at the long-term follow-up demonstrated beneficial effects of DBS despite missing the threshold of 30% improvement over baseline.

Conclusion: Approximately 8% of patients represent a more aggressive phenotype of DYT1 dystonia characterized by younger age at onset, faster disease progression, and cranial involvement, which seems to be associated with long-term suboptimal responses to DBS (e.g., secondary worsening). This information could be useful for both clinicians and patients in clinical decision making and patient counseling before and following DBS implantations. Patients with this phenotype may have different neuroplasticity, neurogenetics, or possibly distinct neurophysiology.

Keywords: DYT1, dystonia, deep brain stimulation, globus pallidus internus, pallidum

INTRODUCTION

DYT1 (DYT-*TOR1A*) is the most common cause of inherited isolated dystonia, and almost all patients possess the same mutation in the *TOR1A* gene (c.907_909delGAG; Charlesworth et al., 2013). Dystonia symptoms of DYT1 patients most often begin in an arm or leg during childhood or adolescence (Lee et al., 2012). Dystonia spreads to other body regions and becomes generalized over months to years in up to half of patients (Fasano et al., 2006; Lee et al., 2012). Cranial involvement is however uncommon.

Globus pallidus internus deep brain stimulation (GPi DBS) improves motor function and quality of life in dystonia patients and is considered a therapeutic option for patients with medically-refractory dystonia (Vidailhet et al., 2005; Volkmann et al., 2012; Tsuboi et al., 2019). In 2000, excellent DBS outcomes in patients with DYT1 were first reported by Coubes et al. (2000). Subsequently, retrospective studies and a meta-analysis suggested that *TOR1A* mutation-positive status was a clinical predictive factor for a better DBS outcome (Vasques et al., 2009; Andrews et al., 2010; Borggraefe et al., 2010; FitzGerald et al., 2014; Moro et al., 2017; Artusi et al., 2020). Additionally, in the largest cohort to date of patients with DYT1 dystonia who underwent GPi DBS (n = 47), improvement in dystonia severity by >80% was maintained up to 7 years after surgery (Panov et al., 2013). In contrast, there have been a minority of individual DYT1 cases with suboptimal responses to GPi DBS (Krause et al., 2004, 2016; Starr et al., 2006; Mehrkens et al., 2009; Cif et al., 2010; Markun et al., 2012; Miyagi and Koike, 2013; Ben-Haim et al., 2016; Pauls et al., 2017; Tsuboi et al., 2019). These less-than-expected responses in some cases could be attributable to suboptimal lead positions, non-optimized programming, or skeletal deformities. However, there are cases with suboptimal outcomes that remain unexplained, and there seem to be emerging cases of secondary worsening (Cif et al., 2010; Miyagi and Koike, 2013; Tsuboi et al., 2019). Because only a few cases of DYT1 dystonia are operated each year even in expert centers, the number of reported patients with suboptimal responses is limited. Consequently, the clinical characteristics of this cohort remain undefined.

We performed a multi-country multi-center retrospective study to investigate the characteristics of patients with DYT1 dystonia who experienced suboptimal responses to DBS. Additionally, we compared this unique cohort of patients to a historical cohort of DYT1 DBS patients to better define the potential characteristics which may differentiate responses.

MATERIALS AND METHODS

Study Design

This retrospective study was approved by the University of Florida Institutional Review Board (IRB201900356), and each participating center had local IRB approval for the inclusion of their data in this study. We collected patient information that met the following inclusion criteria: (1) isolated dystonia; (2) a c.907_909delGAG mutation in the *TOR1A* gene; (3) bilateral GPi DBS performed at one of the participating expert centers; (4) no history of prior stereotactic brain surgery other than DBS; (5) preoperative clinical assessments with postoperative assessments at 1 year or longer; and (6) suboptimal responses to DBS (defined as <30% improvement in the Burke-Fahn-Marsden Dystonia Rating Scale motor score (BFMDRS-M) or the Unified Dystonia Rating Scale (UDRS) at the last follow-up compared with the baseline status (Burke et al., 1985; Comella et al., 2003). This 30% threshold was chosen arbitrarily as a clinically relevant response (Pauls et al., 2017). Earlier studies reported an excellent correlation between the BFMDRS-M and UDRS (0.977) and that percentage improvement after DBS in dystonia patients was similar between these scales (Comella et al., 2003; Susatia et al., 2010). Therefore, we considered percentage improvement based on these scales equivalent. The DBS programming data, the DBS lead positions, and the changes in motor scores, as well as detailed descriptive clinical information, were collected and analyzed.

The Historical Cohort

To create a historical cohort of DYT1 patients treated with GPi DBS, a literature search was conducted using PubMed/Medline, Embase, and Cochrane databases in May 2019 with the following search terms: deep brain stimulation, neurostimulation, DBS, DYT1, and TOR1A. The search syntax is available in **Supplementary Material**. The reference lists for each of the identified articles were used to explore additional relevant publications. We considered both pure DYT1 cohorts and mixed cohorts including DYT1 patients for inclusion. The inclusion criteria were as follows: (1) DYT1 dystonia; (2) bilateral GPi DBS; (3) no history of prior stereotactic brain surgery other than DBS; and (4) preoperative clinical assessments with postoperative assessments at 1 year or longer. The minimum

required information for individual patients was the age at onset, the age at DBS surgery, disease duration before DBS, and preoperative and postoperative motor scores according to either the BFMDRS-M or the UDRS. For articles in which only two of the following were provided (i.e., age at onset, age at DBS, and disease duration before DBS), the missing value was calculated using the other values. For articles presenting motor scores only in line graphs, we extracted the data from the figures using a graph digitizer software (Plot digitizer)[1]. We identified and excluded all possible duplicated patients by examining demographics, motor scores, and the authors' affiliations.

Statistical Analysis

Normal distribution of data was tested using the Shapiro–Wilk test. We compared the demographics and outcome measurements between the groups using independent *t*-tests, Mann–Whitney *U* tests, chi-square tests, or Fisher's exact tests, as appropriate. Statistical significance was set at $p \leq 0.05$. All analyses were performed using IBM SPSS statistics 25 (IBM Corp., Armonk, NY, USA).

RESULTS

The Multi-country Cohort

From a total of 132 DYT1 patients who underwent DBS in our institutions, we collected the detailed clinical information of 18 DYT1 patients with reported suboptimal DBS responses. However, a thorough review of the case files led to an additional seven exclusions. Patients 12 and 13 had suboptimal responses to DBS as a result of suboptimal lead positions, and patient 14 had a secondary worsening of dystonia because of lead migration. These three patients revealed marked improvement following the surgical repositioning of the DBS leads. Patients 15, 16, and 17 had excellent responses to DBS (>80%) followed by worsening of dystonia; however, these patients had persistent improvement ≥30% at the last follow-up. Despite a marked improvement in the BFMDRS-M, functional improvement in patients 15 and 18 was compromised by skeletal deformities and action-induced muscle spasms, respectively. The clinical information of patients 12–18 is presented in **Supplementary Table S1**.

Compared to the preoperative baseline status, the remaining 11 patients (**Table 1**) had improvement that was less than 30% (range −81.8% to 29.7%) at the last clinical follow-up with a mean follow-up duration after implantation of 12.6 years (range 1.0–18.3 years). Nine patients had a family history of dystonia. The region of onset was the upper extremity in four patients and the lower extremity in seven with a mean age at onset of 6.9 years (range 5–10 years). In all patients, the dystonia became generalized within 2.5 years (mean 1.9 years, range 0.8–2.5 years), and the patients underwent DBS at a mean age of 12.5 years (range 8–23 years) with a mean disease duration before DBS of 5.6 years (range 2–17 years). All of the patients were initially treated with bilateral GPi DBS. Individual changes in the BFMDRS-M/UDRS are summarized in **Figure 1A**. Importantly, all patients showed motor improvement

[1]http://plotdigitizer.sourceforge.net/

TABLE 1 | Patient characteristics of the multi-country cohort.

Patients	Sex	Family history	Age at onset (years)	Region of onset	Body distribution before DBS							Disease duration before dystonia generalization (years)	Disease duration before DBS (years)	Age at DBS (years)	follow-up after DBS (years)	BFMDRS or UDRS			New regions after DBS	Additional DBS surgeries
					UF	LF	Lx	N	UE	LE	T					Baseline	Best	Last FU		
Pt 1	M	+	5	LE	-	+	-	+	+	+	+	2 years	6	11	9	55	32	57	UF	L STN
Pt 2	M	-	6	UE	-	-	+	-	+	+	+	2 years	2	8	12	33	9	60	UF, LF	R GPi, R STN
Pt 3	F	+	6	LE	-	-	+	-	+	+	+	2.5 years	3	9	12	101.5	48	95	LF	Bil GPi
Pt 4	M	+	8	UE	-	+	+	+	+	+	+	2 years	9	17	8	35.5	25	29.5	UF	Bil GPi
Pt 5	M	+	6	LE	+	+	-	+	+	+	+	2 years	17	23	17.5	112	46.5	86		Bil GPi
Pt 6	F	+	7	LE	-	+	+	+	+	+	+	1.5 years	8	15	6	46	28	35	UE	Bil GPi
Pt 7	M	+	10	UE	-	-	-	+	+	+	+	2.5 years	3	13	12.5	64	44	45	UF, LF, Lx	Bil GPi
Pt 8	F	+	9	LE	-	-	-	+	+	+	+	2 years	2	11	15	42	4.5	60	Lx	Replacement of Bil GPi
Pt 9	M	+	7	LE	-	-	-	+	+	+	+	9 months	2	9	1	78	15	88		Bil STN
Pt 10	F	-	6	UE	-	-	-	-	+	+	-	2 years	5	11	13	32	2	24	LF, Lx, N, T	Bil STN
Pt 11	M	+	6	LE	-	-	+	+	+	+	+	2 years	5	11	10	74	11	59	UF, LF	Bil STN

Regions: UF, Upper face; LF, Lower face; Lx, Larynx; N, Neck; UE, Upper extremity; LE, Lower extremity; T, Trunck; Additional surgery: Bil, Bilateral; GPi, Globus pallidus interna; L, Left; R, Right; STN, Subthalamic nucleus; BFMDRS-M, Burke-Fahn-Marsden Dystonia Rating Scale motor score; DBS, deep brain stimulation; UDRS, Unified Dystonia Rating Scale.

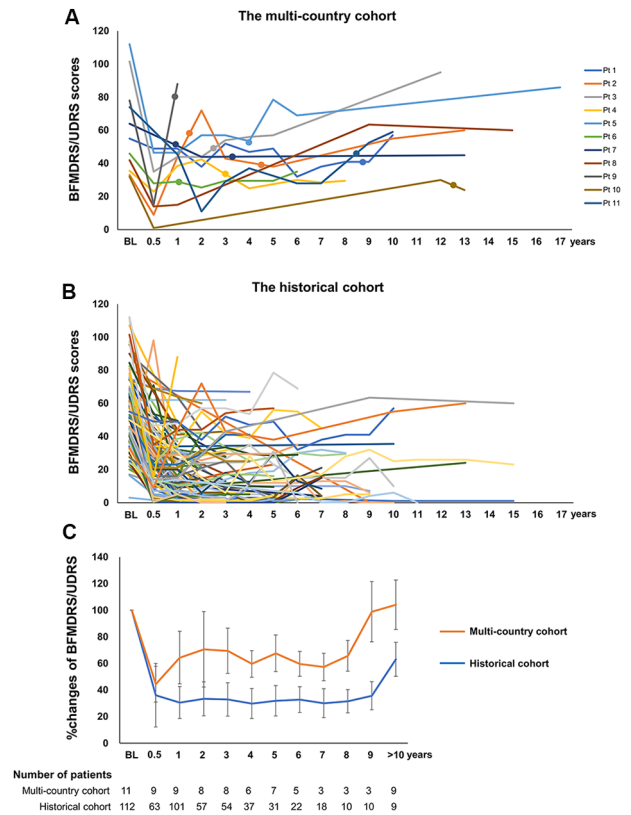

FIGURE 1 | (A) Individual changes of the Burke-Fahn-Marsden Dystonia Rating Scale motor (BFMDRS-M) or Unified Dystonia Rating Scale (UDRS) in the multi-country cohort. **(B)** The closed circles on each line indicate additional GPi or subthalamic nucleus (STN) implantations. Individual changes of the BFMDRS-M or UDRS in the historical cohort. **(C)** Comparison of percent improvement of the BFMDRS-M/UDRS in the multi-country cohort and the historical cohort. Orange and blue line graphs represent mean scores for the multi-country cohort and the historical cohort, respectively. Whiskers represent standard errors. BFMDRS-M, Burke-Fahn-Marsden Dystonia Rating Scale motor score; UDRS, Unified Dystonia Rating Scale.

of ≥30% postoperatively (mean improvement of 59% at 6 months) but subsequently experienced secondary worsening of dystonia symptoms starting between 6 months and 3 years after DBS. Maximal motor improvement was observed between 6 months and 2 years with the improvement of 30–50% in four patients, 50–80% in four, and >80% in three. Cranial involvement was observed in six patients before surgery, and four patients developed cranial dystonia following surgery. Pseudo-dystonic orofacial movement or speech disorders due to the current spread into the surrounding structures were carefully ruled out by the participating expert DBS centers by use of empirical programming of the device and/or stopping the stimulation temporarily. The subscores, as well as the total scores of the BFMDRS/UDRS, were available for nine patients (**Supplementary Table S2**). In all the patients, the worsening of the subscores at long-term follow-ups was observed not only in the cranial regions but also in the limbs and trunk. The lead positions were measured at each expert center and judged optimal (**Supplementary Table S3**). Various stimulation settings were attempted through multiple programming sessions: i.e., single monopolar, double monopolar, or bipolar stimulation with combinations of different voltage, pulse width, and stimulation frequency. All patients underwent additional DBS surgeries targeting the GPi or subthalamic nucleus (STN). The timing of additional implantations for individual patients is shown in **Figure 1A**. Five patients underwent implantation of a second pair of leads within the bilateral GPi; three underwent additional bilateral STN implantation; one underwent replacement of bilateral GPi leads because of lead fractures; considering the asymmetric nature of dystonia symptoms, one underwent additional implantation within the unilateral STN, and one underwent additional implantation within the unilateral STN and GPi. There were no patients with meaningful benefits following additional implantations.

Despite these interventions, the improvement at the last follow-up was less than 30% as compared with the baseline status. When the stimulation was turned off, all the patients in the cohort experienced immediate worsening at the long-term follow-up.

The Historical Cohort

The flowchart of the systematic search and review process is shown in **Figure 2**. The list of 37 studies used for the historical cohort is presented in **Supplementary Table S4**. Twenty-four duplicated patients and five patients with reported suboptimal lead positions were removed. Consequently, a total of 112 DYT1 patients who met the inclusion criteria were included in the historical cohort. All the patients were treated with bilateral GPi DBS. Individual changes of BFMDRS-M/UDRS revealed sustained improvement of dystonia in most patients (**Figure 1B**). As shown in **Figure 1C**, the multi-country and historical cohorts showed distinct trajectories in the long-term. At the group level, the historical cohort experienced mean improvement of 64% at 6 months after surgery and had sustained improvement of approximately 65–70% up to 9 years; mean improvement at ≥10 years was less impressive (37%) because of worsening of scores in a subset of patients with a variable length of follow-up periods. Note that the historical cohort included a total of eight patients with suboptimal DBS responses from our earlier studies who were also included in the multi-country cohort (Cif et al., 2010; Krause et al., 2016; Tsuboi et al., 2019).

Comparison Between the Multi-country Cohort and the Historical Cohort

We compared the historical cohort with the multi-country cohort who manifested suboptimal DBS responses for unexplained reasons (**Table 2**). Mean motor improvement at the last follow-up from baseline were 0% and 66% for the multi-country and historical cohorts, respectively. Compared with the historical cohort, the multi-country cohort had a significantly younger age at onset ($p = 0.025$), younger age at DBS ($p = 0.019$), and a significantly longer follow-up period after DBS ($p < 0.001$). Additionally, cranial involvement was more common in the multi-country cohort compared with the historical cohort

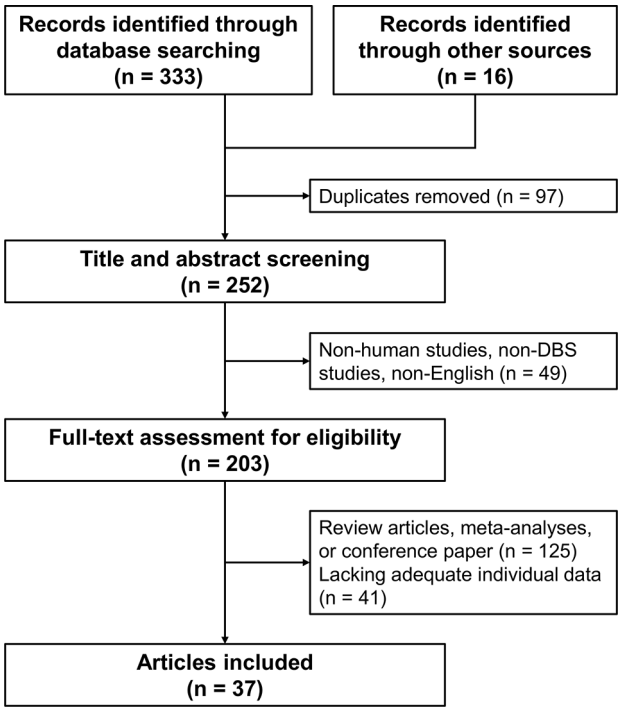

FIGURE 2 | Flowchart of the literature search.

(before DBS, 64% vs. 45%, $p = 0.074$; before or after DBS, 91% vs. 47%, $p = 0.001$).

Suboptimal and Good Responders in the Historical Cohort

In the historical cohort, 16 of 112 patients (14%) experienced suboptimal responses to DBS for unclear reasons at the last follow-up (<30% improvement). The clinical characteristics of the suboptimal and good responders are presented separately in **Table 3**. Individual data are shown in **Supplementary Tables S5, S6**, respectively. Mean motor improvement at the last follow-up from baseline was 4% and 77% for the suboptimal and good responders, respectively. Compared with the good responders, the suboptimal responders had a significantly younger age at onset ($p = 0.005$) and a significantly longer follow-up period after DBS ($p = 0.020$). Cranial involvement was more common in the suboptimal responders compared with the good responders (before DBS, 75% vs. 39%, $p = 0.077$; before or after DBS, 83% vs. 43%, $p = 0.007$).

The suboptimal responders can be divided into two groups (**Table 4** and **Supplementary Table S5**): those with short disease duration before DBS (2–9 years) and those with very long disease duration before DBS (17.5–36 years). Both groups had similar age at onset (7.1 vs. 7.7 years old, $p = 0.681$) and similarly high rates of cranial involvement (both 75%, $p = 0.745$). However, the possible contribution of fixed skeletal deformities to suboptimal DBS response was described only in those with very long disease duration before DBS ($n = 3$).

DISCUSSION

The present study aimed to investigate the clinical characteristics of a multi-country cohort of patients with DYT1 dystonia who experienced suboptimal responses to DBS. Because only a few cases of DYT1 dystonia are operated each year even in expert centers, this dataset, though difficult to obtain, is crucial for the field. A few retrospective studies and a recent meta-analysis of mixed cohorts of inherited or idiopathic isolated dystonia patients reported that the *TOR1A* mutation-positive status was associated with a better DBS response, whereas the reasons underpinning suboptimal responses remained mostly unexplored (Vasques et al., 2009; Andrews et al., 2010; Borggraefe et al., 2010; FitzGerald et al., 2014; Moro et al., 2017). Our findings suggest that a subset of DYT1 patients may have a relatively more aggressive phenotype of DYT1 dystonia characterized by younger age at onset, faster disease progression before DBS, and cranial involvement. Patients with this phenotype may be more likely to experience suboptimal responses to DBS.

There is a surprising lack of published information on suboptimal responses to DBS in DYT1 dystonia despite a growing number of reported cases. Panov et al. (2013) reported that 47 DYT1 patients experienced an improvement in BFMDRS-M by greater than 80% up to 7 years after surgery;

TABLE 2 | Comparison between the multi-country and historical cohorts.

	n	The multi-country cohort	*n*	The historical cohort	*p*
Age at onset (years)	11	7.0 ± 1.5	112	8.4 ± 2.8	0.025[a]
Age at DBS (years)	11	12.0 ± 5.0	112	18.6 ± 10.8	0.019[a]
Disease duration before DBS (years)	11	6.1 ± 4.9	112	10.2 ± 10.8	0.362
Gender (%male, male/female)	11	64%	101	56%	0.451
BFMDRS-M at baseline[b]	9	65.0 ± 28.8	107	61.2 ± 24.1	0.451
UDRS at baseline[b]	2	43.7 ± 11.0	5	44.0 ± 15.6	1.000
Cranial involvement before DBS	11	64%	76	45%	0.074
Cranial involvement before or after DBS	11	91%	76	47%	0.001[a]
Follow-up period after DBS (months)	11	10.5 ± 4.7	112	4.5 ± 4.0	<0.001[a]
%improvement of motor scales[c]	11	0% ± 35%	112	66% ± 33%	<0.001[a]

Data are presented as mean ± SD unless otherwise indicated. [a]P < 0.05 (significant). [b]Motor assessments were done using either BFMDRS-M or UDRS. [c]% improvement at the last follow-up compared with the preoperative scores. BFMDRS-M, Burke-Fahn-Marsden Dystonia Rating Scale motor score; DBS, deep brain stimulation; UDRS, Unified Dystonia Rating Scale.

TABLE 3 | Comparison between the suboptimal and good responders of the historical cohort.

	n	Suboptimal responders	*n*	Good responders	*p*
Age at onset (years)	16	7.3 ± 2.0	96	8.6 ± 2.9	0.005[a]
Age at DBS (years)	16	21.1 ± 12.9	96	18.2 ± 10.5	0.645
Disease duration before DBS (years)	16	13.7 ± 12.0	96	9.6 ± 10.5	0.277
Gender (%male, male/female)	15	67%	86	55%	0.386
BFMDRS-M at baseline[b]	14	61.2 ± 24.1	93	51.7 ± 21.9	0.189
UDRS at baseline[b]	2	44.0 ± 15.6	3	46.7 ± 3.1	1.000
Cranial involvement before DBS	12	75%	64	39%	0.077
Cranial involvement before or after DBS	12	83%	64	43%	0.007[a]
Follow-up period after DBS (years)	16	7.3 ± 5.8	96	4.0 ± 3.4	0.020[a]
%improvement of motor scales[c]	16	4% ± 29%	96	77% ± 20%	<0.001[a]

Data are presented as mean ± SD unless otherwise indicated. The two groups were compared using independent t-tests, Mann–Whitney U tests, chi-square tests, or Fisher's exact tests. [a]P < 0.05 (significant). [b]Motor assessments were done using either BFMDRS-M or UDRS. [c]% improvement at the last follow-up compared with the preoperative scores. BFMDRS-M, Burke-Fahn-Marsden Dystonia Rating Scale motor score; DBS, deep brain stimulation; UDRS, Unified Dystonia Rating Scale.

TABLE 4 | Comparison of the suboptimal responders based on disease duration before DBS.

	n	Patients with short disease duration before DBS	*n*	Patients with long disease duration before DBS	*p*
Age at onset (years)	9	7.1 ± 1.7	7	7.7 ± 2.4	0.681
Age at DBS (years)	9	11.4 ± 3.6	7	33.5 ± 9	<0.001[a]
Disease duration before DBS (years)	9	4.4 ± 2.8	7	25.8 ± 7.1	<0.001[a]
Gender (%male, male/female)	8	50%	7	86%	0.182
BFMDRS-M at baseline[b]	7	58.3 ± 23.3	7	64.1 ± 26.3	0.833
UDRS at baseline[b]	2	44.0 ± 15.6	0	NA	NA
%improvement of motor scales[c]	9	−5.8 ± 35.7	9	16.2 ± 9.4	0.252
Cranial involvement before DBS	8	75%	4	75%	0.745
Cranial involvement before or after DBS	8	88%	4	75%	0.576
Follow-up period after DBS (months)	9	107.3 ± 70.9	7	61.3 ± 63.5	0.338

Data are presented as mean ± SD unless otherwise indicated. The two groups were compared using independent t-tests, Mann–Whitney U tests, chi-square tests, or Fisher's exact tests. [a]P < 0.05 (significant). [b]Motor assessments were done using either BFMDRS-M or UDRS. [c]% improvement at the last follow-up compared with the preoperative scores. BFMDRS-M, Burke-Fahn-Marsden Dystonia Rating Scale motor score; DBS, deep brain stimulation; NA, not available; UDRS, Unified Dystonia Rating Scale.

however, there was no description of patients with suboptimal DBS responses. Markun et al. (2012) observed improvement in BFMDRS-M by 70.3% in 14 DYT1 patients with a mean follow-up of 2.7 years and only commented on patients with skeletal deformities associated with suboptimal improvement. Cif et al. (2010) observed 59% improvement in 26 DYT1 patients with a mean follow-up of 6.2 years. Their cases showed less improvement compared with the former two cohorts; however, they included five cases (19%) who had suboptimal long-term DBS responses. Details of these (Cif et al., 2010) suboptimal patients are included as part of the multi-country cohort. Finally and importantly, most cases in the historical cohort also revealed sustained improvement in the long-term as contrasted to our multi-country cohort. The rate of suboptimal DBS responses due to unexplained reasons was approximately 8% (11 out of 132) in the multi-country cohort, which seems comparable to 14% in the historical cohort. Note that the data from the historical cohort should be interpreted with caution because of limited clinical information available on DBS programming and lead locations.

All 11 patients in our multi-country cohort initially experienced dystonia improvement of more than 30% postoperatively with subsequent worsening. Intriguingly, secondary worsening of dystonia symptoms began between 6 months and 3 years after DBS without any identifiable reasons, e.g., secondary skeletal deformities, cervical myelopathy, lead migrations, device malfunction, and suboptimal programming (Krauss et al., 2002; Anheim et al., 2008; Isaias et al., 2008; Picillo et al., 2016; Morishita et al., 2017; Pauls et al., 2017; Tsuboi et al., 2019). All the patients underwent additional DBS surgeries targeting the STN or GPi; however, these extra leads did not seem to provide a robust benefit. This finding is in agreement with the earlier study reporting variable responses to additional DBS implantations within DYT1 patients (Cif et al., 2012). Importantly, we observed a clear worsening of dystonia symptoms when DBS was turned off at the long-term follow-up visits, reinforcing the idea that DBS may still be a useful intervention even if the clinical outcomes are less robust. However, we cannot determine the relative contribution of disease progression and loss of benefits to secondary worsening because of the lack of formal on- and off-stimulation motor score comparisons (this was a limitation of the multi-country cohort and several cases treated worldwide). The involvement of body parts unaffected before surgery suggests disease progression likely played a role.

To the best of our knowledge, available studies have not analyzed the relationship between cranial involvement and DBS responses in DYT1 patients. Cranial involvement is less common in patients with DYT1 dystonia, with a range reported between 12.0% and 28.2% (Lee et al., 2012). However, cranial involvement in the multi-country cohort (before DBS, 64%; before or

after DBS, 91%) was more frequently observed compared with the historical cohort and compared with the literature (Lee et al., 2012). Similarly, in the historical cohort, the suboptimal responders also showed a higher rate of cranial involvement as compared with the good responders. These findings strongly suggest the possible association between cranial involvement and suboptimal DBS responses in DYT1 patients.

The multi-country cohort had a young age at onset of dystonia ranging from 5 to 10 years old. The mean age at onset of the multi-country cohort was significantly younger when compared with the historical cohort (7.0 vs. 8.6 years old). The multi-country cohort required DBS treatment significantly younger than the historical cohort (mean, 12.0 vs. 19.0 years old) with relatively shorter disease duration (mean, 6.1 vs. 10.5 years, $p > 0.05$). Notably, dystonia evolved quickly to become generalized within 2.5 years after onset in all the patients of the multi-country cohort, and the motor symptoms progressed. Although the precise information on the time to a generalization of dystonia was not available for the historical cohort, the mean time to generalization of dystonia in DYT1 patients was previously reported at 3.1–8.4 (range, 1–30) years (Fasano et al., 2006; Lee et al., 2012), which was longer than that in the multi-country cohort. These results corroborate the multi-country cohort had faster disease progression with a younger age at onset.

Despite early intervention with DBS, the multi-country cohort experienced suboptimal outcomes in the long-term. This result appears to be contradictory to the earlier dystonia studies reporting the association between better outcomes and shorter disease duration before DBS (Isaias et al., 2011; Lumsden et al., 2013; Artusi et al., 2020). In the suboptimal responders included in the historical cohort, only those with very long disease duration before DBS were reported to have fixed skeletal deformities, and age at onset was similar between these two groups. Therefore, fixed skeletal deformities are thought to be responsible for their suboptimal DBS responses at least to some extent (Isaias et al., 2008; Pauls et al., 2017). Nevertheless, the multi-country cohort experienced secondary worsening following initial good responses to DBS without any identifiable reasons, and these patients were characterized by younger age at onset, faster disease progression before DBS, and cranial involvement. Because this phenotype of DYT1 dystonia is relatively less common (approximately 8%), analyses at the group level may not identify the presence of this phenotype. Thus, the present case series revealed a possible aggressive phenotype of DYT1 dystonia and provided detailed observations.

Although the genetics of DYT1 dystonia appear simple because virtually all cases have the same pathogenic deletion variant (c.907_909delGAG), the reduced penetrance and variable clinical phenomenology suggest that other genetic or environmental modifying factors influence phenotypic expression and that these factors may factor into responses to DBS or other treatments (Charlesworth et al., 2013; Weisheit et al., 2018). Dystonia patients carrying different variants in the *TOR1A* gene have been reported, but the consensus has yet to be reached regarding their pathogenicity (Martino et al., 2013; Siokas et al., 2019). A polymorphism in exon 4 of the DYT1 gene (rs1801968, D216H) was reported to affect the clinical penetrance of DYT1 (Risch et al., 2007). Additionally, the multi-country cohort was not tested for other dystonia-causing genes such as DYT-*THAP1* and DYT-*GNAL*, which are known to have a higher incidence of cranial involvement. Furthermore, some variants in brain-derived neurotrophic factor (BDNF) and apolipoprotein E (APOE) have also been reported to lead to an increased incidence of dystonia, possibly *via* altered neural plasticity (Siokas et al., 2019). These findings lead us to speculate on the intriguing possibility that variants within the *TOR1A* gene or other genes may affect the phenotypic manifestation of dystonia and the consequent DBS responses. The data from the current study cannot support or refute this hypothesis. Another unanswered question is the reason for secondary worsening after good initial responses to DBS. Curiously, secondary worsening of dystonia has also been reported in other genetic forms of dystonia, such as DYT-*THAP1* or *GNAO1* mutations (Panov et al., 2012; Brüggemann et al., 2015; Koy et al., 2018). Future neurophysiological and functional imaging studies will hopefully shed further light on the underlying pathophysiology.

There are several weaknesses in this work that should be considered. Because only a few cases of suboptimal responses to DBS are recorded even in expert centers, accumulating enough cases is challenging. Assembling this cohort required a multi-country effort. We would argue that collecting 11 patients with suboptimal outcomes provided valuable information. We could not analyze the whole cohort of the participating centers, which included patients with successful DBS outcomes. Because most studies included were observational unblinded studies, we did not perform a formal risk of bias assessments for the historical cohort. Although the findings from the historical cohort were similar to those from earlier single-center cohorts, the possibility of publication bias must be considered (Markun et al., 2012; Panov et al., 2013). Also, we had to exclude some articles because of insufficient individual clinical information. The historical cohort lacked the data of disease duration before dystonia generalization. The data from the historical cohort should be interpreted with caution because detailed information on DBS programming and lead locations were not available in most publications. The rate of suboptimal DBS responses in the historical cohort might increase with longer follow-up periods. The leads in the multi-country cohort were subjectively judged to be well-placed locally in each DBS center, based on expert opinions. We could not analyze the relationship between lead positions and DBS responses with a unified methodology because the digital imaging data were no longer available for some patients. Ideally, the accuracy of targeting within the posteroventrolateral GPi should be examined using advanced imaging analyses. Importantly, lead locations may potentially impact short-term effects as well as long-term therapeutic outcomes. The multi-country cohort attempted various stimulation settings through multiple programming sessions without a standardized programming protocol. Because

the therapeutic effects of DBS in DYT1 patients are highly variable, we cannot exclude the possibility that there is room for improvement with higher stimulation intensity or different combinations of stimulation settings (Kupsch et al., 2011; Cif et al., 2013; Picillo et al., 2016). Finally, the threshold for a suboptimal response was chosen arbitrarily to exceed a placebo effect.

CONCLUSION

Approximately 8% of patients represent a more aggressive phenotype of DYT1 dystonia characterized by younger age at onset, faster disease progression, and cranial involvement, which seems to be associated with suboptimal DBS responses in the long-term (e.g., secondary worsening). Importantly, the on-/off-stimulation comparison at the long-term follow-up demonstrated beneficial effects of DBS despite missing the 30% threshold for improvement over baseline. Therefore, DBS may still be a useful intervention, even if the clinical outcomes are less robust. Additional rescue STN or GPi DBS implantations may not provide meaningful improvement if the original leads were placed optimally. Patients with this phenotype may have different neuroplasticity, neurogenetics, or possibly distinct neurophysiology, although the exact differences underpinning DBS outcomes are unknown. Future studies should explore whether genetic variants within the *TOR1A* gene or other genes may determine DBS responses. This information could be useful for both clinicians and patients in clinical decision making and patient counseling before and following DBS implantations.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Florida Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TT: research project conception, organization, and execution; statistical analysis design and execution; manuscript writing of the first draft. LC, PC, JO, DR, YM, AL, PD, IH, FM, NS, LO, AW, and KF: research project execution; manuscript review and critique. JC: statistical analysis review and critique; manuscript review and critique. MO: research project conception, organization, and execution; manuscript review and critique.

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MO is an associate editor for the New England Journal of Medicine Journal Watch Neurology. MO has participated in CME and educational activities on movement disorders (in the last 36 months) sponsored by PeerView, Prime, QuantiaMD, WebMD, Medicus, MedNet, Henry Stewart, and by Vanderbilt University. The institution and not MO receives grants from Medtronic, Abbvie, Allergan, and ANS/St. Jude and the principal investigator (PI) has no financial interest in these grants. MO has participated as a site PI and/or co-investigator for several NIH, foundation, and industry-sponsored trials over the years but has not received honoraria.

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CASE REPORT
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Case Report on Deep Brain Stimulation Rescue After Suboptimal MR-Guided Focused Ultrasound Thalamotomy for Essential Tremor: A Tractography-Based Investigation

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Essential tremor (ET) is the most prevalent movement disorder in adults, and can often be medically refractory, requiring surgical intervention. MRI-guided focused ultrasound (MRgFUS) is a less invasive procedure that uses ultrasonic waves to induce lesions in the ventralis intermedius nucleus (VIM) to treat refractory ET. As with all procedures for treating ET, optimal targeting during MRgFUS is essential for efficacy and durability. Various studies have reported cases of tremor recurrence following MRgFUS and long-term outcome data is limited to 3–4 years. We present a tractography-based investigation on a case of DBS rescue for medically refractory ET that was treated with MRgFUS that was interrupted due to the development of dysarthria during the procedure. After initial improvement, her hand tremor started to recur within 6 months after treatment, and bilateral DBS was performed targeting the VIM 24 months after MRgFUS. DBS induced long-term tremor control with monopolar stimulation. Diffusion MRI tractography was used to reconstruct the dentatorubrothalamic (DRTT) and corticothalmic (CTT) tracts being modulated by the procedures to understand the variability in efficacy between MRgFUS and DBS in treating ET in our patient. By comparing the MRgFUS lesion and DBS volume of activated tissue (VAT), we found that the MRgFUS lesion was located ventromedially to the VAT, and was less than 10% of the size of the VAT. While the lesion encompassed the same proportion of DRTT streamlines, it encompassed fewer CTT streamlines than the VAT. Our findings indicate the need for further investigation of targeting the CTT when using neuromodulatory procedures to treat refractory ET for more permanent tremor relief.

Keywords: essential tremor, focused ultrasound, deep brain stimulation, tractography, thalamus, MRI

INTRODUCTION

Essential tremor (ET) is the most prevalent movement disorder in adults. Treatment options for medically refractory cases include a variety of ablative and deep brain stimulation (DBS) procedures, usually targeting the ventralis intermedius (VIM) nucleus of the thalamus (Flora et al., 2010; Louis and Ferreira, 2010).

Recently, Elias et al. (2016) reported the results of a randomized control trial demonstrating the efficacy of unilateral MRI-guided focused ultrasound (MRgFUS) targeting the VIM in treating refractory ET. Out of the 56 patients who received MRgFUS thalamotomy of the VIM, 5 patients (8.9%) experienced the return of their tremor symptoms within 12 months postoperatively, with tremor scores worsening by 23% (Elias et al., 2016). In a 2-year follow up study, however, 4% of the original cohort subsequently received DBS due to unsuccessful or suboptimal treatment with MRgFUS (Chang et al., 2018). A retrospective comparative evaluation of RF thalamotomy, DBS, or MRgFUS for ET patients revealed this loss of effect is shared across modalities (Halpern et al., 2019). Moreover, compared to 6-months post-procedure, the 3-year follow-up study found that even though the primary outcome metric for the trial (i.e., the hand combined tremor-motor score) was significantly improved, there was a slight but significant increase in the median total Clinical Rating Scale for Tremor (CRST) score over time (Kim et al., 2017). The mechanism for this recrudescence remains elusive and is undoubtedly multifactorial, but a detailed review of the anatomic aspects of a suboptimal MRgFUS thalamotomy may guide the future management of these patients (Ravikumar et al., 2017).

One approach for understanding this loss of efficacy is utilizing diffusion-weighted MRI (dMRI) imaging to assess the white-matter fiber tracts being modulated by MRgFUS. Tractography studies have demonstrated that lesions must target the cerebello-thalamo-cortical network for treatment of ET (Coenen et al., 2014). The two major groups of white-matter fiber tracts involved in this network are the dentatorubrothalamic tract (DRTT) and the corticothalamic tract (CTT). These two pathways have been found to be necessary targets for the treatment of ET (Tian et al., 2018).

We present a tractography-based investigation of a patient treated with MRgFUS thalamotomy for ET, whose procedure was prematurely aborted due to new onset dysarthria. Immediately post-procedure, the patient experienced tremor relief and the dysarthria partially improved, but her tremor symptoms, most notably hand tremor, began to return 6 months postoperatively. The patient subsequently received DBS, and the surgery was well-tolerated and efficacious at the long-term.

Using a multimodal imaging strategy, we reconstructed the MRgFUS lesion and the volume of activated tissue (VAT) produced by the DBS electrode and the patient's specific programming. We then used probabilistic tractography to assess the relationships between the MRgFUS lesion, DBS VAT, and the white matter fiber tracts associated with tremor control. This methodology offers a unique understanding of the specific fiber tracts modulated in both MRgFUS and DBS, in order to shed light on why DBS yielded a better long-term outcome in our patient.

CASE DESCRIPTION

A 70-year-old female with medically refractory ET was evaluated at our movement disorders clinic after nearly 30 years of tremor. Her tremor began in her left hand and eventually progressed to her right hand, head and voice. Eventually, she required assistance for her activities of daily living, including eating, writing, and dressing due to the severity of her tremor. She tried numerous medication therapies including combinations of propranolol, primodone, and gabapentin, in addition to chemodenervation with botulinum toxin. Despite all treatment attempts, she only achieved suboptimal tremor control.

At presentation, she was found to have postural tremors bilaterally in her upper extremities, significantly worsening with action and improving with rest. Her handwriting as well as her straight line and spiral drawing tests were markedly abnormal (**Figure 1**). She had head tremor and her voice was tremulous with audible oscillations. Her bedside cognitive status, as assessed by the Montreal Cognitive Assessment (MoCA) test, was within normal limits. There was no evidence of parkinsonism on examination. The CRST A subscore was 30 at the time of presentation in 2015, reflecting her postural and kinetic tremors (**Figure 1**). The patient presented with options of continued medical management, bilateral DBS, unilateral DBS, or MRgFUS as part of an ongoing clinical trial. At the time of initial presentation and evaluation, the patient was most distressed by her dominant hand tremor, and thus, after presented with the options, elected to proceed with MRgFUS focused on relief for her dominant upper extremity tremor.

The patient underwent a left MRgFUS thalamotomy in August 2015. The series of sonications is described in **Supplementary Table S1**. The left VIM nucleus target was guided by 3T MRI using standard coordinates from the mid-commissural point (MCP): –13.3 mm, –6 mm, 0 mm (∼10 mm from the ventricular wall) for sonications 1–19, 1 mm medial from the canonical stereotactic target. This target was chosen to provide about 2 mm of a safety margin from the thalamo-capsular boundary based on the patient's preoperative MRI imaging. There were adjustments to the location of the sonication's focus in order to sonicate the center of the planned target. By sonication 19, the patient's tremor was largely relieved, but the lesion's boundaries were approaching the internal capsule. For sonication 20, the target was moved 1 mm medially to avoid the internal capsule. For final sonication 21, the target was moved an additional 1 mm medial to continue the ablation but ensure no breach of the internal capsule. At the conclusion of sonication 21, transient dysarthria was noted on the patient's clinical examination, and the procedure was terminated. Out of the 21 sonications performed, four of them reached a temperature greater than 55°C, and the maximum temperature attained was 61°C. The highest energy sonication reached 15940 J (797 W for 20 s). The SDR was 0.51. There were no cavitations. The procedure was aborted due to new-onset dysarthria. The patient experienced a significant improvement in her tremor at 2-week follow-up. Her only new symptom was transient dysarthria that initiated during MRgFUS treatment. Over the next 6 months, however, she noticed progressive tremor recurrence and worsening of

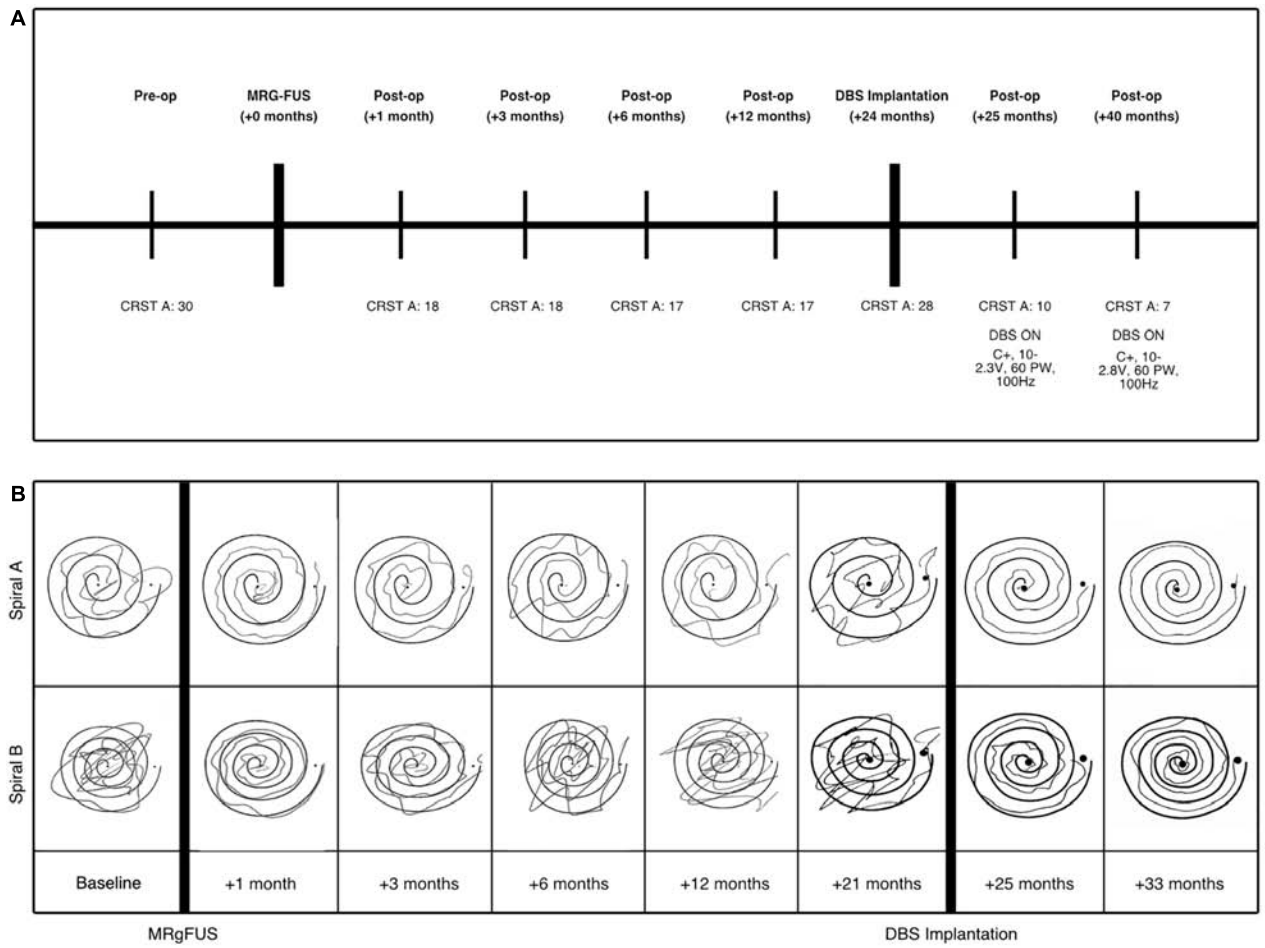

FIGURE 1 | (A) Clinical timeline of patient's procedures and DBS programming parameters following FUS and lead implantation. The patient's tremor was evaluated using the Clinical Rating Scale for Tremor (CRST) A subsection, which evaluates tremor, including those of the upper extremities. **(B)** "Archimedes spiral" drawings (right hand only) during the B subsection of the CRST assessment to evaluate hand tremor at each time point to demonstrate tremor progression over time after MRgFUS procedure. Spiral A is wide, compared to the narrow spiral B (acquired as part of the CRST B).

her tremor symptoms despite partial improvement of dysarthria (see **Supplementary Table S2**).

After discussion with and further evaluation of the patient through a multidisciplinary DBS review board, she was deemed a candidate for DBS targeted to the VIM nucleus. Approximately 24 months after her initial left MRgFUS, DBS (Medtronic Activa PC) leads were bilaterally placed without complication using frameless robotic-assisted stereotactic navigation (Ho et al., 2019). Based on the dysarthria previously experienced that was presumed to be due to the relatively medial location of the MRgFUS treatment, DBS leads were placed using target coordinates of -13, -6.5, and 0 mm from the MCP (5.9 mm anterior to PC). The target was more lateral in order to minimize dysarthria, and more posterior so that the trajectory did not enter blood vessels, ventricles, or sulci. Intraoperative electrophysiological monitoring and postoperative imaging demonstrated satisfactory lead placement. A standard monopolar testing protocol was performed to evaluate the threshold of efficacy for each contact and any adverse effects. With stimulation at 1.5 V, there were no adverse effects with activation of contacts C1-C3, however, the patient experienced transient right lip paresthesia with activation of left hemisphere contact C0, which was the contact located closest to the MRgFUS lesion. At 3–4 V, the patient experienced slight dysarthria when left hemisphere contact C1 was activated. When C1 in the right hemisphere was activated at 3.0 V, her dysarthria worsened. Contact C2 was chosen for monopolar activation at 2.7 V in the left hemisphere and 2.0 V in the right hemisphere, which maximized her tremor suppression and minimized adverse effects. At her last evaluation (16-month follow-up after DBS), she had consistent and effective tremor control, with a CRST score of 7 (**Figure 1**). The left lead was active at contact 2 set at 2.8 V, pulse width 60 ms and 100 Hz. The right lead was active at electrode 10 set at 2.3 V, pulse width 60 ms and 100 Hz. The patient had excellent tremor suppression following monopolar activation of the DBS leads, as shown by sustained decrease in CRST and significant improvement drawing coherent spirals.

METHODS

MRI Imaging Acquisition and Preprocessing

T1-weighted and T2-weighted structural 3T MRI images were acquired before and after FUS. Diffusion-weighted images were acquired from the patient before MRgFUS (3T, 2 mm isotropic, TR/TE = 8500/81.6 ms, b = 2500 s/mm^2, 60 directions, 582 s) and before DBS implantation (3T, 2 mm isotropic, TR/TE = 8000/60.7 ms, b = 1000 s/mm^2, 30 directions, 502 s). Computed tomography (CT) images with 1 mm slice thickness were obtained postoperatively after DBS implantation. FSL's "topup" tool was used to estimate and correct non-zero off-resonance fields caused by susceptibility distribution of the subject's head via analysis of forward and reverse phase encoded B_0 image acquisitions (Andersson et al., 2003). FSL's "eddy" tool was used to correct for the eddy current caused by rapid switching on and off of the diffusion gradient (Smith et al., 2004).

Lesion Volume, Electrode Reconstruction, and Volume of Activated Tissue Estimation

MRgFUS results in three distinct zones of ablation that can be viewed on a T2-weighted image (Wintermark et al., 2014). The lesion region of interest (ROI) was created by including the voxels that are within the two inner zones (the third outer zone being vasogenic edema) on an MRI acquired the same day following MRgFUS thalamotomy. Lead-DBS was used for localization and visualization of the DBS electrode contacts (Horn et al., 2019). Linear and nonlinear transformations were computed from the MNI 152 2009c template to the T1 and T2-weighted images, as well as the postoperative CT. The DBS Intrinsic Template Atlas (DISTAL) was subsequently transformed onto the native T1-weighted images and used to localize the electrodes as well as the MRgFUS lesion in reference to the VIM (Ewert et al., 2018). The VAT was estimated using a finite element modeling method based on the characteristics of the brain tissue activated and the DBS programming voltage and estimated impedance (Madler and Coenen, 2012).

Probabilistic Tractography and Statistical Analysis

Tractography was performed with MRtrix using constrained spherical deconvolution to estimate the white-matter fiber orientation distribution from the diffusion signal of the dMRI images (Smith et al., 2013). Using probabilistic tractography, the DRTT was filtered to include white-matter tracts that are seeded at the dentate nucleus and terminate in the thalamus, along with sending collaterals to the red nucleus. Freesurfer was used to segment the structural T1-weighted images to generate ROIs for the thalamus, and dentate nucleus (Desikan et al., 2006; Fischl, 2012). The red nucleus was drawn using guidance from an expert neuroradiologist. The CTT was filtered to include only white-matter tracts seeded at the precentral gyrus and terminate at the thalamus. Freesurfer was used to generate masks encompassing the precentral gyrus.

A mask of the MRgFUS lesion was overlaid on the pre-MRgFUS tractography streamlines, and a mask of the VAT was overlaid onto the pre-DBS streamlines. The proportion of streamlines of each tract that were incorporated by the lesion and VAT were calculated by dividing the raw number of streamlines of the DRTT and CTT that intersected the lesion and VAT, by the total number of streamlines within the DRTT and CTT.

DIAGNOSTIC ASSESSMENT AND RESULTS

The MRgFUS lesioning procedure in the VIM resulted in immediate tremor suppression. The patient's CRST A score decreased from 30 to 18 as a result. Her tremor suppression remained stable for 6 months, then began worsening. Twenty-four months after the MRgFUS procedure, the patient's CRST A score had increased to 28, and at this time, the patient received DBS electrode implantation. Subsequent programming reduced her tremor, resulting in a CRST A score of 7 after optimizing DBS programming parameters.

Probabilistic tractography reconstructed streamlines of the DRTT (**Figure 2**) and CTT (**Figure 3**) for the pre-FUS (A) and pre-DBS (B) diffusion weighted images. The lesion after MRgFUS, and the VAT from DBS, were overlaid onto each respective image to select the voxels that were modulated by each modality.

The MRgFUS lesion's volume was calculated to be 20.28 mm^3. The estimated VAT from the unilateral left VIM DBS at the patient's last programming settings was 233.16 mm^3. The VAT's x, y, and z coordinates relative to the MCP were -15.5, -2.5, and -7 mm. The center of the lesion was located 3.75 mm closer to the midline than the active DBS VAT, and 5 mm more ventral. The lesion location in the pre-FUS image captured 12.9% of the DRTT streamlines and 4.4% of the CTT streamlines, while the DBS VAT location of the pre-DBS image encompassed 13.6% of the DRTT streamlines and 29.7% of the CTT streamlines, respectively.

For visualization purposes, the lesion and VAT were reconstructed in 3D alongside the DBS electrodes and the internal and external nuclei of the VIM, defined by the DISTAL atlas (**Figure 4**).

DISCUSSION

Tremor relief that is not sustained after MRgFUS treatment is troublesome to patients and presents a significant management challenge. For these patients in whom treatment has failed, it may be appropriate to offer repeat or rescue procedures (Tuleasca et al., 2017; Wang et al., 2018; Weidman et al., 2019). However, in the described case, the scant availability of repeat MRgFUS efficacy, the side effect of dysarthria, and patient preference for bilateral therapy made DBS a favorable alterative, not to mention its ability to be used somewhat reversibly and bilaterally. Using patient-specific probabilistic tractography, we investigated

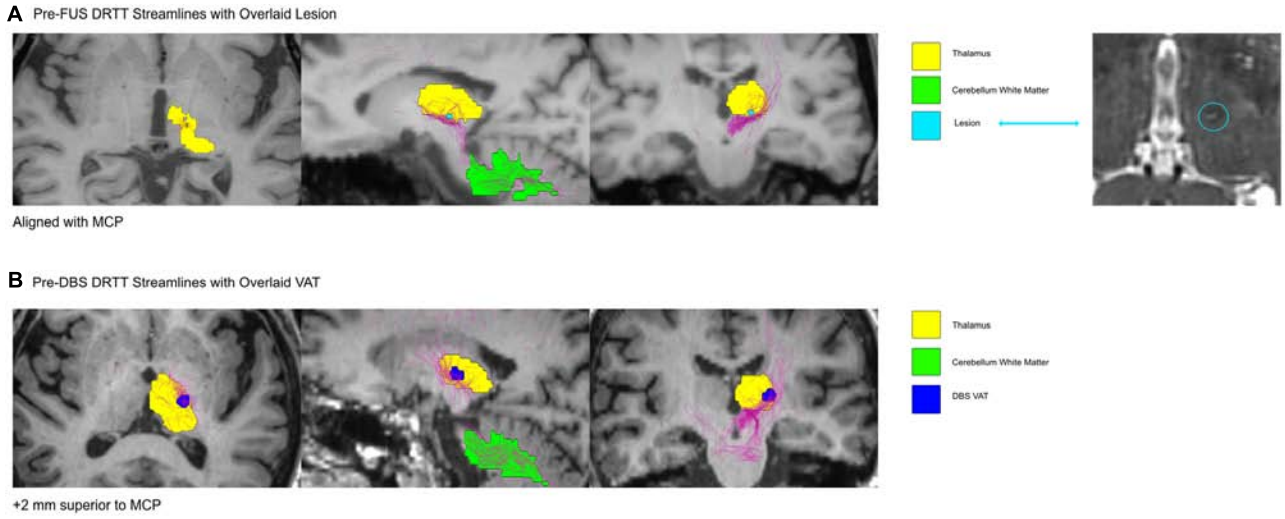

FIGURE 2 | The DRTT shown in the Pre-FUS and Post-FUS volumes. In **(A)**, the lesion after MRgFUS was overlaid onto the pre-FUS image, to isolate the voxels that encompassed the lesion before the MRgFUS procedure. In **(B)**, the DBS VAT was overlaid onto the Pre-DBS image. The DRTT was isolated from all tracts generated via probabilistic tractography by only including the streamlines that intersected the ROI masks for the cerebellum white matter (dentate nucleus), thalamus, and red nucleus.

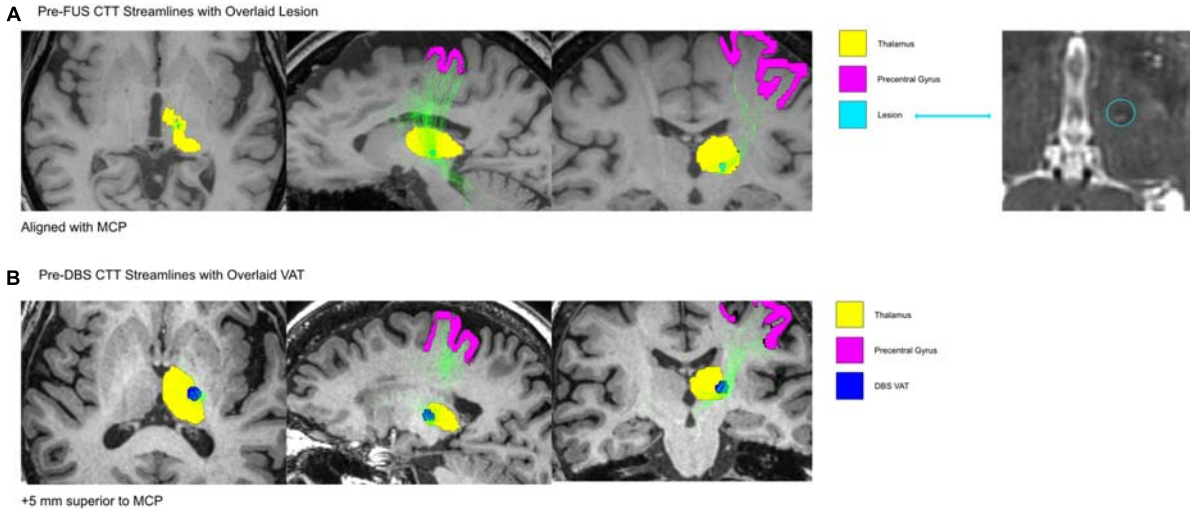

FIGURE 3 | The CTT shown in the Pre-FUS and Post-FUS volumes. In **(A)**, the lesion after MRgFUS was overlaid onto the pre-FUS image, to isolate the voxels that encompassed the lesion before the MRgFUS procedure. In **(B)**, the DBS VAT was overlaid onto the Pre-DBS image. The CTT was isolated from all tracts generated via probabilistic tractography by only including the streamlines that intersected the ROI masks for the precentral gyrus and thalamus.

this case of medically refractory ET treated with MRgFUS and subsequently DBS to retrospectively evaluate the topography and fiber tracts modulated in both procedures in order to understand their differential efficacy and side-effect profile. Importantly, the MRgFUS lesion in this case was not optimized due to aborting the procedure. However, we feel optimizing targeting based on reports such as this may prevent future MRgFUS treatment failures.

Our technique of comparing the overlap in the lesion/VAT module volume with patient-specific tracts suggested the difference in treatment outcomes may be explained in part by the DBS VAT. The MRgFUS lesion was located ventromedially to the VAT (**Figure 4**), and was also significantly smaller, comprising roughly 10% of the volume of the VAT. The MRgFUS lesion was placed medially to avoid heat extending into the internal capsule, and thus sonications were moved serially more medially as the procedure continued to avoid heating of the pyramidal tract. DBS electrodes were placed in a similar trajectory, with the most distal contact (contact 0) bordering the lesion location. During programming, the patient received the most tremor suppression when contact 2 was activated, moving the VAT dorsolaterally.

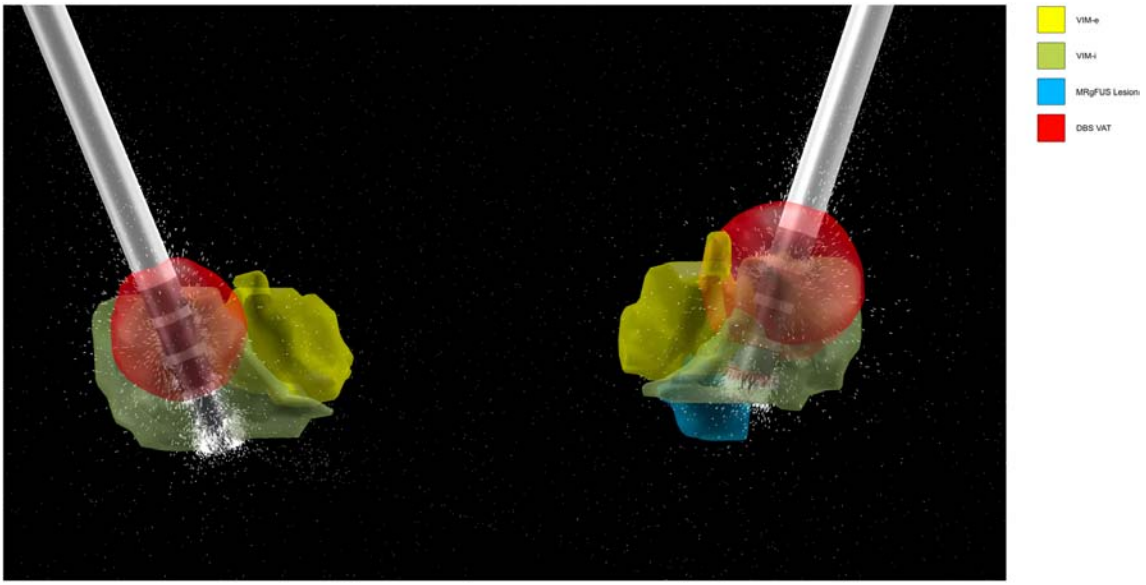

FIGURE 4 | Bilateral DBS (left hemisphere on right side, right hemisphere on left side) 3D lead reconstruction and VAT generation in LEAD-DBS. DBS electrode contact spacing models design of Medtronic 3389. The dashes represent the directionality of the induced electric field from the activated contact, in this case contact 2. The lesion and VAT are localized alongside the internal and external segments of the VIM (VIM-i and VIM-e, respectively) defined by the DISTAL atlas.

Although the tractography findings suggest that more accurate targeting and larger VAT resulted in more sustained tremor relief, our case also adds to a further body of evidence about the variable efficacy of MRgFUS thalamotomy. It is noteworthy that despite suboptimal targeting and premature cessation of sonications due to dysarthria, the initial MRgFUS treatment resulted in tremor relief, albeit temporarily. The onset of tremor recurrence within 1 year postoperatively has been reported in numerous cases in the literature, even without lesions complicated by dysarthria (Wang et al., 2018; Halpern et al., 2019). This suggests several plausible explanations for loss of tremor suppression efficacy over time after MRgFUS. First, the lesion created may have a penumbra region of edemanous brain where reversible neuromodulatory rather than neuroablative effects predominate. Additionally, ongoing pathologic remodeling occurring among Purkinje and other cell types in the cerebello-thalamic tremor circuit may lead to progressive worsening of tremor (Louis and Faust, 2020) in the face of a well-targeted MRgFUS lesion. Further investigation should be conducted on the time course of cellular mechanisms of thalamic MRgFUS lesions in tremor model systems as well as neuroimaging studies to uncover predictive imaging biomarkers for tremor recurrence.

Additionally, our tractography analysis here investigates a single patient's structural connectivity, but insight can be drawn into the differences in streamline counts within the DRTT and CTT, which have been reported to be necessary when using tractography to define patient-specific neuromodulatory targets for ET (Coenen et al., 2014). The negligible difference in the proportion of DRTT streamlines modulated by MRgFUS and DBS indicates that both modalities targeted this tract in a similar way, although a different location within the DRTT was modulated in each procedure. However, when comparing DBS stimulation to MRgFUS, we found a large increase in the proportion of CTT streamlines residing within the DBS VAT, compared to those found within the patient's MRgFUS lesion volume. Although prior work has shown that disruption of cerebellar input into the ventral thalamus is necessary to disrupt tremor pathophysiology (Gallay et al., 2016), the pattern suggests that targeting the DRTT alone may not be sufficient, thus future investigations should explore the role of modulating the CTT to maintain clinical effectiveness of tremor relief and balancing the use of imaging to guide targets with intra-procedural findings. This is in line with findings by Tian et al., which report that the most efficacious target, in a cohort of ET patients who received MRgFUS thalamotomy, encompassed both the CTT and DRTT (Coenen et al., 2014).

Our findings demonstrate modeling white-matter fiber tracts using probabilistic tractography may serve as a method to inform and optimize targeting of initial MRgFUS lesions and tailor rescue procedures for those with recurrent or persistent tremor. We have demonstrated that the larger size of the DBS VAT, compared to the MRgFUS lesion, incorporates a larger area of white-matter to be targeted, allowing for the inclusion of more fibers of the CTT, as it has been reported that the size of the lesion is positively correlated to improved treatment outcome (Federau et al., 2018).

Dysarthria is a common adverse effect of neuromodulatory procedures targeting the VIM, including both MRgFUS and DBS. While every attempt is made to mitigate this effect across procedural modalities, indirect targeting of VIM lends itself to suboptimal accuracy of sonications and DBS lead placement. This effect may be caused by stimulation or sonications of the

posterior limb of the internal capsule. Activation of ventral contacts in the VIM have also shown to stimulate the homuncular representation of the head (Montgomery, 2010). Moreover, the patient's absence of dysarthria after successful DBS treatment suggested the dysarthria was due to medial sonications as the DBS lead was relatively lateral. Using tractography to optimize targeting is one approach that we highlight in this case study to attempt to mitigate such troublesome adverse effects. We believe our case underscores the importance of tractography-based targeting, which becomes particularly relevant given that VIM targeting is indirect due to our inability to segment thalamic nuclei via conventional MRI (Coenen et al., 2014). There have been reported attempts to directly modulate white-matter tracts via DBS, such as the DRTT through targeting the posterior subthalamic area (PSA), which appear to be effective at suppressing tremor (Dembek et al., 2020). The findings of our case report further support the idea that indirect VIM targeting may not be sufficient alone to optimize outcomes for ET (Benabid et al., 1991). Tractography utilizes the diffusion signal of the white matter tracts in the brain, which is personalized to each patient and more directly tells us where to target. In particular, the canonically activated contacts for VIM DBS are usually ventrally located (Gallay et al., 2016), but the most effective contact in our patient was the more superior contact 2. Moreover, Boutet et al. (2018) have shown that medially placed lesions in the VIM were associated with 41 times the likelihood of speech adverse effects. Our case report supports these findings.

A limitation of this work comes from the relatively low spatial resolution of dMRI at roughly 2 mm isotropic. This indicates that tractography-based targeting should be used alongside other targeting methods, such as atlas coregistration, intraoperative microelectrode recordings, and/or real-time patient examination, to ensure accurate tract localization. Another limitation includes that our dMRI acquisitions taken pre-MRgFUS and pre-DBS had different acquisition parameters. We have accounted for this difference by comparing the proportion of streamlines targeted by each method, rather than the raw streamline count, which may be more affected by varying acquisition parameters. It is also important to note that in this case, the DRTT was within the lesional zone of the MRgFUS, and the CTT was additionally included within the DBS VAT; further investigation should be conducted to determine the effects of including CTT targeting by MRgFUS. The findings of this report highlight the need for prospective validation of tractography-based targeting and modeling of modulation by lesioning and electrical stimulation modalities such as DBS.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the patient for the publication of this case report.

AUTHOR CONTRIBUTIONS

SS was the main author on this case report. DB, JP, YH, MJ, and VN helped with data acquisition, analysis, and editing. VS was the neurologist involved with clinical evaluation and care of the patient. PG, VS, KP, and JM were involved in the clinical trial for MRI-guided Focused Ultrasound that our patient was enrolled in and assisted with the methodologies for data acquisition and analysis. CH was the neurosurgeon in the clinical trial involved in the localization of the lesions and assessments post-procedure.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00191/full#supplementary-material

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An International Survey of Deep Brain Stimulation Utilization in Asia and Oceania: The DBS Think Tank East

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Introduction: To evaluate the current utilization and challenges in fully implementing the use of deep brain stimulation (DBS) treatment in Asia and Oceania.

Methods: We conducted a medical literature search to identify DBS research performed by investigators with a primary affiliation in Asian and Oceania countries between March 1, 2013, and March 1, 2019, followed by an international survey-based study. Additionally, we obtained added information regarding the DBS challenges and opportunities from the technology/industry perspective within China and Japan. We also described the current situation of DBS in India.

Results: Most publications (390/494; 78.95%) in the English language originated from East Asia. In West Asia, Turkey, Israel, and Iran accounted for most DBS publications. We found no publications from the remaining 35 Asian countries. Lack of community referrals to tertiary centers was identified as the most common limitation for the widespread use of DBS in Asia (68.97%). In China, despite an increasing number of centers performing DBS surgeries, most of them accomplished less than 10 cases per year. In contrast, the number of DBS cases in Japan has been decreasing. Centers offering DBS surgeries as well as corresponding fellowship training in India are limited.

Conclusion: Appropriate referrals, access, infrastructure, and the presence of full multidisciplinary DBS teams are common limitations of DBS in Asia. Most centers in China, Japan, and India performed less than 10 cases per year and a future study is expected to address the impact on quality in centers performing such few cases.

Keywords: deep brain stimulation, Asia, Oceania, China, Japan, India

INTRODUCTION

Deep brain stimulation (DBS) is a safe and effective treatment for medically refractory brain disorders. DBS was approved by the United States Food and Drug Administration as a treatment for essential tremor and Parkinson's disease (PD) in 1997, dystonia in 2003, obsessive-compulsive disorder (OCD) in 2009, and epilepsy in 2018 (Okun, 2014; Li and Cook, 2018). DBS has been recently studied in small clinical trials as a potential treatment for other psychiatric disorders, e.g., major depression (Crowell et al., 2019), addiction (Chen et al., 2019; Zhang et al., 2019), and Tourette syndrome (Johnson et al., 2019; Ramirez-Zamora et al., 2019).

Expertise gained from surgical ablation has strongly influenced the clinical use of DBS, in particular the choice of targeted brain regions. The well-established long-term efficacy of bilateral high-frequency stimulation applied to different brain regions, coupled with the partially reversible nature of DBS and the possibility of reducing dopaminergic medications in PD patients has led to the global evolution toward DBS over ablative procedures to treat motor fluctuations and complications in PD (Krack et al., 2019). However, even in PD, less than 2% of eligible patients worldwide undergo DBS (Chan et al., 2014; Willis et al., 2014; Kestenbaum et al., 2015; Lee, 2015; Poortvliet et al., 2015; Ezat et al., 2017; Wagle Shukla et al., 2018).

Barriers to widespread adoption of DBS therapy include difficulties in predicting response and identifying appropriate candidates. There has been a reluctance of clinicians to refer patients for surgery, a shortage of personnel trained in DBS programming and issues about access to expert centers. Logistical barriers include expensive procedural costs and lack of insurance coverage. In many centers, long waiting lists for DBS surgery and the fear of brain surgery are common concerns, particularly in developing countries (Abosch et al., 2013).

A critical aspect of the effectiveness of DBS is patient selection. Another important aspect related to DBS success is choosing the appropriate brain target and surgical approach including factors such as the patient's symptom profile, age, and cognitive status (Okun et al., 2004; Moro et al., 2016). These choices rely heavily on the expertise of the multidisciplinary team and vary from center to center. Most DBS studies have been published in European and North American countries (Hu et al., 2017) and there has been limited information regarding the local use and challenges of DBS in other world regions. More than two-thirds of people in the world reside in Asia and Oceania. To facilitate ongoing communication among these countries, the First 2019 DBS Think Tank East meeting was held on June 3rd, 2019 in Kyoto, Japan. A goal of this meeting was to provide a detailed survey of DBS practices within Asia and Oceania.

The objective of the international survey was to collect and share information on the current status of DBS surgery in Asia and Oceania and to achieve a better understanding of the local DBS challenges and opportunities. A complete literature review of DBS cases in Asia and Oceania was performed in addition to the survey. We present the results of the survey and the literature review.

MATERIALS AND METHODS

Study Design

We designed this international survey study in March 2018 for the 2019 DBS Think Tank East meeting, which was held on June 3rd, 2019 in Kyoto, Japan. A 54-question internet-based survey was developed (designed with SurveyMonkey[1]) to ascertain various aspects of DBS surgical practice in Asian and Oceania regions including but not limited to: demographic information, DBS center information, number of different kinds of DBS surgeries (in 2018), team composition, specific surgical information, side effects, post-surgery management, number of patients, number of surgeries, as well as information on cost. The study conformed to the American Association for Public Opinion Research (AAPOR) regarding informed consent from the participants and compliance with human research ethics.

Survey Question Formulation and Survey Tool

We initially conducted a literature review using the PubMed database searching for DBS studies published in English from Asia in the last 5 years at the stage of meeting preparation (i.e., between March 1, 2013, and March 1, 2018). The period was subsequently extended to March 1, 2019, to include more information before the meeting in June 2019. The Mesh term (or team) "DBS" was entered in the "Title/Abstract" field and country name, including "China," "Japan," "Korea," "Mongolia," etc. in the "Affiliation" field. Full country lists are included in **Table 1**. Basic science animal experiments, reviews, and publications using a language other than English were excluded. Searching results were manually verified. Only the corresponding author's affiliation was used to define the "nationality" of the article. Subsequently, we contacted all corresponding authors by email to participate in this survey and to complete the electronic questionnaire. As stated in the invitation email, completion of the survey by participants was considered as implied consent. Responses were collected from May 17th, 2019 to July 8th, 2019.

Statistical Analysis

The survey results have been summarized descriptively. Quantitative data are presented as the median and interquartile range (IQR; 25th–75th percentile) and qualitative data are presented as "percentage."

RESULTS

DBS Development in Asia and Australia

We identified 494 studies, the majority of which [390/494 (78.95%)] were from East Asia (e.g., China, Japan, South Korea). Of the 114 centers identified from publications, 73 were in

[1]https://www.surveymonkey.com/r/eastdbs

East Asia or Australia. For West Asia, Turkey, Israel, and Iran contributed to the most publications. There were thirty-five countries (71%) without any English publications on DBS according to our searching strategy (**Table 1**).

TABLE 1 | Publications and deep brain stimulation centers in Asia and Oceania.

No.	Country	No. of publications[a]	Publications[a] per 10 million person	No. of centers identified from publications	Centers per 10 million person	Population (10 million)[b]	Ratio publications/ centers	GDP per capita (US dollars)[c]
1	China	210	1.46	23	0.16	143.38	9.13	9,770.85
2	Japan	91	7.17	22	1.73	12.69	4.14	39,286.74
3	Korea [d]	89	17.37	10	1.95	5.12	8.90	31,362.75
4	Turkey	24	2.88	13	1.56	8.34	1.85	9,311.37
5	Australia	22	8.73	18	7.14	2.52	1.22	57,305.30
6	Iran	19	2.29	10	1.21	8.29	1.90	5,627.75
7	India	16	0.12	6	0.04	136.64	2.67	2,015.59
8	Israel	13	15.29	4	4.71	0.85	3.25	41,614.00
9	New Zealand	1	2.08	2	4.17	0.48	0.50	41,966.01
10	Saudi Arabia	3	0.87	2	0.58	3.43	1.50	23,219.13
11	Singapore	2	3.45	1	1.72	0.58	2.00	64,581.94
12	Philippines	2	0.19	1	0.09	10.81	2.00	3,102.71
13	Malaysia	1	0.31	1	0.31	3.19	1.00	1,1238.96
14	Nepal	1	0.35	1	0.35	2.86	1.00	1,025.80
15	Lebanon	0	0	0	0	0.69	NA	8,269.79
16	Thailand	0	0	0	0	6.96	NA	7,273.56
17	Afghanistan	0	0	0	0	3.80	NA	520.90
18	Armenia	0	0	0	0	0.30	NA	4,212.07
19	Azerbaijan	0	0	0	0	1.00	NA	4,721.18
20	Bahrain	0	0	0	0	0.16	NA	24,050.76
21	Bangladesh	0	0	0	0	16.30	NA	1,698.26
22	Bhutan	0	0	0	0	0.08	NA	3,360.27
23	Brunei	0	0	0	0	0.04	NA	31,627.74
24	Burma	0	0	0	0	5.40	NA	1,325.95
25	Cambodia	0	0	0	0	1.65	NA	1,512.13
26	Cyprus	0	0	0	0	0.12	NA	28,159.30
27	East Timor	0	0	0	0	0.13	NA	2,035.53
28	Georgia	0	0	0	0	0.40	NA	4,344.63
29	Indonesia	0	0	0	0	27.06	NA	3,893.60
30	Iraq	0	0	0	0	3.93	NA	5,878.04
31	Jordan	0	0	0	0	1.01	NA	4,247.77
32	Kazakhstan	0	0	0	0	1.86	NA	9,331.05
33	Kuwait	0	0	0	0	0.42	NA	34,243.95
34	Kyrgyzstan	0	0	0	0	0.64	NA	1,281.36
35	Laos	0	0	0	0	0.72	NA	2,567.54
36	Maldives	0	0	0	0	0.05	NA	10,223.64
37	Mongolia	0	0	0	0	0.32	NA	4,103.70
38	Oman	0	0	0	0	0.50	NA	16,418.93
39	Pakistan	0	0	0	0	21.66	NA	1,472.89
40	Palestine	0	0	0	0	0.50	NA	NA
41	Qatar/Katar	0	0	0	0	0.28	NA	69,026.47
42	Sri Lanka	0	0	0	0	2.13	NA	4,102.48
43	Syria	0	0	0	0	1.71	NA	2,032.62
44	Tajikistan	0	0	0	0	0.93	NA	826.62
45	The United Arab Emirates	0	0	0	0	0.98	NA	43,004.95
46	Turkmenistan	0	0	0	0	0.59	NA	6,966.64
47	Uzbekistan	0	0	0	0	3.30	NA	1,532.37
48	Vietnam	0	0	0	0	9.65	NA	2,563.82
49	Yemen	0	0	0	0	2.92	NA	944.41

[a]We searched in Pubmed Database and included hurman studies published in English from Asia Between March 1, 2013, and March 1, 2019. The term "Deep brain stimulation" was entered in the "Title/Abstract" field and country name, including "China," "Japan," "Korea," etc. in the "Affiliation" field. Basic science animal experiments, reviews, and publications using a language other than English were excluded. **Supplementary information** *from manufacturers was also used for DBS center identification. [b]Population data is obtained from World Population Prospects 2019 (total population, both sexes combined, as of 1 July 2019), United Nation (https://population.un.org/wpp/Download/Standard/Population/). [c]Data is obtained from The World Bank, GDP per capita (most recent year https://data.worldbank.org/indicator/NY.GDP.PCAP.CD). [d]"Korea" was used for both South Korea and North Korea. There were no publications from North Korea. Data on the population as well as GDP per capita include only South Korea.*

Experience of Neurologists and Neurosurgeons

We received 37 answers from 32 DBS centers across nine countries. Most responses were from East Asia and Australia [27/37 (73%); **Supplementary Table S1**]. Most centers interviewed [31/36 (86%)] were major referral centers in their respective countries. The median number of DBS surgery centers interviewed was 14 (IQR 10–18) years (**Supplementary Figure S1A**).

Among the 37 respondents, 22 (60%) were neurosurgeons and 11 (30%) were neurologists. Additionally, two physiologists, one psychiatrist, and one neuro-engineer participated (**Supplementary Figure S1C**). Approximately half [18/37 (49%)] of respondents specialized in functional neurosurgery and approximately one-quarter [9/37 (24%)] identified as specialists in movement disorders; the rest practiced in the fields of neurophysiology, neuropsychiatry, and in general medicine (**Supplementary Figure S1D**). The median years of clinical experience was 13.0 (IQR 8.5–17.0) years, which was similar to the time engaged in utilizing neuromodulation techniques [14.0 (IQR 8.5–19.5) years; **Supplementary Figure S1B**]. Despite the relatively long history of DBS, 10/24 (42%) respondents had not performed more than 25 surgeries in 2018, and only one team reported performing more than 200 DBS surgeries in the previous year (**Supplementary Figure S1E**).

Management of DBS: Surgical Team Members, Software and Hardware

Perioperative management of DBS is usually a multidisciplinary effort that involves neurologists, neurosurgeons, physical therapists, psychiatrists, psychologists, and case managers. Our data suggested that in Asia the team usually involves more neurologists [3 (IQR 2–3.75)] than neurosurgeons [2 (IQR 1–3); **Supplementary Table S2, Supplementary Figure S2A**]. The number of physicians or therapists increased at centers with larger surgical volumes (**Supplementary Table S3**).

Most centers [31/33 (94%)] used microelectrode recording (MER) to identify appropriate brain areas for implantation. Only one center preferred to implant using intraoperative magnetic resonance imaging (MRI) or computed tomography (CT) for lead localization (**Supplementary Figure S2B**). Leksell SurgiPlan and Stealth were the two most popular planning software programs utilized for stereotactic neurosurgery [26/32 (81%); **Supplementary Figure S2C**]. Approximately 5% (95% CI 5–10%) of all procedures were reported as unsatisfactory related to hardware (1.6% of all cases, 95% CI 1–2%) or surgery-related (1% of all cases, 95% CI 1–2%) complications (**Supplementary Figure S2D**). Neurologists were responsible for postoperative DBS programming in over half of the centers (21/32 [66%]). Most teams offered DBS programming, DBS troubleshooting, and non-DBS outpatient movement disorder evaluations [28/29 (97%), 22/29 (76%), and 23/29 (79%), respectively]. A large proportion of centers also endorsed conducting preclinical research [23/29 (80%)]. Nearly half of the DBS centers [14/29 (48%)] did not provide rehabilitation services for DBS patients. It was unclear if the teams worked consistently in a multidisciplinary fashion and how multidisciplinarity was defined.

Since DBS is a well-established treatment option for PD, essential tremor (ET), and dystonia, we further investigated and compared the preferred clinical workflow for these three disorders. Simultaneous bilateral lead implantation was predominantly performed for PD [28/29 (97%)], ET [23/29 (79%)], and dystonia [28/29 (97%); **Supplementary Figure S2E**].

Various DBS devices are available for clinicians and patients to use. Device reliability was the most important factor in the decision [23/29 (80%)], followed by customer support [17/29 (59%)] and programming feasibility [16/19 (55%)]. However, patient preference, as well as insurance coverage (i.e., the final cost to the patient and other funding considerations), played a minor role. Unsurprisingly, economic issues affected DBS centers in developing countries (p = 0.000023). Only one center in Iran and one in Turkey decided on device selection based on government-related factors (**Supplementary Table S4**). Insurance and government support covered the expenses for device and hospital services in all of the DBS centers in developed countries (p = 0.005) making DBS potentially more accessible to patients in these regions (**Supplementary Table S5**). Conversely, in developing countries, out-of-pocket payment served as the main form of reimbursement (p = 0.000023).

Major Obstacles for DBS Accessibility and Development

More than half of responders [16/29 (55%)] indicated that the main limiting factors for access to surgery included: (1) insufficient referrals due to limited understanding of DBS by general medical providers [20/29 (69%)]; (2) fear of brain surgery by patients [17/29 (59%)]; and (3) high cost of the device and procedure [12/29 (41%)], with cost issues most notable in developing countries (p = 0.001; **Supplementary Table S6**). DBS is an established treatment for some neurological movement-related diseases and is a promising investigational approach for psychiatric disorders (e.g., OCD and depression). Lack of funding was a major barrier to increasing scientific research. The survey also uncovered difficulties in recruiting patients and in publishing results (**Supplementary Table S7**).

DBS in China and Japan

DBS was introduced in China in 1998 (source of information Beijing Tiantan Hospital) and has undergone considerable development in the past 20 years. In the last 3 years, the number of DBS centers in China has increased, with over 200 DBS leads implanted per year/center. More than 100 Chinese hospitals performed less than 10 cases annually (**Figure 1A**). In contrast, the number of DBS implantations in Japan has decreased since 2015 (**Figure 1B**). While 966 cases underwent DBS implantation in 2015, there were only 761 cases in 2018 (according to Medtronic Japan). Among the 44 institutions approved as training centers (≥18 cases/3 years) by the Japanese Society for Stereotactic and Functional Neurosurgery (JSSFN) in 2019, most centers performed less than two cases per month. Although our survey did not investigate factors associated with these

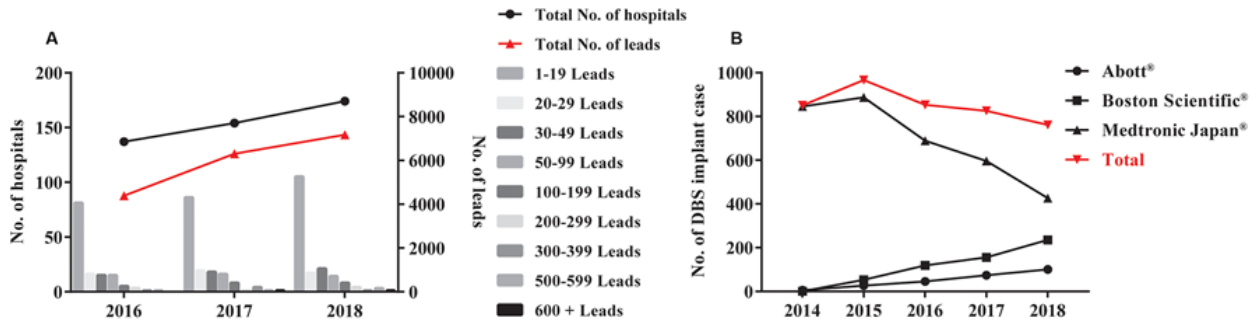

FIGURE 1 | The number of deep brain stimulation (DBS) implant cases in China **(A)** and Japan **(B)**. **(A)** DBS surgery became more popular in China in recent years. Histogram with different gray bars shows the number of hospitals performing DBS electrode implantation each year on the left Y-axis. The total number of hospitals is then indicated by the black "•" The total number of implanted leads is shown by the red "•" on the right Y-Axis. **(B)** Japan performed less DBS surgeries since 2015. Red "▼" shows the total number of DBS implanted cases between 2014 and 2018 in Japan. Black "•," "■," and "▲" indicate each number of DBS implant cases of three main manufacturers (Abott®, Boston Scientific®, and Medtronic Japan®, respectively) in Japan.

small numbers, possibly, these numbers were influenced by the introduction of focused ultrasound (FUS) and other advanced therapies, e.g., levodopa gastrointestinal gel. Since November 2016, when the FUS obtained approval for the treatment of essential tremor, 210 cases were treated with FUS (November 2016 to October 2019).

DBS in India

The first DBS surgery in India was performed in a private hospital, Jaslok Hospital and Research Center, by Prof. Paresh Doshi (Ganapathy, 2013). There has been a steady increase in interest in DBS over the past 20 years. Currently, 3/4 premier state-run neuroscience centers perform DBS surgeries regularly, which include All India Institute of Medical Sciences in New Delhi, National Institute of Mental and Neurosciences (NIMHANS) in Bengaluru, and Sree Chitra Tirunal Institute for Medical Sciences and Technology in Trivandrum. In total, 12 centers offer DBS with at least 10 DBS surgeries occurring per year, and another 12–15 centers with much fewer numbers of cases per year. Generally, most provide DBS surgeries for all movement disorders. Two centers, Jaslok Hospital and NIMHANS, also perform DBS for psychiatric disorders. The DBS surgical programs in most hospitals are actively supported by movement disorder specialists. Though not all surgeons have formal fellowship training in functional neurosurgery, the neurologists in most centers have obtained fellowship training specialized in movement disorders, either in India or overseas. The movement disorder fellowship is offered in 8–10 centers in India, whereas Jaslok Hospital provides the unique functional neurosurgical training. Three societies, the Indian Society for Stereotactic and Functional Neurosurgery, the Neuromodulation Society, and the Movement Disorders Society of India, are involved in DBS in India. Two major companies, Medtronic and Boston Scientific, provide most of the DBS implants in India. SceneRay and Abbott are, however, just entering the market. The use of DBS has increased and though an exact estimate cannot be made, approximately 450 DBS surgeries/year are being performed in India.

India has a legacy of lesional surgeries for movement disorders (Doshi, 2009). Most centers perform such interventions mainly for unilateral dystonia, including task-dystonia, and tremors (Doshi et al., 2017). All centers refrain from offering bilateral lesional surgeries. Compared to developed nations, the number of patients undergoing lesional surgery (or DBS) for essential tremors is very low.

Most DBS surgeries are self-funded. However, there is currently an increasing tendency for insurance reimbursements. Owing to the social customs of family support in India, many PD patients are funded by their children who are now earning adequately. There is also a growing trend towards seeking DBS for a moderately advanced disease by neurologists and patients compared to 10 years ago.

DISCUSSION

These data provide a detailed and previously unknown description of DBS practices and practice patterns in centers from Asia and Oceania. These data will serve as a reference for addressing the challenges and limitations of DBS in these regions. We also hope that through the DBS Think Tank East there will be dialogue including relevant stakeholders and medical societies to discuss potential solutions and opportunities to the challenges uncovered by the survey. Though outcomes including clinical effectiveness and adverse events were not obtained, we believe that the information highlights important challenges and barriers in the field.

Of the 51 countries identified, only Japan, Korea, Israel, Australia, and New Zealand are considered "developed countries" (UNDP, 2018). These are also the most active countries in terms of DBS usage for both clinical practice and research. China has had a rapid increase in surgical volume and publications since 2009. This increase coincides with the period when local manufacturers, including PINS and SeneRay, produced less expensive and more accessible products. A DBS neurostimulator (battery source) and bilateral leads have an estimated expense of 250,000–350,000 Renminbi (RMB;

approximately $32,000–42,000 USD). It is estimated that from 1998 to 2003, approximately 312 patients in China received DBS; from 2003 to 2009, this number increased to approximately 1,700. Following the commercialization of products from Chinese enterprises, over 15,000 patients have received DBS, and over 180 hospitals now offer DBS. Finally, an increasing number of institutions have launched DBS programs in China, but most centers perform less than 10 cases per year and are unclear whether proper teams and adequate quality can be maintained at hospitals with such low volumes. In contrast, the number of DBS cases in Japan has been decreasing over the last few years. This might be due in part to the advent of FUS, but more data are required to understand the underpinnings of the recent decline.

Research on DBS in Asia has been limited. The major barrier for DBS research has been a lack of funding from governments and industry. Our data suggest that 77% (38) of Asian countries have not published on DBS. In comparison, 402 DBS publications from Canada alone were revealed when employing a similar search strategy to ours. DBS in Asia is evolving and many barriers and challenges are remaining. Many countries still do not have access to DBS and most DBS publications favor East Asia and Oceania. In West Asia, Turkey, Israel, and Iran accounted for most of the DBS publications.

Financial cost continues to be a significant barrier to DBS research and its widespread clinical adoption. The hardware is expensive, the surgery is costly, and when factoring in follow-up care these factors add up to a significant expense. Some experts have however argued that long-term there can be savings made from DBS (e.g., fewer medications, decreased morbidity). Cost is problematic in the developing world, where few citizens can afford the hardware and treatment costs. This situation is unfortunate given the high prevalence of movement disorders and other conditions amenable to DBS intervention. The development of low-cost hardware may aid in ameliorating this problem. Lower cost hardware, is, according to our data, mostly available in China.

One issue that stood out was the lack of referrals (20/29; 69%) for DBS. This was a major impediment to DBS clinical practice in these regions. Once referred and implanted another interesting issue that emerged was that DBS programming was performed by a mix of 66% neurologists and 34% neurosurgeons. This pattern of care differs from practice patterns in Western countries, where teams are composed mainly of nurses and neurologists and it is rare to have neurosurgeons programming patients. It was surprising that many Asian centers did not have full multidisciplinary teams. The evolution of DBS in these regions may eventually favor larger expert centers; however, this will be addressed by a future survey. Educational outreach is a critical unmet need across these regions and is necessary to improve access and understanding of DBS therapies.

Our survey has several limitations. First, we are only able to obtain information from limited countries. We attempted to gather information about manufacturers used in Asian countries. However, this information is considered confidential by some manufacturers. Similarly, the number of patients implanted would be a better indicator of the popularization of DBS, but some manufacturers prefer to share with us the number of leads. Second, we selected the dates in our search strategy based on likely capturing DBS centers with "active" and publications in recent years as supposed to include all articles. We are aware that this strategy may filter out some centers with prior DBS experience and publications before 2013 (e.g., paper from Thailand published in 2010; Nunta-Aree et al., 2010).

In clinical practice, microelectrode recordings remain widely used for target refinement during surgery (94%) and the DBS programming team consists primarily of neurologists (66%) and neurosurgeons (34%). There was a lack of community referrals to tertiary centers and this factor was identified as the most common limitation for the widespread use of DBS in Asia. In China, there has been an increasing number of centers performing DBS surgeries. In contrast, the number of DBS cases in Japan has been decreasing, which might be related to the use of novel non-craniotomy approach FUS lesioning and the availability of other advanced treatment options. Whether this new technology has impacted DBS use was not directly examined by our survey. Appropriate referrals, access, infrastructure, and the lack of full multidisciplinary DBS teams are common limitations for DBS in Asia. Most centers in China and Japan performed less than 10 DBS cases per year and it is unclear if low volumes will result in suboptimal outcomes, which is a worry of experts in the field. We know that the success of DBS relies on excellent patient selection and the utilization of large multidisciplinary teams. Such teams seem to be lacking in Asia and their establishment this will be a critical next step for the field to evolve in this region. Global educational and training programs will be needed to scale up DBS and a focused effort will be necessary to address financial barriers and improve the quality of care delivery.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving humans were reviewed and approved by the ethics committee of Ruijin Hospital Shanghai Jiao Tong University School of Medicine. Completion of the survey by participants was considered as implied consent, which adhered to the guidelines for the American Association for Public Opinion Research (AAPOR).

AUTHOR CONTRIBUTIONS

CZ, AR-Z, BS, and MO: conception and design. CZ, ZL, and YL: analysis and interpretation. YL, DL, FM, JC, TM, TI, SF, GO, TC, VV, PD, YW, JL, JZ, KF, BP, LA, and AW: data collection.

CZ, ZL, AR-Z, and MO: writing the article. AR-Z, BS, and MO: critical revision of the article. ZL and YL: statistical analysis. All authors have read and approved the final version of the article.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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PERSPECTIVE
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Perspective: Evolution of Control Variables and Policies for Closed-Loop Deep Brain Stimulation for Parkinson's Disease Using Bidirectional Deep-Brain-Computer Interfaces

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A deep brain stimulation system capable of closed-loop neuromodulation is a type of bidirectional deep brain-computer interface (dBCI), in which neural signals are recorded, decoded, and then used as the input commands for neuromodulation at the same site in the brain. The challenge in assuring successful implementation of bidirectional dBCIs in Parkinson's disease (PD) is to discover and decode stable, robust and reliable neural inputs that can be tracked during stimulation, and to optimize neurostimulation patterns and parameters (control policies) for motor behaviors at the brain interface, which are customized to the individual. In this perspective, we will outline the work done in our lab regarding the evolution of the discovery of neural and behavioral control variables relevant to PD, the development of a novel personalized dual-threshold control policy relevant to the individual's therapeutic window and the application of these to investigations of closed-loop STN DBS driven by neural or kinematic inputs, using the first generation of bidirectional dBCIs.

Keywords: brain-computer interface (BCI), beta oscillations, Parkinson's disease, deep brain stimulation, subthalamic nucleus, closed-loop neurostimulation, kinematics, brain-machine interface (BMI)

INTRODUCTION

Continuous deep brain stimulation (DBS) is an established therapy for cardinal motor signs in Parkinson's disease (PD; Krack et al., 2003; Deuschl et al., 2006; Schuepbach et al., 2013; Edwards et al., 2017). Current DBS systems operate in an open-loop manner: the neurostimulator cannot sense the neural signals from the brain that interfaces with the deep brain electrode(s), and which it is modulating. It applies a continuous regular train of electrical pulses of fixed frequency, amplitude, and pulse width, which cannot automatically adjust to different symptoms, the individual's state of activity or medication cycle. These limitations may contribute to dyskinesias and speech,

mood, and cognitive impairments (Weaver et al., 2005; Deuschl et al., 2006; Williams et al., 2010). A major unmet need in neuromodulation for neuropsychiatric diseases is the development of a closed-loop neurostimulator: a bidirectional deep brain-computer interface (dBCI), in which neural signals are recorded, decoded and then used as the input commands for neuromodulation at the same site in the brain (Mussa-Ivaldi et al., 2010; Fetz, 2015).

One challenge for bidirectional dBCIs in movement disorders is the need to discover neural inputs relevant to pathological motor behaviors. Such neural inputs need to be robust, reliable, specific to the individual and their activity state, and which can be recorded during stimulation. Unlike traditional BCIs where the normal neural code is used to restore function, the neural signals available from DBS leads in PD represent pathological neural code; the desired neural activity has to be extrapolated from animals or simulations (Wichmann et al., 1994; Nini et al., 1995; He, 2014; Feingold et al., 2015). Another challenge for bidirectional dBCIs is to discover control policies (patterns and parameters of neurostimulation) that will optimize specific motor behaviors.

In this perspective, we will outline the work done in our lab regarding the evolution of the discovery of neural and behavioral control variables relevant to PD, the development of a novel personalized dual-threshold control policy relevant to the individual's therapeutic window and the application of these to investigations of closed-loop STN DBS driven by neural or kinematic inputs, using the first generation of bidirectional dBCIs.

Deconstructing the Resting-State Neural Code Relevant to Parkinson's Disease

Exaggerated neuronal oscillations and synchrony in alpha and beta frequencies (8–30 Hz) have been demonstrated in the sensorimotor network during the resting state in PD, which can be termed the resting state beta oscillopathy (Bergman et al., 1994; Nini et al., 1995; Bevan et al., 2002; Levy et al., 2002; Brown, 2003; Schnitzler and Gross, 2005). Many early reports were limited to one short neural recording and it was questioned whether the beta oscillopathy was a stable feature across individuals (Priori et al., 2013). Our intra-operative recordings demonstrated that the resting state beta oscillopathy was stationary, in that it re-occurred, unchanged, over time despite intervening periods of movement or neurostimulation (Bronte-Stewart et al., 2009). In freely moving individuals with PD, the resting state beta spectral profile was conserved in different resting postures (Quinn et al., 2015). It was also similar and coherent between the STNs of an individual, although different among individuals, and was coherent with the motor cortex-STN hyper direct pathway efferent projection sites, suggesting that it is a property of the widespread sensorimotor network (de Solages et al., 2010; Whitmer et al., 2012). A computerized peak detection algorithm confirmed the presence of a resting state beta oscillopathy in 129 out of 130 STNs (Shreve et al., 2017).

Initially, it was debated whether the beta oscillopathy was an epiphenomenon or linked to Parkinson's disease pathophysiology. Evidence suggesting that it is related to progressive pathophysiology was supported by the demonstration that it only emerged several days after inducing Parkinsonism in rodents and was not evident after acute blockade of dopamine receptors (Mallet et al., 2008), and from neural recordings in the non-human primate model of progressive Parkinsonism (Dorval et al., 2015; Muralidharan et al., 2016; Wang et al., 2017). Intra-operative bilateral STN neural recordings (112 STNs) in individuals with PD demonstrated that there was significantly greater resting-state beta band power in the more affected STN when compared to the lesser affected STN, further suggesting a relationship to disease progression (Shreve et al., 2017). As part of a longitudinal study, the resting state beta band power increased over time in the untreated STN, in two individuals with PD, who had bilateral STN DBS leads placed but who chose to have only one side activated (Trager et al., 2016).

The demonstration that the STN beta oscillopathy was attenuated by therapeutic doses of dopaminergic medication and intensities of STN DBS established it as a biomarker of the Parkinsonian state (Brown et al., 2001; Levy et al., 2002; Priori et al., 2004; Kühn et al., 2006; Wingeier et al., 2006; Bronte-Stewart et al., 2009; Giannicola et al., 2010; Eusebio et al., 2011; Whitmer et al., 2012; Quinn et al., 2015). This resulted in the use of the resting state STN beta oscillopathy as a relevant neural input for adaptive DBS using a single threshold control policy, externalized leads, and a customized external neurostimulator in the acute, peri-operative state (Little et al., 2013). Consequently, the control policy that was embedded in the first generation of fully implanted bidirectional dBCIs (Activa™ PC+S-NexusE, Medtronic PLC, Minneapolis, MN, USA), was a single linear discriminator, corresponding to a single threshold of beta power. Using this we demonstrated that 60 min of closed-loop STN DBS was superior to clinical open-loop DBS for progressive bradykinesia (**Figures 1B,C**).

Bradykinesia (V_{rms}) improved dramatically ON compared to OFF DBS (**Figures 1A,B**), and improved further on closed-loop DBS (**Figure 1C**). Progressive bradykinesia, or the waxing-waning and decreasing amplitude and speed of movement over time, was measured as the coefficient of variation of angular velocity (CV_{vel}). CV_{vel} was lower on closed-loop compared to open-loop DBS (12% compared to 24%, respectively) demonstrating the superiority of closed-loop DBS. Both forms of DBS improved progressive bradykinesia compared to OFF DBS (CV_{vel} = 121%). There was a 63% reduction in the total electrical energy delivered during closed-loop DBS using a single active electrode compared to the optimized clinical DBS settings, which used a triple monopole.

Decoding Neural Activity During Incremental Neuromodulation for Bradykinesia Led to the Development of the Dual-Threshold Control Policy Algorithm for Bidirectional dBCIs

Initially, it was difficult to discern between the effect of intensity and the effect of duration of STN DBS on the attenuation of beta

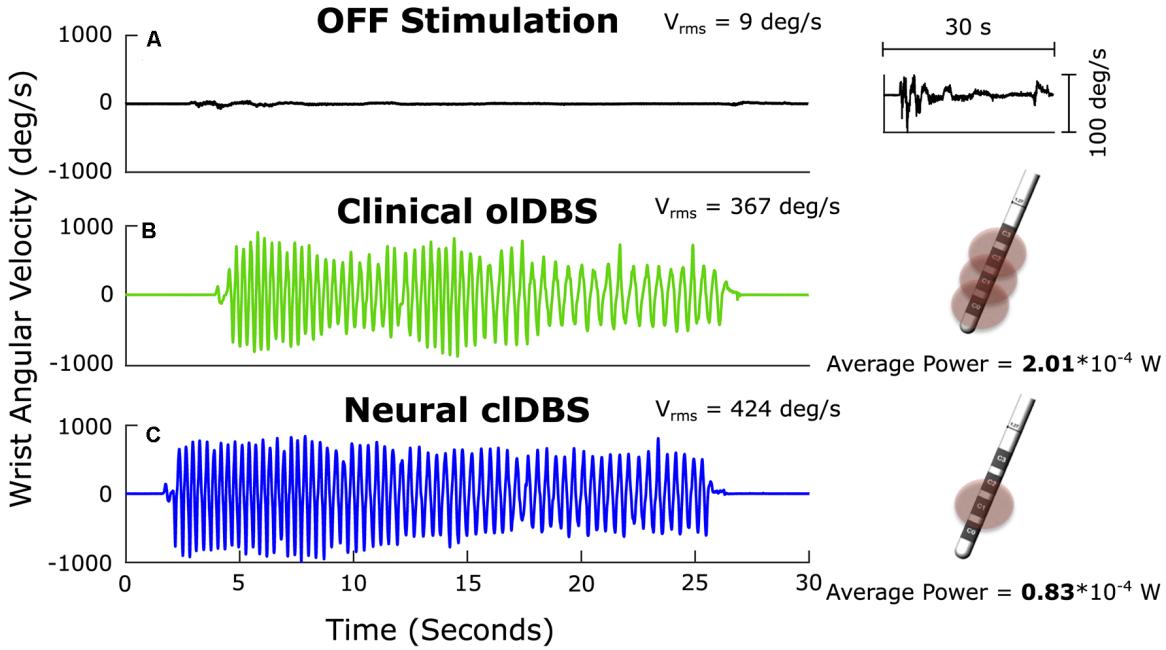

FIGURE 1 | Angular velocity traces measured during repetitive wrist flexion-extension OFF deep brain stimulation (DBS; **A**); the insert on the right at higher magnitude demonstrates the severe progressive bradykinesia, ON open-loop STN DBS (oIDBS; **B**) and after 60 min of closed-loop STN DBS (cIDBS) **(C)**. Schematic of the DBS lead demonstrates the use of a triple monopole during oIDBS and a single monopole during cIDBS. V_{rms}: the root mean square angular velocity averaged over the trial.

band power, as there is a cumulative effect of longer periods of DBS on beta band power attenuation (Bronte-Stewart et al., 2009; Eusebio et al., 2011). We demonstrated that resting-state beta band power was attenuated in a dose-dependent manner during randomized epochs of different intensities of STN DBS (Whitmer et al., 2012).

A challenge for closed-loop DBS is to maintain a therapeutic effect while varying stimulation in real-time. Different control policies may have different goals and time scales. For instance, control policies that adjust DBS in real-time based on the appearance of symptoms [e.g., tremor or freezing of gait (FOG)] or based on rapid fluctuations of beta band power require a faster time scale (Malekmohammadi et al., 2016; Tinkhauser et al., 2017a; O'Day et al., 2020a; Petrucci et al., 2020a) compared to a control policy that adjusts DBS amplitude based on longer changes in beta band power due to fluctuating dopaminergic medication levels or the sleep-wake cycle (Arlotti et al., 2018; Velisar et al., 2019; Gilron et al., 2020). The control policies discussed in the next sections focused on time scales on the order of milliseconds. Initial single threshold control policies allowed for an "on-off" switch of neurostimulation based on the resting state beta power (Little et al., 2013); however, complete attenuation of STN beta power and/or decreasing DBS intensity toward completely off may not be optimal for motor performance (Blumenfeld et al., 2017). We developed a novel, customized, dual-threshold control policy based on the inverse relationship between DBS intensity and beta band power, and the direct relationship between DBS intensity and the improvement of bradykinesia off medication (Velisar et al., 2019). The effect of increasing DBS intensity on bradykinesia identified a minimum DBS intensity (V_{min}) that resulted in the minimally acceptable improvement in bradykinesia in each individual. The beta power measured at V_{min} was chosen as the upper beta power threshold. The lower beta threshold was the beta power halfway between that corresponding to V_{min} and that corresponding to V_{max}. V_{max} represented the DBS intensity above which adverse effects occurred for that individual. This resulted in a customized dual threshold policy that established a therapeutic window of DBS intensity where improvement in bradykinesia was acceptable. The policy instructed the dBCI to increase intensity when beta power exceeded the upper threshold, to stay constant when beta power remained between the dual thresholds and to decrease when beta power fell below the lower threshold. We implemented the customized dual threshold control policy and reported successful closed-loop STN DBS for bradykinesia and tremor in PD using a chronically implanted bidirectional dBCI [Activa™ PC+S-NexusD3, Medtronic PLC, Minneapolis, MN, USA (Velisar et al., 2019)]. Closed-loop DBS resulted in ∼57% less total energy delivered compared to open loop DBS. We have recently demonstrated the superiority of closed loop STN DBS over clinical DBS for FOG in an individual; this experiment used beta power inputs and the customized dual threshold policy based on titrations of DBS intensity and measures of gait impairment and FOG (Petrucci et al., 2020b).

The temporal dynamics of beta band power (termed beta bursts) have been associated with clinical assessments of

disease severity and with kinematic measures of bradykinesia, gait impairment, and FOG (Tinkhauser et al., 2017b; Anidi et al., 2018). There is a similar dose dependency between DBS intensity and beta burst duration both during rest and movement: increasing intensities of STN DBS were associated with shorter mean beta band durations and improved bradykinesia (Anderson et al., 2020). This dose-dependency of beta bursts suggests that a similar dual-threshold control policy in bidirectional DBCIs that monitors prolonged beta burst durations, as opposed to beta power specifically, could keep the DBS intensity within a therapeutic window.

Optimization of Control Variables and Policies in Bidirectional dBCIs in Freely Moving Activity States

The ultimate goal of closed-loop DBS using a bidirectional dBCI is that neurostimulation will seamlessly adjust its parameters specific to the individual, their activity state, and their medication cycle (Arlotti et al., 2018). The ability to record synchronized neural and kinematic signals in freely moving individuals with PD using the implanted, sensing dBCI (Activa™ PC+S, Medtronic PLC), led to the discovery of neural and kinematic signals that corresponded to abnormal movements such as bradykinesia, gait impairment, and FOG. These recordings have demonstrated that STN beta band power can be tracked during ongoing movement in PD, that the peak frequency of the beta band did not change among rest, or finger, limb and axial movements, and that there was a subject-specific band of elevated beta power that was conserved throughout a variety of gait tasks (Blumenfeld et al., 2017; Anidi et al., 2018; Neuville et al., 2020). These contributions demonstrate that control policy algorithms in closed-loop DBS will be able to track, and do not need to adjust the frequency of, the beta band neural input in freely moving people with PD.

Such synchronized recordings also revealed STN neural signatures that differentiated individuals with PD who exhibit FOG (freezers) from those who did not freeze (non-freezers) during non-freezing gait. Beta band power was lower, mean beta burst durations were longer, and there was greater beta Sample Entropy in freezers compared to non-freezers during non-freezing gait; freezers' gait was also more arrhythmic than that of non-freezers, even during "normal" walking (Syrkin-Nikolau et al., 2017; Anidi et al., 2018). In freezers, mean beta band burst durations were longer and alpha band (8–12 Hz) Sample Entropy was higher during periods of FOG, compared to during non-freezing gait. There was no difference in burst duration between the two groups in the resting state and burst duration was not correlated with mean power.

During open loop STN DBS at both 60 Hz and 140 Hz, gait arrhythmicity and FOG improved and beta band power and burst durations decreased in freezers (Anidi et al., 2018; O'Day et al., 2020b). The normal gait rhythmicity and shorter burst durations were left unchanged during DBS in the non-freezers. This revealed a functional relevance of beta-band burst durations as neural inputs for closed-loop DBS for gait impairment and FOG using bidirectional dBCIs. Sixty Hertz DBS resulted in improved rhythmicity in both progressive limb bradykinesia and during forward-walking tasks (Blumenfeld et al., 2017; Anidi et al., 2018; O'Day et al., 2020b). A superior effect of 60 Hz to high-frequency DBS for FOG has been reported (Moreau et al., 2008; Xie et al., 2015), suggesting the need for control policies to include adjustments in neurostimulation intensity and frequency. A method of frequency-switching would allow a bidirectional dBCI to vary both intensity and frequency for optimal behavioral improvement and finer granularity of the effects of DBS.

Using Relevant Behavioral Signals as Inputs to dBCIs in Parkinson's Disease

Kinematic signals specific to pathological episodic motor behaviors in PD, such as tremor and FOG, may be useful inputs to drive closed-loop neuromodulation. Resting tremor is a cardinal motor feature of PD and is an ideal behavioral input for closed-loop DBS: it is easily measured using a smartwatch, may be intermittent, and is different among individuals with PD, suggesting continuous neurostimulation may not be necessary. This was confirmed in the first behaviorally driven closed-loop DBS study, where resting tremor served as the input to the dBCI (Activa™ PC+S-NexusD system, Medtronic PLC) and dual thresholds of tremor intensity defined the control policy (Malekmohammadi et al., 2016). Resting tremor was successfully attenuated and the time that the demand-based DBS system was activated varied from 11% to 99% (average of 51.5%) of the time the continuous open-loop DBS was on. This highlights the possibility for more precise therapy for individuals with tremor-dominant PD, who may benefit from a dBCI system that is not continuous. During resting tremors, underlying beta oscillations may be attenuated and neural inputs to dBCIs may not adequately control tremors (Shreve et al., 2017; Velisar et al., 2019). Enabling the capability for an additional or back up behavioral input may be an advantage for future bidirectional dBCIs.

Neural and Kinematic Inputs Using Intensity- and Frequency-Based Control Policies to Provide Closed-Loop STN DBS for FOG in Parkinson's Disease

The progress in the discovery of relevant control variables and policies for closed-loop DBS in PD fueled technological advances in the capabilities of bidirectional dBCIs. This has led us to the first series of investigations into the safety, feasibility, and efficacy of both neural and kinematic closed-loop STN DBS for FOG, using relevant neural and kinematic inputs and control policies that modulate either DBS intensity or frequency, using the investigative, next-generation bidirectional dBCI, the Summit™ RC+S system (Medtronic PLC, Minneapolis, MN, USA; **Figure 2**; O'Day et al., 2020a; Petrucci et al., 2020a).

The Summit™ RC+S system can run both single and dual-threshold embedded algorithms. Similar to the Activa™ PC+S-Nexus-D/E systems, the Summit™ RC+S system has an Application Programming Interface (API) that allows for the development of distributed algorithms. We designed a

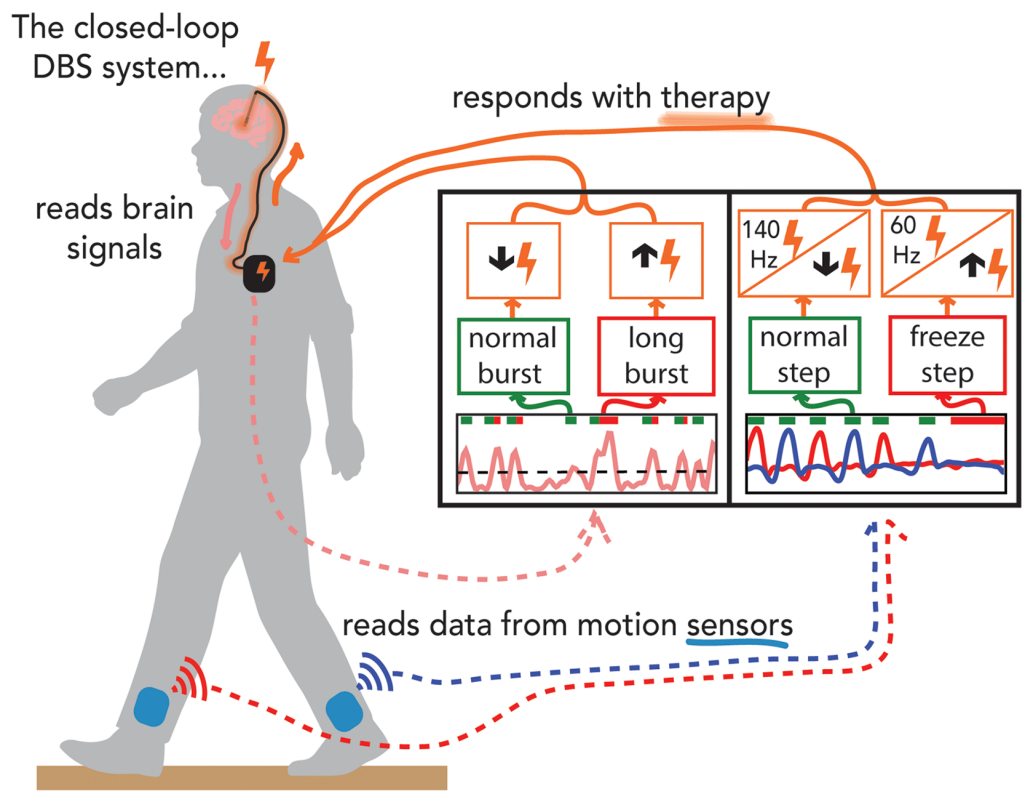

FIGURE 2 | Demonstration of experiments performed on the preclinical benchtop system using the Summit application programming interface. Schematic of the fully implanted bidirectional deep brain-computer interface (dBCI) with data from the benchtop experiments. Left-hand panel: the neural input was beta band burst duration from the filtered local field potential; the single threshold control policy decided whether a neural burst was normal or long (pathological), and adapted closed-loop deep brain stimulation (clDBS) by decreasing or increasing stimulation intensity respectively. Right-hand panel: the kinematic input was the shank angular velocity streamed from wearable inertial measurement units; a dual-threshold control policy was based on whether the step was determined to be normal, uncertain, or part of freezing of gait episode and adapted clDBS by either **(I)** decreasing, not changing, or increasing stimulation intensity, OR, **(II)** by switching to 140 Hz, staying unchanged or switching to 60 Hz, respectively (right panel).

preclinical benchtop system using the accompanying Summit API (Medtronic Inc.) that allows for external control of the RC+S neurostimulator using a PC-in-the-loop (**Figure 2**). The benchtop system played back previously recorded neural data and recorded output stimulation from the developed system. We used STN beta burst durations as the neural inputs and developed a novel faster time scale single threshold control policy algorithm that only increased stimulation intensity after the burst duration exceeded the inferred normal duration from simulated 1/f data, red bars in the left-hand panel in **Figure 2** (Anderson et al., 2020). The benchtop system successfully adjusted stimulation in real-time in response to prolonged beta burst durations and demonstrated the feasibility of the algorithm by responding to pre-recorded STN data from an individual with PD (Petrucci et al., 2020a). We also successfully demonstrated for the first time the feasibility of kinematic closed-loop DBS for FOG using kinematic inputs relevant to impaired gait or FOG and policies that responded with adjustments of stimulation frequency or current intensity (**Figure 2**, right-hand panal) (O'Day et al., 2020a). This was done using real-time human subject kinematic data and kinematic data previously recorded from an individual with PD with gait impairment and FOG, allowing for real-time testing and iteration of these novel control policies using the test bench version of the Summit^{TM} RC+S dBCI.

CONCLUSION

The ability to record neural signals from DBS leads implanted in deep brain structures has made it possible to deconstruct the neural code relevant to PD and establish that the STN beta oscillopathy is a robust and reliable input for closed-loop DBS using bidirectional deep Brain-Computer Interfaces (dBCIs) in freely moving people. This led to the first demonstration of the feasibility and efficacy of closed-loop DBS for progressive bradykinesia in PD, using beta band power as the input, a single threshold control policy, and a fully embedded bidirectional dBCI. Synchronized neural and kinematic recordings during incremental DBS intensities in freely moving individuals with PD resulted in novel customized dual-threshold control policy algorithms for closed-loop DBS, where DBS intensity fluctuated within a personalized safe and therapeutic window, driven by relevant beta band power or burst duration inputs. Beta driven closed-loop DBS using the dual-threshold algorithm and an implanted dBCI was demonstrated to be safe, feasible,

and efficacious for bradykinesia, tremor, and FOG. The dual threshold algorithm was also used to demonstrate the efficacy of closed-loop DBS for tremor using tremor power as the input. Neural and kinematic characterization of gait impairment and FOG in PD and during 60 Hz and 140 Hz DBS has contributed to personalized neural and kinematic inputs, and frequency and intensity-based control policies for closed-loop STN DBS therapy for FOG in PD using next-generation bidirectional dBCIs.

The advances in discovery, innovation, and collaboration have led to the next generation of fully embedded investigative bidirectional dBCIs, in which both single and dual-threshold control policy algorithms are available (Percept^{TM}, Summit^{TM} RC+S, Medtronic PLC, Minneapolis, MN, USA). Evolution in the understanding of relevant inputs and control policies in the first generation bidirectional dBCIs for PD and epilepsy has fueled similar discoveries for treatment of other neuropsychiatric disorders (Kundu et al., 2018; Rudebeck et al., 2019; Senova et al., 2019; Mankin and Fried, 2020). Advances in the understanding of the oscillopathies and circuitopathies of neuropsychiatric diseases are developing in parallel with advances in bidirectional dBCI technology. This is contributing to a paradigm shift in therapy, which will be more precise, customized to an individual's neural code, and will seamlessly adjust to their state of activity and medication cycle.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Stanford University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HB-S, MP, JO'D, JP, YK, KW, GO and SH contributed to the conceptualization of the work and the writing and editing of the manuscript. MP, JO'D, MA, and KW contributed to the visualization of the results. MA contributed to software and data curation, as well as formal analysis.

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Conflict of Interest: Dr. HB-S serves on the Scientific Advisory Board for Medtronic PLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Human Neuroscience

BRIEF RESEARCH REPORT
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The UF Deep Brain Stimulation Cognitive Rating Scale (DBS-CRS): Clinical Decision Making, Validity, and Outcomes

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To more efficiently communicate the results of neuropsychological assessment to interdisciplinary teams, the University of Florida Neuropsychology Service developed a Deep Brain Stimulation-Cognitive Rating Scale (DBS-CRS). This tool condensed results of a 3-h exam into a five-point scale ranging from 1 (least) to 5 (most) cognitive concern for DBS surgery. In this study, we evaluated the role of the DBS-CRS in clinical decisions by the interdisciplinary team to proceed to surgery, its relationship to objective neuropsychological scores, and its predictive utility for clinical outcome. We retrospectively examined 189 patients with Parkinson's disease who were evaluated for DBS candidacy (mean age 64.8 [*SD* 9.2], disease duration 8.9 years [*SD* 5.0], UPDRS-Part III off medication 38.5 [*SD* 10.5], Dementia Rating Scale-II 135.4 [*SD* 6.0]). Approximately 19% of patients did not proceed to surgery, with neuropsychological red flags being the most commonly documented reason (57%). Patients who underwent DBS surgery had significantly better DBS-CRS scores than those who did not ($p < 0.001$). The two strongest and unique neuropsychological contributors to DBS-CRS ratings were delayed memory and executive function, followed by language and visuoperception, based on hierarchical linear regression that accounted for 77.2% of the variance. In terms of outcome, DBS-CRS scores were associated with higher quality of life, less severe motor symptoms, and better daily functioning 6 months following DBS surgery. Together, these findings support the construct and predictive validity of the DBS-CRS as a concise tool for effectively communicating pre-DBS cognitive concerns to an interdisciplinary team, thereby aiding decision making in potential DBS candidates.

Keywords: Parkinson's disease, deep brain stimulation, cognition, neuropsychology, scale validation

INTRODUCTION

Deep brain stimulation (DBS) is a powerful treatment which can be used for many of the motor symptoms, and also the motor fluctuations, associated with Parkinson's disease (PD). DBS involves the implantation of electrical leads deep into the brain and can be applied to one of several target sites—typically the subthalamic nucleus (STN) or the globus pallidus internus (GPi); the

DBS leads deliver high-frequency stimulation and are controlled by a pulse generator usually implanted in the chest wall. Since approval by the U.S. Food and Drug Administration in 1997, more than 150,000 DBS surgeries have been performed, and careful patient selection has emerged as a major determinant for clinical success (Wagle Shukla and Okun, 2016). Selection involves precise diagnosis by fellowship-trained movement disorders neurologists, an assessment of medication response, an interdisciplinary screening, optimal pre-surgical medication management, and formal neuropsychological testing (Okun et al., 2005). Potential DBS candidates are screened for accurate diagnosis, functional disability, and duration, severity, and progression of motor and non-motor symptoms. Many centers follow at least a minimal interdisciplinary team approach, considering neurological, neurosurgical, psychiatric, occupational/physical therapy, and neuropsychological assessment (Abboud et al., 2014).

A major goal of pre-DBS neuropsychological testing is to provide the patient and the treatment team with information pertinent to the risk-benefit ratio of pursuing surgery; this includes whether patients can successfully meet pre- and post-operative demands (i.e., informed consent, medication and device adherence, coping with stress). It also includes the identification of any cognitive or psychological contraindications to DBS (i.e., dementia or cognitive profiles atypical for PD, thus suggestive of another disease) (Tröster, 2017). To address these questions, the interpretation of neuropsychological test scores must be individualized to each patient and relies on clinical judgment to place scores in the context of factors such as age, ethnicity, disease duration, educational and occupational attainment, mood, motivation, and situational factors arising during testing. Further, the neuropsychologist will consider qualitative aspects not typically captured by traditional scoring methods (i.e., the patient's approach to a task). While complex and nuanced formulation of the neuropsychologist's conclusions are important to document, a recent nationwide survey revealed that most referral sources pay the greatest attention to diagnosis and to recommendations (Postal et al., 2018). Thus, there is a need for a simplified method to convey a concise summary of DBS screening related neuropsychological findings.

In order to communicate the results of the pre-DBS neuropsychological evaluation more efficiently to an interdisciplinary team, the neuropsychology service at the University of Florida (UF) created a Likert rating scale—the UF Deep Brain Stimulation Cognitive Rating Scale (DBS-CRS)—which ranges from 1 (least) to 5 (most) cognitive concern for surgery. Although the scale has been used at UF clinically since 2013, the relationship of DBS-CRS scores to the decision to proceed to surgery and to objective neuropsychological test scores had not been previously examined. Important questions remain such as whether the recommendations communicated via the DBS-CRS had an effect on the decision to proceed to surgery. Other questions also emerged including what patterns of neuropsychological performance drive clinical decision making, thereby leading to higher (worse) scores on the DBS-CRS and thus potentially raising a red flag for DBS cognitive risk. Finally, we were interested in whether scores on the DBS-CRS were predictive of quality of life post-DBS surgery.

The current study had three aims. First, we wanted to determine how recommendations communicated via the DBS-CRS impacted the decision to proceed to surgery by the interdisciplinary team. We hypothesized that cognitive concerns would emerge as the most common reason for a recommendation against DBS surgery. In these cases, we predicted that higher (worse) DBS-CRS scores would be present. This hypothesis was based on the assumption that other common reasons for not proceeding with DBS surgery (i.e., unusually low response to levodopa, psychogenic/overlay symptoms, unstable psychiatric symptoms, etc.) would have been informally identified and excluded prior to a formal interdisciplinary evaluation for DBS candidacy.

Second, we sought to learn what aspects of the objective neuropsychological examination raised concerns for cognitive risk and thus led to worse scores on the DBS-CRS. In PD, a 'fronto-executive' profile on neurocognitive testing is a common result (Zgaljardic et al., 2003), and this result corresponds to underlying disease pathology and subtle deficits. These subtle deficits would not be viewed as a worrisome risk factor for DBS surgery. What would serve as a 'red flag' would be more blatant atypical profiles (e.g., primary progressive aphasia, memory retention and naming deficits suggestive of Alzheimer's syndrome) or profiles that reflected more pervasive and severe neuropsychological deficits (executive, memory, and otherwise), thus leading to worse ratings. To address this question, we performed regression analyses to examine the contribution of neuropsychological domains to the DBS-CRS score and multivariate analysis of variance to examine the cognitive patterns across DBS-CRS scores.

Third, we examined whether scores on the DBS-CRS were associated with self-reported quality of life during the 6-month period following DBS surgery. We focused on quality of life, as it is closest to a patient centric perspective for this analysis, rather than focusing on strict cognitive outcomes (Floden et al., 2015). We hypothesized that better scores on the DBS-CRS would be associated with improved scores on a validated quality of life measure, the Parkinson's Disease Questionnaire-39 (PDQ-39; Jenkinson et al., 1997). Finally, we also examined mood/motivation scores (Beck Depression Inventory II; Beck et al., 1996; Apathy Scale; Starkstein et al., 1992) and the motor and activities of daily living (ADL) scores derived from the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987).

METHOD

Design

This study involved a retrospective chart review of individuals with PD who were potential DBS surgery candidates at the UF Norman Fixel Institute for Neurological Diseases. Data encompassed information prior to potential DBS surgery (i.e., demographic information, motor symptom severity and ADL scales, medication use, neuropsychological and mood/motivation

measure scores, DBS consensus conference meeting notes, and subsequent DBS surgery notes). Six-month follow-up included quality of life, mood/motivation, and motor scales. Study procedures were approved by the University of Florida Institutional Review Board. **Figure 1** depicts the overall study flow of participants through the various procedures, which are described in detail in the following sections.

Participants

Participants included 189 patients being considered for DBS surgery between 2013 and 2018. This time range was based on when the DBS-CRS began to be used (2013) and an arbitrary stop point of 2018 for data collection. Referral for DBS surgery was generally contingent on motor symptom responsivity to levodopa (typically 30–40% reduction) and absence of conspicuous dementia. All DBS candidates underwent a 2-day "Fast Track" evaluation consisting of independent evaluations by specialists in the following areas: neurology, neurosurgery, neuropsychology, psychiatry, physical and occupational therapy, speech and swallowing therapy, and social work.

To be included, participants had a diagnosis of PD, as determined by UF movement disorders neurologists, and were a candidate for first-time DBS surgery. Exclusion criteria included: (a) history of previous neurosurgery; (b) diagnosis of any additional or comorbid movement disorders (i.e., dystonia or combined PD-essential tremor diagnoses) as determined by UF movement disorders neurologists. For follow-up analyses, patients were excluded if they experienced an intra-operative adverse event (e.g., stroke), post-operative infection, or had bilateral DBS surgery.

Neuropsychological, Mood, and Quality of Life Measures

All DBS candidates completed a battery of neuropsychological, mood, and motivation measures that took between 2 and 3 h to complete. The battery consisted of a cognitive screening measure, the Dementia Rating Scale -2 (DRS-2; Jurica et al., 2001), and standard neuropsychological measures of attention/working memory, delayed recent memory, language, visuoperception, and executive function. Specific tests are shown in **Table 1** and are grouped by cognitive domain based on theoretical considerations (Kirsch-Darrow, 2010; Jones et al., 2014, 2017). Norms for each test were derived from test-specific manuals or previously published norms (Heaton et al., 2004) and then converted to z-scores. For each cognitive domain (e.g., memory, executive function, etc.), a composite score was computed by averaging individual z-scores of tests within a domain to create a domain-specific composite. We did not include the DRS-2 within our domain composites—instead, using it as a general index of cognitive impairment.

Mood and motivation measures included the Beck Depression Inventory II (BDI-II; Beck et al., 1996), the Apathy Scale (AS; Starkstein et al., 1992), and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). Participants also completed a health-specific *quality of life scale*, the Parkinson's Disease Questionnaire -39 (PDQ-39; Jenkinson et al., 1997; Martinez-Martin et al., 2011). Additionally, we obtained Part II scores from the UPDRS (ranging from 0 to 52), an indicator of patient-reported activities of daily life, as another proxy for quality of life. *Motor disease severity* was indexed by the motor exam from the UPDRS Part III (ranging from 0 to 72). On these measures, higher scores indicated greater severity of symptoms and worse quality of life.

UF Deep Brain Stimulation – Cognitive Rating Scale (DBS-CRS)

Patients were assigned a cognitive risk rating based on the neuropsychological findings by a board-certified neuropsychologist (DB) in conjunction with neuropsychology trainees. A five-point Likert scale, known as the Deep Brain Stimulation- Cognitive Rating Scale (DBS-CRS), was used to clearly and simply convey concerns, if any, about the potential cognitive risks for moving forward with DBS surgery. The rating guidelines included the following.

(1) Scores of 1 were reserved for individuals who were deemed "cognitive superstars," with no areas of cognitive impairment.
(2) Scores of 2 reflected minimal cognitive weaknesses that were isolated to the executive domain.
(3) Scores of 3 were given to individuals with more pronounced executive impairments, but consistent with cognitive sequelae of PD.
(4) Scores of 4 reflected cognitive impairment, worse than expected for PD, or atypical impairments (i.e., global memory difficulties) that might be suggestive of other disease entities (i.e., amnestic Mild Cognitive Impairment).
(5) Scores of 5 indicated severe cognitive impairment, including PD dementia, or other cognitive patterns suggestive of other diagnoses (e.g., primary progressive aphasia). Surgery was not recommended.

Regarding memory, poor performance on word list learning tasks was viewed as a more frontally mediated deficit and part of the executive profile based on a robust literature with non-demented PD and older adults (Tremont et al., 2000; Zahodne et al., 2011). However, co-occurrence of impaired recent memory for semantically meaningful information, like novel stories, was viewed as prognostic of a true amnestic profile.

In summary, these DBS-CRS ratings were based on clinical judgment and interpretation of the neuropsychological exam. They served to distil and communicate recommendations by neuropsychology to the interdisciplinary team.

Interdisciplinary Consensus Conference

Each DBS surgery candidate was discussed at an interdisciplinary monthly conference, where the team arrived at a consensus decision regarding recommendations for DBS surgery. Reasons for not proceeding with surgery were coded in the following categories: Cognitive concerns only, Cognitive concerns plus another concern, Neurological concerns only, Psychiatric concerns only, General health concerns only, or Multiple reasons

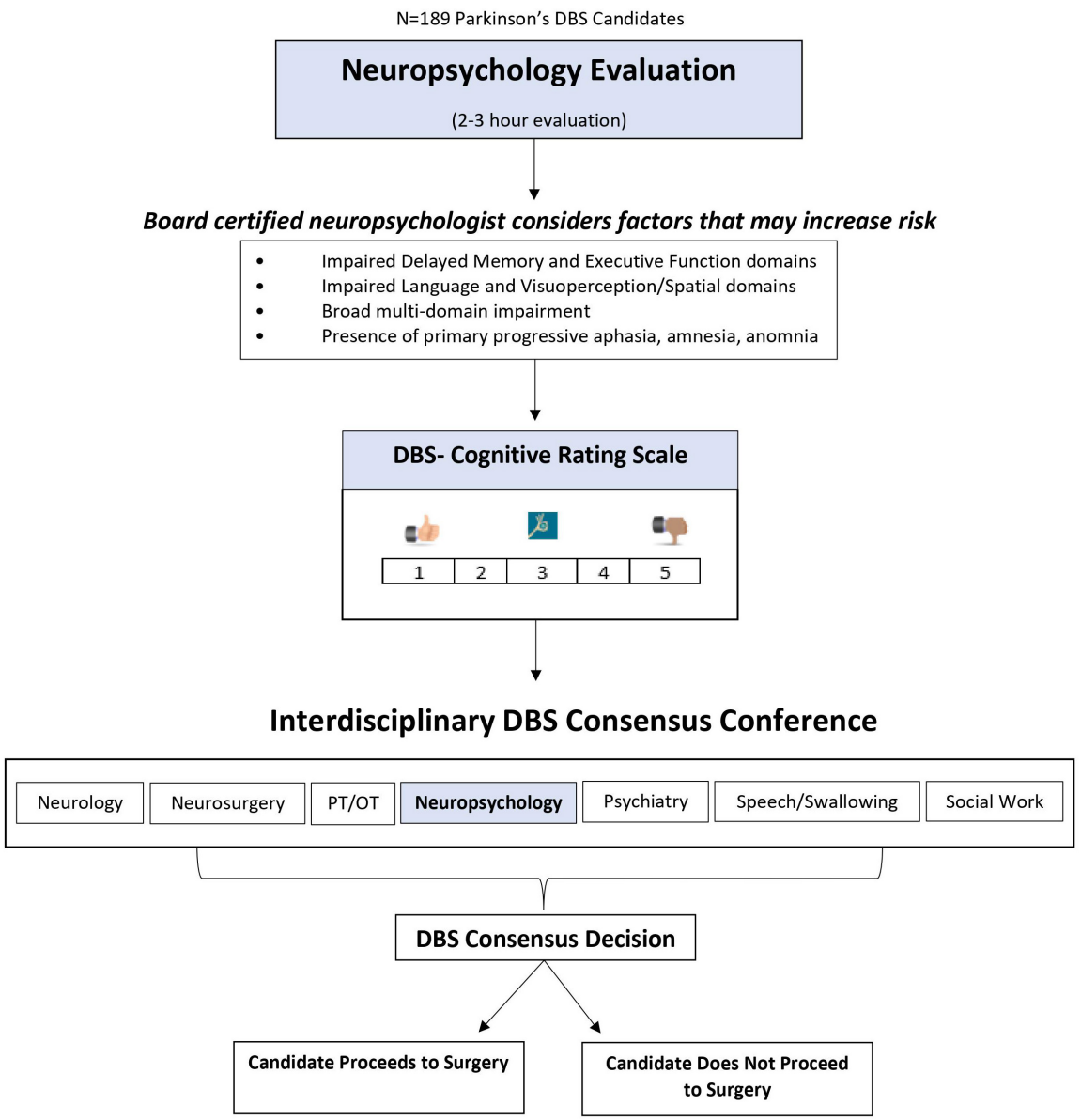

FIGURE 1 | Overview of Neuropsychology's use of the DBS-CRS in deep brain stimulation surgery candidate selection.

(excluding cognitive concerns). Confirmation of DBS surgery was based on medical chart review. Patients who were cleared for DBS surgery but later decided not to proceed were coded as "Patient choice." The reasons for not proceeding ranged from 'fears' about being constrained by the head ring (i.e., claustrophobia) to improved symptoms following dopaminergic medication optimization.

Statistical Analysis

SPSS Version 25 (IBM, 2017) was used to conduct all the following analyses. Due to the clinical nature of our data, not all participants completed all measures. Thus, we used pairwise exclusion criteria for the analyses. Exact analyses used are specified within the results.

RESULTS

Sample Characteristics

As shown in **Table 2**, the final sample of 189 Parkinson's patients ranged in age from 38 to 83, with an average age of 64.8 years. As a group, the participants were well-educated, predominantly male (72.5%), and Caucasian (93.7%), and had an almost 9-year duration of a PD diagnosis. Scores on UPDRS motor exam (III) reflected moderate disease severity when tested off dopamine

TABLE 1 | Neuropsychological tests within each cognitive domain composite.

Cognitive domain	Tests	Raw score used
Delayed Recent Memory	HVLT-R	Delayed Total Recall
	WMS-III Logical Memory	Delayed Total Recall
Executive Functioning	Stroop Test (Interference Trial)	Total Number of Correct Items
	TMT Part B	Completion Time
	Letter Fluency (FAS)	Total Number of Words (All Three Trials)
Language	BNT	Total Correct Spontaneous Responses
	Semantic Fluency (Animals)	Total Number of Words
Visuoperceptual Functioning	Benton JOLO	Total Items Correct
	Benton FRT	Total Items Correct
Attention/Working Memory	WAIS-III Digit Span Forward	Total Number of Points
	WAIS-III Digit Span Backward	Total Number of Points

WMS-III, Weschler Memory Scale-Version III (Wechsler, 1997b); HVLT-R, Hopkin's Verbal Learning Test-Revised (Brandt, 1991); Stroop Test is the Golden version (Golden, 1978); TMT Part B, Trails Making Test Part B (Army Individual Test Battery, 1944); Letter Fluency (FAS) (Spreen and Benton, 1977); BNT, Boston Naming Test (Kaplan et al., 1983); Semantic Fluency (Animals) (Goodglass and Kaplan, 1983); Benton JOLO, Benton Judgment of Line Orientation (Benton et al., 1978); Benton FRT, Facial Recognition Test (Benton et al., 1994); WAIS-III, Weschler Adult Intelligence Scale-Version III (Wechsler, 1997a).

medications. This score improved by 36% when tested "on medication," a general indicator of potentially good responsivity of PD symptoms to DBS surgery (Hartmann et al., 2019). As a group, scores on indices of depression (BDI-II), apathy (AS), and anxiety (STAI) were below clinical cutoff, though there was substantial variability across participants. Approximately 37% of the sample were taking antidepressant medications, and 36.5% were taking anxiolytic medications.

The DBS-CRS ratings across the PD patients ranged from 1 to 5, with a mean of 2.69 (SD = 1.00) and were slightly kurtotic in distribution (z-kurtosis = −1.92, $p < 0.03$; Kolmogorov–Smirnov, $p < 0.001$). Examining the relationship of DBS-CRS scores and other PD disease characteristics revealed that DBS-CRS scores did not significantly correspond with years since diagnosis ($p > 0.05$), but they did correspond to motor symptom severity whether on or off medications (UPDRS Part III; r's = 0.26, p's < 0.001). As a group, performance on a dementia screener (DRS-2) was above the clinical cutoff, though scores ranged from 100 (impaired) to 144 (maximum possible). Scores on individual cognitive composites from the neuropsychological exam indicated worst performance in the executive domain, which is typical for individuals with PD. Results of a repeated measures analysis of variance [ANOVA; $F(3.60,442.63) = 25.54$, $p < 0.001$] and Bonferroni corrected pairwise comparisons reflected the following pattern of significant findings (p's < 0.05): Executive Function < Delayed Memory < (Language = Visuoperceptual = Attention/Working Memory).

The DBS-CRS and Proceeding to DBS Surgery

Of the 189 patients who underwent DBS Fast Track evaluation, 35 (18.5%) did not proceed to DBS surgery. The most common reason was cognitive concern (57%) and included 10 individuals for whom cognition was the sole reason and another 10 for whom cognition was one of multiple reasons. The next most common reason for not proceeding with DBS surgery was patient choice (23%) because of reasons such as claustrophobia (related to the head rim used during surgery) or adequate response to dopaminergic medications. Other patients did not proceed due to psychiatric concerns only (9%), multiple reasons (excluding cognitive concern; 6%), general health concerns (3%), and neurological concerns (3%).

Comparison of characteristics of patients who did and did not proceed to DBS surgery is shown in **Table 2**. Patients who proceeded to DBS surgery (DBS+) had significantly better (i.e., lower) DBS-CRS scores than those who did not (DBS−). Indeed, 85% of the patients who did not proceed with DBS surgery due to cognitive concerns (alone or along with other reasons) received DBS-CRS scores of 4 or 5, with the remainder receiving scores greater than 3.

Further comparisons of the DBS+ and DBS− groups indicated that the two groups differed on motor (UPDRS on and off) and cognitive symptoms. Motor-wise, scores on the UPDRS-III, both on and off medication, were significantly better for those who underwent surgery (DBS+) relative to those who did not (DBS−). Cognitively, patients who had surgery (DBS+), relative to those who did not (DBS−), scored significantly better on the DRS-2 and all neuropsychological domain composites, except visuoperception. In contrast, the DBS+ and DBS− groups were similar across age, education, sex distribution, disease duration, mood scales, and use of anti-depressant and anti-anxiety medications.

Clinical Decision Making (DBS-CRS): Contribution of Neuropsychological Domains to DBS-CRS Scores

To identify what domains of the neuropsychological exam contributed to the DBS-CRS ratings, we performed a hierarchical linear regression. The first block in the model included 'non-cognitive' variables that were significantly correlated with DBS-CRS ratings, based on Spearman rho analyses. These variables included education and scores on the BDI-II, AS, and the STAI (both trait and state scores) and can be conceptualized as 'covariates.' Block 2 included the five cognitive

TABLE 2 | Sample characteristics and comparisons between those who proceeded to surgery (DBS+) versus those who did not (DBS−).

Measure	Overall sample		DBS + (*n* = 154)		DBS− (*n* = 35)		Significance testing (DBS+ vs. DBS−)	
Variable	***Mean/%***	***SD***	***Mean/%***	***SD***	***Mean/%***	***SD***	***Z Statistic^***	***p-Value***
Age	64.79	9.15	64.32	9.01	66.91	9.88	−1.71	0.088
Education (years)	14.94	2.63	14.95	2.61	14.89	2.77	0.32	0.753
Years Since Diagnosis	8.90	4.98	8.65	4.66	10.01	6.17	−1.01	0.312
% Male[1]	72.5%		70.8%		80%			0.512
% Caucasian[1]	93.7%		94.8%		88.6%			0.601
UPDRS III, on medication	24.92	10.27	23.91	9.62	29.45	11.91	−2.71	0.007*
UPDRS III, off medication	38.53	10.54	37.74	9.84	42.00	12.74	−2.07	0.039*
% Change in UPDRS from off to on meds	−35.9%	18.54	−37.2	18.27	−30.0	18.89	1.73	0.083
% Taking Antidepressant Medication[1]	37.0%		36.4		40.0%			0.688
% Taking Antianxiety Medication[1]	36.5%		39.0%		25.7%			0.142
BDI-II, raw total	10.29	7.03	9.97	6.63	11.76	8.62	−0.77	0.444
STAI: State Anxiety, percentile	66.91	30.07	65.81	29.72	72.16	31.67	−1.39	0.164
STAI: Trait Anxiety, percentile	61.96	30.85	60.05	30.75	71.19	30.18	−1.89	0.059
Apathy Scale, raw total	11.84	5.94	11.83	6.03	11.91	5.56	−0.17	0.864
DBS-Cognitive Rating Scale (1 to 5)	2.69	1.00	2.47	0.89	3.66	0.90	−5.88	<0.001*
Dementia Rating Scale-2, raw total	135.36	6.04	136.40	4.83	130.62	8.41	4.29	<0.001*
Cognitive Composites (z-scores)[#]								
Delayed Memory	−0.38	1.07	−0.21	1.04	−1.15	0.89	4.92	<0.001*
Executive Functioning	−0.61	0.90	−0.49	0.83	−1.20	1.00	3.74	<0.001*
Language	−0.07	0.95	0.05	0.92	−0.60	0.92	3.65	<0.001*
Visuoperceptual Functioning	0.13	0.77	0.17	0.78	−0.10	0.74	1.79	0.073
Attention/Working Memory	0.15	0.82	0.22	0.83	−0.19	0.68	2.48	0.013*

*UPDRS, Unified Parkinson's Disease Rating Scale; BDI-II, Beck Depression Inventory -II; STAI, State-Trait Anxiety Inventory. [#]z-score has a mean of 0 and SD of 1; z-score composites computed from performance on neuropsychological tasks within a domain. ^Used Mann–Whitney U-test to determine significant group differences. [1]Used Pearson chi-square goodness of fit to determine significance group differences. *Difference was significant at alpha = 0.05.*

domain composite scores: Executive Function, Delayed Memory, Attention/Working Memory, Language, and Visuoperception.

Regression results indicated an overall significant model [$F(10,111) = 37.65$, $p < 0.001$] that accounted for 77.2% of the variance. The first block of education and mood scores significantly predicted DBS-CRS scores [$F(5,116) = 2.59$, $p = 0.029$] and accounted for 10.1% of the variance. Adding the second block of cognitive composites significantly improved the model [$\Delta R^2 = 0.67$, $\Delta F(5,111) = 65.6$, $p < 0.001$]. After bootstrapping, due to non-normality of the data, the relative strengths of the individual cognitive domain predictors of the DBS-CRS scores were as follows: Delayed Memory ($\beta = -0.44$, $p = 0.001$), Executive Function ($\beta = -0.39$, $p = 0.001$), Language ($\beta = -0.14$, $p = 0.023$), and Visuoperception ($\beta = -0.12$, $p = 0.021$). The only domain that was not significant was Attention/Working Memory ($\beta = 0.06$, $p = 0.223$). Thus, the two strongest and unique contributors to the DBS-CRS scores were performance on delayed recent memory and executive function tasks.

A subsequent multivariate analysis of variance (MANOVA) examined the pattern of the neuropsychological domain scores associated with the DBS-CRS ratings. To maximize interpretative clarity, we created three Subgroups based on DBS-CRS ratings: (a) those with relatively good ratings ($N = 67$, ratings 1 to 2), (b) those with more average ratings ($N = 91$, ratings of 2.5 to 3.5), and (c) those with poor ratings ($N = 31$, ratings of 4 to 5). **Figure 2** depicts neuropsychological domain scores for these three subgroups. Results of the MANOVA were significant [Hotelling's trace, $F(10,232) = 19.17$, $p < 0.001$], as were subsequent *post hoc* analyses (univariate and Bonferroni *t*-tests). Neuropsychological performance was significantly better as a function of DBS-CRS ratings, with Subgroup 1 > Subgroup 2 > Subgroup 3. This pattern was present for four of the cognitive domains (Executive Function, Delayed Memory, Language, Visuoperception) based on *post hoc* comparisons. For the Attention/Working Memory domain, performance was as follows: Subgroup 1 > (Subgroup 2 = Subgroup 3). These findings align with view that poorer DBS-CRS ratings are associated with worse cognitive performance across neuropsychological domains.

DBS-CRS and DBS Outcome: Quality of Life, Mood, and UPDRS

We sought to uncover whether ratings based on the DBS-CRS were associated with improved DBS outcomes during the 6-month period following surgery. Of the 154 patients who underwent DBS, 38 received leads in the STN (Right = 15, Left = 22, Bilateral = 1), 114 received leads in the GPi (Right = 44, Left = 67, Bilateral = 3), and 2 received leads in

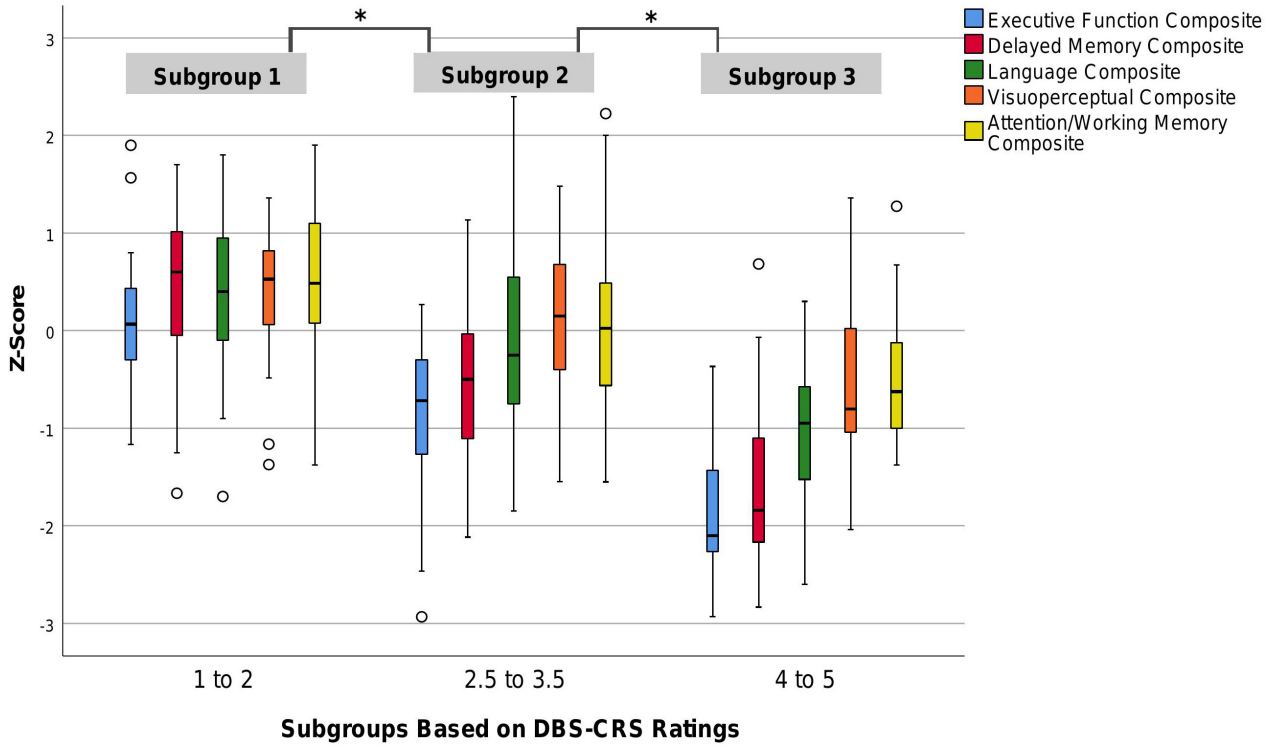

FIGURE 2 | Performance on domain-specific cognitive composites by patients in three DBS-CRS subgroups: Strong (1–2), Average-Expected (2.5–3.5), Poor (4–5). z-score for composite has mean of 0, SD of 1; circles represent outliers; *$p < 0.005$ difference among each subgroup (Executive Function (F[2,121] = 59.40, $p < 0.001$); Delayed Memory (F[2,121] = 47.87, $p < 0.001$); Language (F[2,121] = 16.51, $p < 0.001$); Visuoperception (F[2,121] = 18.46, $p < 0.001$); Attention/Working Memory (F[2, 121] = 5.81, $p = 0.004$)); Bonferroni corrected comparison of domain-specific cognitive composite across subgroups: Executive Function, Delayed Memory, Language, and Visuoperception (group 1 > group 2 > group 3, all p's < 0.05); Attention/Working Memory (group 1 < [group 2 = group 3], p's < 0.05, $p > 0.05$, respectively).

the Pedunculopontine nucleus. Because the DBS-CRS score did not differ between patients who received STN (mean = 2.33, SD = 0.82) versus GPi (mean = 2.52, SD = 0.91) DBS (Mann–Whitney U = 1,874.50, $Z = -1.26$, $p = 0.209$), we combined them into a single group for follow-up analyses.

Follow-up correlation and regression analyses focused on quality of life (PDQ-39) and mood, though additional motor and ADLs scores from the UPDRS were examined. Neuropsychological data was not available at this time interval. For these analyses, patients were excluded if they experienced an intra-operative adverse event (e.g., stroke, N = 1), post-operative infection (N = 6), had bilateral DBS surgery within the 6-month period (N = 34), or surgery not involving the STN or GPI (N = 2). An additional 16 participants were missing all scores from the PDQ-39. This resulted in a final follow-up sample of 95 participants.

Results of bootstrapped hierarchical linear regressions, controlling for education, revealed that the DBS-CRS served as a significant predictor for three subscales from the PDQ-39: ADLs (β = 0.20, p = 0.047), Cognitive (β = 0.20, p = 0.047), and Communication (β = 0.25, p = 0.013). Thus, higher cognitive risk was associated with worse quality of life post-surgery in three PDQ-39 domains. In additional correlational analyses (Spearman rho), higher cognitive risk (DBS-CRS) was significantly associated with worse post-DBS motor symptoms [UPDRS-Part III (on medication): r = 0.23, p = 0.046], and tended to be associated with worse ADLs post-surgery [UPDRS-Part II: r = 0.207, p = 0.052]. Neither the BDI-II nor the AS demonstrated significant relationships with the DBS-CRS (p's > 0.05).

DISCUSSION

Neuropsychologists' clinical judgment, as summarized by the DBS-CRS tool, plays an important role in the University of Florida's DBS Fast Track evaluation of whether a patient should proceed to DBS surgery. Cognitive concerns, either alone or in combination with other concerns (i.e., psychiatric, neurologic), were the most cited reasons for patients not proceeding to surgery and accounted for 57% of excluded cases. These findings align with a robust literature that cognitive concerns are the primary reason PD patients do not proceed to DBS surgery (Lopiano et al., 2002; Abboud et al., 2014). In our study, comparing patients who did and did not proceed to surgery revealed no differences in demographic factors, most clinical features, or mood/motivation. However, those who did not proceed to

surgery had comparatively worse cognitive performance across the board—on the DBS-CRS, a dementia screener (DRS-2), and all neuropsychological domains except visuoperception—further supporting our study's hypothesis that cognition serves as an important factor in choosing which candidates proceed to DBS surgery.

What aspects of the neuropsychological exam contributed to clinical decision-making regarding DBS-CRS ratings? The strongest contributors, based on regression analyses, were delayed memory and executive function, with a weaker but significant influence from language and visuoperception domains. Indeed, 77.2% of the variance in the DBS-CRS scores were accounted for by cognitive performance, in conjunction with education and mood scores. We suspect that the remaining variance (22.8%) could be explained by non-cognitive factors not assessed in this study such as other medical conditions, cardiovascular risk factors, and frailty. Because this information was collected from the neuropsychological interview and the medical record review, the data could have possibly affected clinicians' judgment.

One question of interest was whether worse DBS-CRS ratings would primarily reflect overall cognitive decline or may also reflect an atypical neuropsychological profile (e.g., atypical PD). Based on patients with the highest DBS-CRS scores (4–5) having significantly worse, broad impairment across most domains, our data are more in alignment with the former view of overall cognitive decline. However, we cannot fully dismiss the importance of atypical profiles, as these profiles may raise concerns about other co-occurring disease entities. These cases tend to be rare during DBS screening at expert centers, but it is clinically salient and critically important to communicate to the interdisciplinary team when uncovered.

A critical test of the utility of the DBS-CRS is whether this summary index would be associated with future adverse behaviors following DBS surgery. To address this point, we focused on quality of life and mood, as these measures provided a more patient centric view of outcome, rather than on cognition. Cognition scores were not available over the 6-month post-DBS surgery period. Indeed, we found that better DBS-CRS scores were linked to better ADLs, Cognition, and Communication scores on the PDQ-39 post-surgery. Moreover, we found that worse cognitive risk (DBS-CRS) was associated with worse motor scores and a trend for worse ADLs on the UPDRS. There was no relationship with mood. At least one prior study has reported that those with impaired cognitive performance did not exhibit improvements in quality of life after STN DBS in the same manner as those without cognitive deficits (Witt et al., 2011). To our knowledge, however, the current study is the first to specifically document the predictive relationship between quantified *cognitive risk* pre-DBS surgery and aspects of quality of life following DBS surgery.

Overall, while DRS-CRS serves as a helpful communication tool to other clinicians, there are limitations to its use. It is not intended to serve as a substitute for a comprehensive neuropsychological evaluation, which typically describes neuropsychological strengths and weaknesses and provides detailed recommendations beyond DBS suitability. In certain cases, those with poor cognitive performance, may be deemed adequate candidates for humanitarian reasons to optimize clinical care. That said, the DBS-CRS rating is an important communication tool that serves as one factor amongst many when assessing DBS candidacy.

Our study had several limitations. First, the majority of DBS-CRS ratings were assigned by the same attending neuropsychologist in conjunction with fellows and trainees. Thus, the generalizability of our findings is uncertain because we do not know how individual clinical judgment skills would affect DBS-CRS score assignment. Thus, future research should examine the inter-rater reliability between different raters at various levels of training. Preliminary work by our group suggests convergence by the clinical team after 3–4 weeks of training (i.e., around 12–15 cases), though this observation will need to be verified in more controlled settings. Generalizability of the scale's use would also be improved with a more racially heterogenous sample. Another potential limitation is that the current study evaluated cognitive performance using theoretically determined domain classifications. Future research could use empirically-derived composite scores to predict DBS-CRS to further evaluate which cognitive impairments best predict the scores. Finally, future work should expand to examine the DBS-CRS' role in predicting cognitive functioning post-DBS surgery and break down DBS candidates by target, as well as incorporate bilateral cases, to better understand individual differences between different DBS treatment regiments.

Overall, the DBS-CRS in this single center cohort was useful in deciding which Fast Track candidates should move onto DBS surgery. The study revealed that cognitive performance involving delayed memory and executive functioning were the strongest predictors of the DBS-CRS. The score on the DBS-CRS predicted the post-DBS surgery quality of life, specifically the ADLs, Cognition, and Communication domains. Based the current study's findings, we believe that that the DBS-CRS has the potential to improve the DBS screening process by providing a simple score to aid decision making in potential surgical candidates.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because "an inquiring party must submit a request to the UF INFORM database committee at the Norman Fixel Institute of Neurologic Diseases, and this request must be approved by the UF IRB." Requests to access the datasets should be directed to "Chuck Jacobson, jacobson@neurology.ufl.edu."

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Florida Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
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Publication of Study Exit Procedures in Clinical Trials of Deep Brain Stimulation: A Focused Literature Review

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Considerable variability exists in the publication of clinical research study procedures related to study enrollment and participant exit from clinical trials. Despite recent efforts to encourage research data sharing and greater transparency regarding research outcomes, reporting of research procedures remains inconsistent. Transparency about study procedures has important implications for the interpretation of study outcomes and the consistent implementation of best practices in clinical trial design and conduct. This review of publications from clinical trials of deep brain stimulation (DBS) using the MEDLINE database examines the frequency and consistency of publication of research procedures and data related to exit from DBS research. Related considerations, such as device explant or continued use, battery and other device hardware replacements, and post-trial follow-up care are also reviewed. This review finds significant variability in the publication and reporting of study exit procedures. Of the 47 clinical trials included in this review, 19% (9) disclosed procedures related to exit from research. Reporting of other exit-related data and study procedures examined in this review was identified in fewer than half of the included clinical trials. The rate of participant retention and duration of follow-up was reported more than any other category of data included in this review. Results inform efforts to improve consistency in research design, conduct, and publication of results from clinical trials in DBS and related areas of clinical research.

Keywords: deep brain stimulation, neuromodulation, research ethics, neuroethics, review, neuro-psychiatric disorders

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INTRODUCTION

Distinct ethical considerations arise as research participants exit clinical trials for investigational brain implants, such as deep brain stimulation (DBS) as compared to their initial entry into the study. Well beyond the initial informed consent process during study enrollment, research participants face complex decisions about the surgical removal or continued use of investigational implants upon exiting from research. The complexity of these decisions and variability in study exit procedures amplifies the importance of the transparent publication of data and study procedures in DBS research, particularly concerning participant withdrawal and study outcomes. Greater

transparency regarding research procedures for exit from clinical research, retention rate, and reasons for attrition will serve to inform human subjects protection and enhance consistent implementation of best ethical practices in brain device research.

This focused literature review examines how frequently and consistently published results from clinical trials of DBS describe procedures for study exit and data related to the number of research participants who exit or withdraw from these studies. Related data on device explant or continued device use by participant, battery, and other device hardware replacements, and post-trial follow-up care are also reviewed. These findings should inform guidelines for data and study procedures disclosed in publications of findings in DBS research.

BACKGROUND

The transparent publication of research findings informs ongoing research efforts and supports evidence-based decisions in medicine. In addition to transparent reporting of research outcomes, transparency regarding study procedures carries important implications for the interpretation of research findings and the development of best practices in clinical trial design and conduct. A desire to reduce reporting bias, including the omission or concealment of adverse events and the exaggeration of reported efficacy, led to the establishment of clinical trials registries such as clinicaltrials.gov in 2000 and the WHO International Trials Registry Platform in 2005 (Joshi and Bhardwaj, 2018). Recent data transparency initiatives call for research data sharing and greater transparency in the publication of research procedures and outcomes (Zorzela et al., 2016; Ioannidis et al., 2017; Munafò et al., 2017). In the United States, updates to the Final Rule for Clinical Trials Registration and Results Information Submission [42 CFR 11.48(a; 5)] expand required disclosures to include submission of "a copy of the protocol and statistical analysis plan (if not included in the protocol), including all amendments" for clinical trials initiated on or after January 18, 2017. This new requirement holds promise to improve publicly available information about clinical trial procedures; however, compliance has been inconsistent across research domains (DeVito et al., 2020; Piller, 2020) and requirements under the final rule do not apply to an important subset of clinical trials, including device feasibility studies.

A lack of standardization of protocol elements has particularly important implications in DBS research in which each clinical trial may contain a relatively small number of research participants. Inconsistent reporting of study procedures limits understanding and replicability of research outcomes, leads to variable research practices in clinical trials of DBS, and constrains the development of best practices in clinical research in DBS and other implanted brain devices. Inconsistent research practices may also exacerbate disparities in access to research opportunities and investigational therapies.

However, there continue to be substantial hurdles to systematically reviewing and identifying inconsistencies in research practices. Deficiencies in reporting of data on adverse events, participant withdrawal, and long-term outcomes contribute to the risk of bias in systematic reviews (Zorzela et al., 2016). In 2015, a PRISMA harms checklist was developed to improve harms reporting in systematic reviews to promote a more balanced assessment of benefits and harms.

While publication of research results in DBS may vary according to journal specifications and manuscript requirements, guidelines such as the CONSORT checklist create some consistency across journals. The CONSORT flow diagram calls for the visual representation of the number of potential participants excluded from study enrollment, the number of participants who did not receive allocated interventions (with reasons), those lost to follow-up (with reasons), and those who discontinued the study intervention (with reasons). Of the 25-item checklist prescribed by the CONSORT 2010 Statement, at least four items relate to procedures for study termination and participant withdrawal: "participant losses and exclusions after randomization, together with reasons" (Item 13b), "dates defining periods of recruitment and follow-up" (Item 14a), "why the trial ended or was stopped" (Item 14b), and "where the full trial protocol can be accessed, if available" (Item 24). Recognizing the need to move the field forward concerning the reporting of data on and procedures for participant withdrawal or exit from research, the following literature review was undertaken.

FOCUSED LITERATURE REVIEW

A focused review of the published results from clinical trials of DBS was carried out using the MEDLINE database[1]. The authors selected studies with English-language published results in which DBS was the primary research intervention. The following search terms were used: DBS, clinical trials, trial registration number, National Clinical Trial (NCT). Trial identifiers, such as NCT numbers, were used to identify any other articles reporting data from the included trial and to access additional trial information[1]; **Supplementary Material** were accessed and reviewed when relevant.

Data Extraction

Two reviewers (LS and AN) independently extracted data from published articles[1]. Two inter-rater disagreements regarding article inclusion and characterization of data were mediated by a third reviewer (PF). Extracted data elements include the publication of study protocol, description of exit procedures, participant retention rate, duration of follow-up, reasons disclosed for study exit or withdrawal, and data on device explant or hardware replacements.

Study Selection and Trial Characteristics

A total of 2,906 titles and abstracts were screened, of which 143 full-length articles met the criteria for further review. Articles were included if they reported procedures or results from a clinical trial in human subjects for which DBS was the primary research intervention. Case reports and articles reporting observational research or basic science findings or reviewing surgical techniques were excluded from this review.

[1]https://clinicaltrials.gov/

TABLE 1 | Examples of robust reporting of study exit-related information.

Description of study exit procedures
"7.14 Discontinuation/withdrawal of participants and "stopping rules": Patients wishing to discontinue participation with the trial will be free to do so. The reasons for withdrawal will be sought from all individuals and recorded. Adverse events will be recorded systematically throughout the trial and from all patients wishing to withdraw. Appropriate medical advice and treatment will be made available to any individuals experiencing adverse events from trial participation. The trial will be stopped prematurely if there are doubts regarding the safety or scientific validity of its continuation, following the principles of Good Clinical Practice and the Medicines for Human Use (Clinical Trials) Regulations 2004 Part 4" (Gratwicke et al., 2018).
"At the end of the 15-month protocol period, the patient has the option to remove the DBS device which can be done in a simple operation with minimal risks. There will be an option for an annual research follow-up for up to 4 years. At the end of the protocol period, or at any point subsequently, the patient has the option to remove the DBS device which can be done in a simple operation with minimal risks. If the participant decides to keep the DBS stimulator *in situ*, they will have routine neurosurgical DBS follow-up every 12 months for clinical care" (Park et al., 2018, p. 6).
"Participants completing the 12-month study were invited to continue in a long-term, naturalistic follow-up study. Study visits occurred every 6 months. Changes in stimulation parameters, medications, and psychotherapy were allowed. For patients continuing with chronic DBS, a rechargeable battery was provided as needed" (Plow et al., 2013, p. 843).
Reporting of data on study exit
"One patient had his DBS system removed after 1 year due to the device becoming the object of his obsession. A second patient requested to have the device removed because it caused him severe distress, and had become a part of his obsession syndrome. He wanted to constantly feel the stimulation. The device was removed without complication 21 months after implantation. After explantation, the patient was lost to follow-up" (Lee et al., 2019, p. 34).
"Four participants withdrew consent before completing the open stimulation phase. . .. More than half (five of nine) of the participants responded positively. These five participants elected to continue DBS at the end of the trial, and their non-rechargeable implantable stimulator was replaced with a rechargeable stimulator for continued use. The remaining four of nine participants elected to have their DBS systems removed before completing the 18-month open stimulation phase" (Plow et al., 2013, p. 657).
Reporting of hardware-related considerations
"Three patients (2.4%) had complete removal of the device during the study: two due to infection, and one due to the patient's choice. Four patients (3.1%) had leads repositioned to improve tremor control; one patient had repositioning at 3 months, one at 1 year, and two more than 2 years after implantation. Extension leads were replaced in seven patients (5.5%) due to malfunction (fracture or intermittent stimulation); three patients had the extension leads replaced at 6 months, one patient had it replaced after 15 months; one patient had it replaced after 18 months, two patients had extension lead replacement after more than 2 years. IPG malfunction occurred in three patients (2.4%), necessitating replacement earlier than expected" (Wharen et al., 2017, p. 23–24).

After the removal of duplicates and articles that did not meet inclusion criteria, 71 articles published between 2007 and 2019 remained and are included in this review. These articles provided data from 47 unique clinical trials. For reporting purposes, this review considers a clinical trial to be the unit of observation. That is, if a data element of interest was included in any publication associated with a single trial, the item is coded as present in publication for that trial. The full PRISMA flow diagram, with reasons for article exclusions, can be found in **Supplementary Figure 1**.

Parkinson's disease (n = 12) and major depression (n = 13) were the most common trial indications, followed by dystonia (n = 4) and Tourette syndrome (n = 3). The following were represented by two or fewer trials: addiction, Alzheimer's disease, anorexia nervosa, chronic pain, cluster headache, essential tremor, Huntington's disease, minimally conscious state, morbid obesity, multiple sclerosis, obsessive-compulsive disorder. Eighteen trials were conducted in the United States (27 international, 2 unknown). Nineteen trials were characterized as "pilot," "feasibility," "planning" or "Phase 1" trials; three were labeled "Phase 2" and the remainder did not specify a specific phase of research.

Publication of Study Exit Procedures

Forty of the included trials were complete at the time of this review. Of these, the median retention rate at the final follow-up was 92% (range 44 to 100%, 37 of 40 complete trials reporting). Among the 45 trials that described the duration of follow-up, the median follow-up time was 12 months (range 1.5–84 months; includes actual follow-up times where available and reported and planned follow-up times otherwise).

Table 1 displays examples of robust reporting of study exit-related information from articles included in this review. **Figure 1** displays the counts and proportions of select reporting items of interest. Rates of reporting for each item were generally low, except for CONSORT 2010 item 14a ("dates defining periods of recruitment and follow-up"). Further details outside the scope of **Figure 1** are described below.

When procedures for study exit were described (n = 9 trials reporting this information), they were located in a published protocol 100% of the time. Nineteen trials reported both the number of research participants who exited the study and the reasons for attrition and three also published detailed study exit procedures. Only three trials reported both explant procedures and detailed exit procedures. Twenty-five trials reported retention rates of less than 100%. Among these, 24 reported numbers of exited research participants and 19 reported reasons for the exit, showing incomplete reporting of CONSORT item 13(b). Only four clinical trials specifically described ethical concerns related to study exit. **Supplementary Table 1** includes all included trials and reporting items identified as present or absent for each.

Only three of the included articles were published before the 2010 publication date of the CONSORT guidelines. None of these included a description of exit procedures, number of exited research participants, nor reasons for exit.

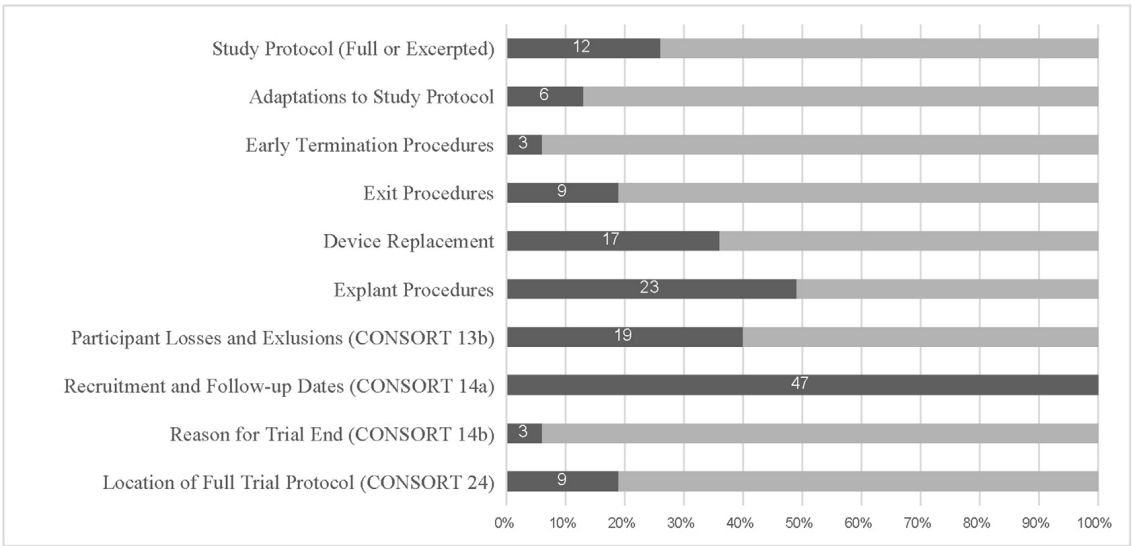

FIGURE 1 | Displays the proportion of trials out of 47 that disclosed each item in at least one publication. Integers inlaid on the bars represent the exact count.

DISCUSSION

Reported study procedures were insufficient to evaluate differences in research practices across clinical trials. Options related to device explant or continued use upon the termination of the study and the provision of post-trial follow-up care were difficult to discern from the published literature included in this review. Fewer than one-fifth (9) of the clinical trials with published research findings described procedures for participant withdrawal or exit upon study termination. Even fewer (6) of the clinical trials with published findings examined in this review described adaptations to study procedures or the study protocol. As DBS research continues to develop and flexible study designs are used more frequently, reporting of adaptations to study procedures or the study protocol may improve.

Reporting of outcomes and data on how many research participants exit from clinical trials was more substantial. However, the reviewed articles show inconsistent adherence to the CONSORT guidelines in reporting this data. CONSORT flow diagrams were frequently used to illustrate information about participant exclusion and retention. Emphasis was placed on representation of the number of potential participants excluded from study enrollment and the number of participants who did not receive allocated interventions (with reasons), rather than a comprehensive explanation of reasons participants were lost to follow-up or discontinued the study intervention. One potential explanation for this is the frequency with which study results are reported before a clinical trial has ended or the final follow-up visit has been completed. Additionally, numerical data may be reported more frequently than reasons for attrition due to the practical challenges of obtaining explanations from participants with whom the study team has lost contact. While it may be more feasible to obtain reasons for discontinuation of study intervention, data collection still may depend upon a participant's willingness to share this reasoning after they have decided to exit from the study.

Ethical Implications of Inconsistent Reporting

Gaps in publicly available information about study exit procedures may conceal variation in procedures related to DBS device removal and post-trial access to DBS devices. Arbitrary variability in exit procedures across clinical trials creates potential disparities in ongoing risks research participants may be exposed to as a result of participation and exit from research (including risks of infection, hardware malfunction, and surgical complications during explant). Similarly, variability in options provided for post-trial use of investigational implants creates disparities in direct benefit associated with research opportunities. In both examples, research participants who might be able to choose between entering different protocols do not have the assurance of uniform protections or the information to distinguish between procedural differences amongst alternatives. These justice considerations suggest an ethical imperative to improve reporting of study exit procedures.

Data on the number of participants who withdraw from a clinical trial may be more ethically complex to report. Concern to protect the confidentiality and to respect a research participant's decision to withdraw from research may limit the amount of data researchers can obtain regarding reasons for participant-initiated withdrawal. However, it is important to disclose criteria investigators use for exclusion or termination of a participant's ongoing participation in a clinical trial. This should always be undertaken in a way that is value-neutral and does not cast blame on research participants.

Transparent reporting of research findings in DBS can enhance the generalizability of knowledge gained from the contributions of research participants. Informed consent to enrollment in a clinical trial of DBS will be enhanced by promoting public availability of information about study procedures and outcomes. Finally, reporting of procedures related to study exit serves to inform research oversight and support the development of evidence-based best practices in DBS research. As investigations into new applications of DBS continue, it is vitally important to enhance consistency in the publication of both study procedures and outcomes from clinical trials of DBS. We encourage DBS researchers to disclose the following data and study procedures consistently to maximize transparency in the publication of DBS research findings concerning those participants who exit the research study: criteria for treatment response/non-response; adaptations to the study protocol, including early termination of the study; data on participant-initiated and investigator-initiated withdrawal from research participation, including reasons; battery and device hardware replacements; options provided related to device explant or continued use (including provisions for post-trial follow-up care and device hardware replacements); and duration of follow-up contact with each study participant. Additional guidelines for the transparent publication of research procedures and findings in DBS and other areas of clinical research are needed. The authors hope the proposed list can serve as a first step in facilitating more consistent reporting practices across clinical trials of DBS and other investigational brain implants.

AUTHOR CONTRIBUTIONS

LS designed the project, performed data collection, data analysis, and led the writing of this manuscript. AN contributed to data collection, data analysis, and the preparation of this manuscript. OH, AM, and PF contributed to data analysis and the preparation of this manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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STN Versus GPi Deep Brain Stimulation for Action and Rest Tremor in Parkinson's Disease

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Objective: To investigate the effects of subthalamic nucleus (STN) and globus pallidus internus (GPi), deep brain stimulation (DBS) on individual action tremor/postural tremor (AT) and rest tremor (RT) in Parkinson's disease (PD). Randomized DBS studies have reported marked benefit in tremor with both GPi and STN and DBS, however, there is a paucity of information available on AT vs RT when separated by the surgical target.

Methods: We retrospectively reviewed the 1-year clinical outcome of PD patients treated with STN and GPi DBS at the University of Florida. We specifically selected patients with moderate to severe AT. Eighty-eight patients (57 STN and 31 GPi) were evaluated at 6 and 12 months for changes in AT and RT in the OFF-medication/ON stimulation state. A comparison of "response" was performed and defined as greater than or equal to a 2-point decrease in tremor score.

Results: STN and GPi DBS both improved AT at 6- and 12-months post-implantation ($p < 0.001$ and $p < 0.001$). The STN DBS group experienced a greater improvement in AT at 6 months compared to the GPi group ($p = 0.005$) but not at the 12 months follow-up ($p = 0.301$). Both STN and GPi DBS also improved RT at 6- and 12-months post-implantation ($p < 0.001$ and $p < 0.001$). There was no difference in RT scores between the two groups at 6 months ($p = 0.23$) or 12 months ($p = 0.74$). The STN group had a larger proportion of patients who achieved a "response" in AT at 6 months ($p < 0.01$), however, this finding was not present at 12 months ($p = 0.23$). A sub-analysis revealed that in RT, the STN group had a larger percentage of "responders" when followed through 12 months ($p < 0.01$).

Conclusion: Both STN and GPi DBS reduced PD associated AT and RT at 12 months follow-up. There was no advantage of either brain target in the management of RT or AT. One nuance of the study was that STN DBS was more effective in suppressing AT in the early postoperative period, however, this effect diminished over time. Clinicians should be aware that it may take longer to achieve a similar tremor outcome when utilizing the GPi target.

Keywords: deep brain stimulation, tremor, parkinson disease, STN, GPi

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INTRODUCTION

The cardinal motor features of Parkinson's disease (PD) include resting tremor, bradykinesia, rigidity and postural instability. Although resting tremor (RT) is one of the most notable features of PD, action tremor (AT) is commonly encountered. Studies estimate that as many as 46 to 92% of PD patients will develop AT at some time during their disease course (Louis et al., 2001; Kraus et al., 2006; Gigante et al., 2015). While RT has a significant impact on the quality-of-life and can be debilitating especially in social situations, AT can interfere with the ability to execute motor tasks (Zimmermann et al., 1994; Forssberg et al., 2000; Louis and Machado, 2015).

Deep brain stimulation (DBS) is an established therapy for the treatment of motor symptoms in PD and has been shown to be more effective than best medical therapy in improving motor function and quality of life in well-selected PD patients (Weaver, 2009). The subthalamic nucleus (STN) and the globus pallidus internus (GPi) are the two most frequently used FDA approved brain targets for the management of medication refractory PD tremor. Several studies have compared the effects of these targets on the combined control of RT and AT (DBS for PD Study Group, 2001; Anderson et al., 2005; Weaver et al., 2012; Odekerken et al., 2013). Recently, our group published a meta-analysis on this topic and found no significant differences in tremor control between the two targets (Wong et al., 2018). Nonetheless, there is a lack of information in the literature specifically describing the longitudinal effects of DBS on AT or in comparing brain targets. A recent retrospective study found equivalent tremor outcomes, however, DBS targets for comparisons involved STN and the ventral intermedius nucleus (VIM) but not the GPi (Parihar et al., 2015). In the current study, we evaluated the longitudinal tremor outcomes in PD patients with moderate to severe AT managed with either STN or GPi DBS. Additionally, we investigated whether pre-surgical or other factors could affect AT tremor outcome.

MATERIALS AND METHODS

Patient Selection

The study was approved by the institutional review board at the University of Florida. We extracted data from a longitudinal research database for a retrospective analysis of tremor outcomes in PD patients receiving DBS surgery at our center from 2004 to 2016. The inclusion criteria for the study comprised the following (1) Diagnosis of PD was established with United Kingdom PD Society Brain Bank Criteria (Hughes et al., 1992) (2) Patients had moderate to severe AT before surgery corresponding to a score of $\geq$2 on item 21 the Unified Parkinson's Disease Rating Scale (UPDRS) part III. (3) Unilateral or bilateral DBS of either STN or GPi nucleus. If the patient received bilateral DBS, we included data only for the most affected tremor side. (4) Patients in the two comparison groups (STN vs GPi) had 12-months follow up data. (5) Patients accomplished optimal programming parameters for the implanted lead within 4–6 months of surgery. The exclusion criteria consisted of (1) Baseline assessments before surgery not documented (2) During the postoperative follow-up, the patient was deemed to have a suboptimal lead placement (3) Patient had prior neurosurgery for PD (4) The patient received a diagnosis of an atypical parkinsonism syndrome any time during follow-up after DBS.

Standard Perioperative Procedures Followed for All Patients

Parkinson's disease patients underwent a multidisciplinary team evaluation consisting of neurology, neurosurgery, psychiatry, neuropsychology, and rehabilitation disciplines. Upon completion of the discussion of the benefits and the risks, DBS surgery was scheduled. Based on our experience from the COMPARE trial and available literature, patients at our center are generally recommended GPi DBS when they report prominent levodopa-induced dyskinesia or when they exhibit concerning cognitive or mood difficulties. The STN target is usually recommended for patients with debilitating tremor, prominent akinesia, rigidity or those who are experiencing prominent dopaminergic medications adverse effects without significant cognitive impairment or dyskinesia (Pollak et al., 2002; Okun and Foote, 2005; Okun et al., 2009; Tagliati, 2012; Williams et al., 2014). However, as multiple factors play a role in target selection, we identified multiple patients in our database managed with GPi DBS despite the presence of significant tremors. Patients receiving bilateral DBS at our center are operated in a staged fashion with approximately 6 months in between lead implantations.

On the day of the surgery, an atlas-based anatomical mapping of the target location was performed on a preoperative CT scan fused with a 3T MRI image (Sudhyadhom et al., 2012). Further guidance for lead implantation was obtained from the intraoperative microelectrode recordings and macrostimulation testing performed in the operation room immediately after the lead was implanted. The DBS lead (model 3387; Medtronic, Minneapolis, MN, United States) was implanted under local anesthesia and for confirmation of lead location, a postoperative CT scan was performed and fused with the preoperative MRI image. Pulse generator implantation (Activa, Soletra, or Kinetra; Medtronic, Minneapolis, MN, United States) surgery was scheduled within 2 weeks of lead implantation surgery. Patients were followed at regular time intervals (every month for the first 6 months, and every 3–6 months for the second half of the first year); they underwent standard procedures for optimization of stimulation settings and adjustment of medication doses.

Outcome Measures and Longitudinal Follow-Up

Patient demographics, perioperative DBS information, and UPDRS scores were collected for patients in each group. Pre-DBS baseline UPDRS scores were collected in the OFF medication state and the post-DBS scores at around 6- and 12-months follow-up were collected in the OFF medication/ON stimulation state. A 2-months margin was applied for follow up at each of the time intervals, e.g., the 6-months post-implantation time point included visits from 4 to 8 months post-surgery. Dopaminergic

medications were withdrawn for a minimum of 12 h for the OFF medication state assessment. We had two patient groups for comparisons (STN DBS vs GPi DBS).

We determined the severity and occurrence of AT in the contralateral arm based on item 21 of the UPDRS part III assessment. We further extracted contralateral side RT (item 20), bradykinesia (summation of items 23–25 for the upper extremity), rigidity (item 22 for the upper extremity) and total motor score (summation of items 18–31). Compared to baseline, the UPDRS change in AT, RT, bradykinesia, rigidity, and total motor score at 6 and 12 months after surgery was calculated for each of patient groups. The primary outcome for the study was the change in AT score at 6 and 12 months compared to baseline in the STN group versus the GPi group. Secondary outcomes analysis included the comparison of changes in RT, bradykinesia, rigidity and total motor scores at these follow-ups. The secondary outcomes also included comparisons of RT vs AT outcomes for each of the targets and the baseline factors impacting these outcomes at 6 and 12 months.

Statistical Analysis

The clinical data was imported into IBM SPSS Statistics 26 software for statistical analysis. We compared the demographics, baseline clinical measures, and UPDRS scores between the two groups using Mann Whitney *U*-tests, Pearson's Chi-squared test or Fisher's exact tests, as appropriate. We set the statistical significance to a threshold of p-value < 0.05. We utilized non-parametric tests for analysis, considering the small sample size and non-normal distribution. The Wilcoxon signed-rank test was used to compare the DBS effects on AT and RT at 6- and 12-months follow-up compared to baseline. A Bonferroni correction was utilized for multiple comparisons, assuming alpha <0.05 and two statistical analyses, corrected p was <0.025. For the between-group (STN vs. GPi) comparison of the change in outcome measures at 6- and 12 months follow-up compared to baseline, we employed a Mann Whitney *U*-test with Bonferroni corrections as previously mentioned.

In the STN and GPi groups, we also identified the "optimal responders" and "suboptimal responders" based on $\geq$2 or $<$2-point change in AT or RT score at each of the follow-ups compared to baseline. While all patients in our group at baseline had AT score $\geq$2, whether there was change in RT $\geq$ 2 or $<$2-points was determined in only those patients with a baseline score =2. We further examined in a binomial logistic regression model whether age at surgery, duration of disease, baseline motor severity, baseline tremor severity, levodopa responsiveness of total motor score, and levodopa responsiveness of AT or RT (depending on AT or RT outcome) influenced the $\geq$2 point decrease in the tremor score at 6 and 12 months follow-up. Levodopa responsiveness for RT and AT was ascertained separately and was defined as a $>$30% decrease in the on-medication score compared to off-medication score. The variance inflation factor (VIF) and tolerance were calculated for all model variables to test for multicollinearity. A VIF threshold of 4 and tolerance threshold of 0.2 was used for the regression model (Hair et al., 2009).

DBS contact locations were measured from a post-operative non-contrast CT head. During pre-operative targeting, modified and digitized Schaltenbrand-Bailey atlases (AC-PC space) were manually fitted to each individual's pre-operative MRI brain using a linear transformation by the neurosurgeon (Sudhyadhom et al., 2012). The two images were then co-registered and reverse normalized into the AC-PC space for comparison across patients. Calculations were performed using MathWorks MATLAB R2016b. We considered the location of an active contact to be the center position of the contact for monopolar settings or the mean position between multiple contacts for bipolar settings. The locations of the active contacts were then visualized as three-dimensional spheres centered at the mean location of the active contacts and with radii given by the standard error of the active contacts. This was further superimposed upon the digitized Schaltenbrand-Bailey atlas. The size of the sphere does not represent the DBS electric field or volume of tissue activated. In this visualization we separated "optimal responders" versus "suboptimal responders" and we separately analyzed AT versus RT and STN versus GPi groups. The left and right hemispheres were collapsed for statistical comparisons. We compared the x, y, and z coordinates of suboptimal versus optimal responders using a t-test or Wilcoxon-signed rank test for normal or non-normal data, respectively, which was assessed using the Shapiro-Wilk test.

RESULTS

We identified 395 PD tremor patients who received DBS at a single center, however, due to various reasons including a baseline AT score that was $<$2, incomplete data at follow-up assessments and DBS targets other than STN and GPi, we excluded 307 patients. As shown in **Figure 1**, 88 PD patients (57 STN, 31 GPi; 68 males, 20 females) were included in the final cohort. Most patients had unilateral DBS with n = 50 unilateral STN, n = 25 unilateral GPi, n = 7 bilateral STN and n = 6 bilateral GPi. The mean ($\pm$SD) age was 61 years ($\pm$9.7; range 39 – 81 years), the mean disease duration was 12 years ($\pm$5.6; range 2 – 30 years), the mean baseline UPDRS III motor score was 45 ($\pm$11.1; range 16 – 77), the mean baseline AT score was 2.4 ($\pm$0.4; range 2 – 4) and the mean baseline RT score was 2.5 ($\pm$1.1; range 0 – 4). The mean total motor, AT, RT, rigidity and bradykinesia scores were not significantly different between the two targets. As shown in **Table 1**, except for the disease duration that was significantly longer in the GPi DBS group (p = 0.006) compared to the STN group, the baseline variables were not significantly different.

DBS Response for Action vs. Resting Tremor and Comparisons Between Targets

The mean baseline AT scores for STN and GPi groups were (2.42 $\pm$ 0.65) and (2.29 $\pm$ 0.46), respectively. Compared to baseline, the mean score and percentage improvement at 6 months follow-up were significant for STN (0.65 $\pm$ 0.86; 73%, $p < 0.001$) and GPi (1.09 $\pm$ 0.83; 52%, $p < 0.001$) groups. Furthermore, compared to baseline, the mean score

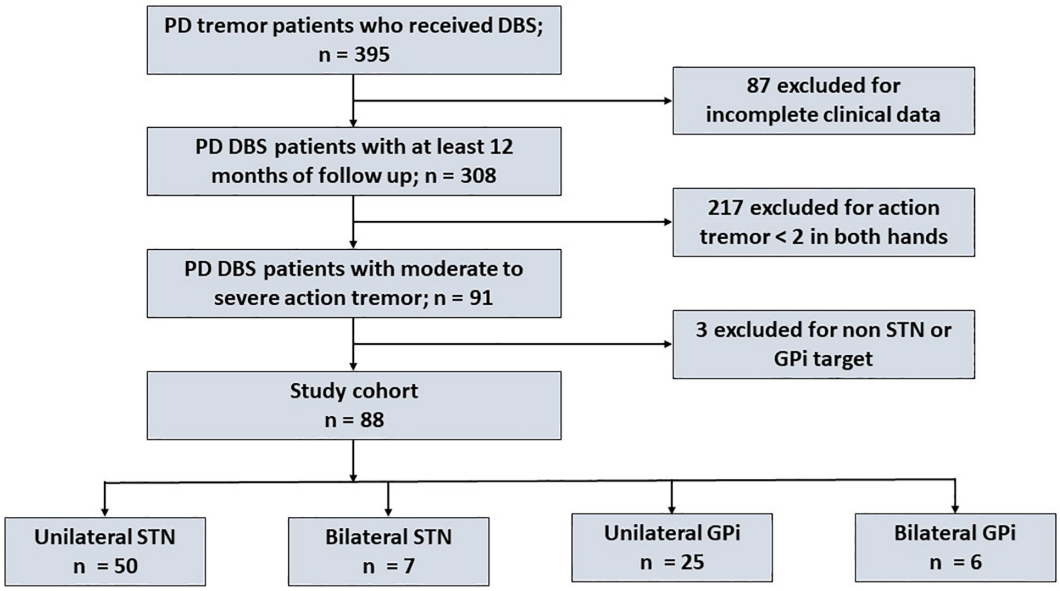

FIGURE 1 | Flow chart illustrating the patient selection process for our study cohort.

improvement maintained significance at 12 months follow-up in the STN (0.69 ± 0.79; 71%, $p < 0.001$) and the GPi (0.81 ± 0.63; 65%, $p < 0.001$) groups. In the between-group comparisons, while the STN group saw a greater improvement in AT at 6 months ($p = 0.005$), the 12 months comparisons were not significant ($p = 0.301$) (**Figure 2**).

The mean baseline RT scores for STN and GPi groups were 2.68 (±1.05) and 2.26 (±1.15), respectively. Compared to baseline, the mean score and percentage improvement at 6 months follow-up was significant for STN (0.86 ± 1.02; 68%, $p < 0.001$) and GPi (1.13 ± 1.08; 50%, $p < 0.001$) groups. At 12 months follow-up, the mean scores continued to further improve in the STN group (0.80 ± 0.13, 70%, $p < 0.001$) as well as in the GPi group (0.88 ± 0.19; 61%, $p < 0.001$). There were no between group differences at 6 months ($p = 0.23$) and 12 months ($p = 0.74$) follow-up.

Given the sample size differences in the AT and rest tremor analyses, the Levene's test for equality of variance was conducted between the STN and GPi groups for the 6- and 12-months comparison. There were no statistically significant differences found in variance between the two groups at the 6- and 12-month time points for the AT and rest tremor comparisons.

The percentage number of "optimal responders" for AT was significantly greater in the STN group at 6 months follow-up ($\chi 2 = 9.6$, $p = 0.01$) however, there was no difference between STN and GPi groups at 12 months follow-up ($\chi 2 = 1.1$, $p = 0.23$). By contrast, the percentage number of "optimal responders" for RT remained significantly higher in the STN group compared to the GPi group at 6 months ($\chi 2 = 10.4$, $p = 0.01$) and at 12 months ($\chi 2 = 4.8$, $p = 0.03$). In the regression analysis for the GPi group, baseline AT severity (i.e., a higher score) significantly predicted the optimal responder rate at 6 months (OR 13.1; $p = 0.02$), but not at 12 months and conversely baseline RT severity predicted the improvement rate at 12 months (OR 7.3; $p = 0.01$) and not at 6 months. In the STN group, baseline RT severity significantly predicted at 6 (OR 9.8; $p = 0.001$) and 12 (OR 11.4; $p = 0.001$) months, whereas there were no predictors identified for the AT outcomes. There was no evidence for effects of the other predictor variables. There were no variables with a VIF greater than 1.7 or a tolerance lower than 0.6. Thus we concluded there was no multicollinearity among the variables selected

TABLE 1 | Baseline characteristics of Parkinson's disease patients receiving STN and GPi DBS.

Patient demographics (*n* = 88)	STN (*n* = 57)	GPi (*n* = 31)	*p*-value
Sex, *n* (male%)	46 (80.70)	22 (70.97)	0.30
Handed, *n* (right%)	48 (84.21)	27 (87.09)	0.72
Age, years (SD)	61 (10.33)	63 (8.12)	0.41
Disease duration, years (SD)	11 (5.02)	15 (5.85)	0.01
Bilateral DBS leads, *n* (%)	7 (12.28)	6 (19.35)	0.38
Levodopa responsiveness, *n* (%)	41 (71.93)	17 (54.84)	0.28
Baseline UPDRS scores			
Total motor score (SD)	44.12 (10.45)	47.32 (11.79)	0.20
Action tremor (SD)	2.42 (0.65)	2.29 (0.45)	0.33
Severe (score 4), *n*	5	0	
Moderately severe (score 3), *n*	14	9	
Moderate (score 2), *n*	38	22	
Rest tremor (SD)	2.68 (1.05)	2.26 (1.14)	0.08
Rigidity (SD)	1.16 (0.81)	1.54 (0.63)	0.14
Bradykinesia (SD)	2.18 (0.76)	2.46 (0.49)	0.23

STN, subthalamic nucleus; GPi, globus pallidus internus; DBS, deep brain stimulation; SD, standard deviation.Levodopa responsiveness is defined as greater than 30% reduction of UPDRS part III total motor score.

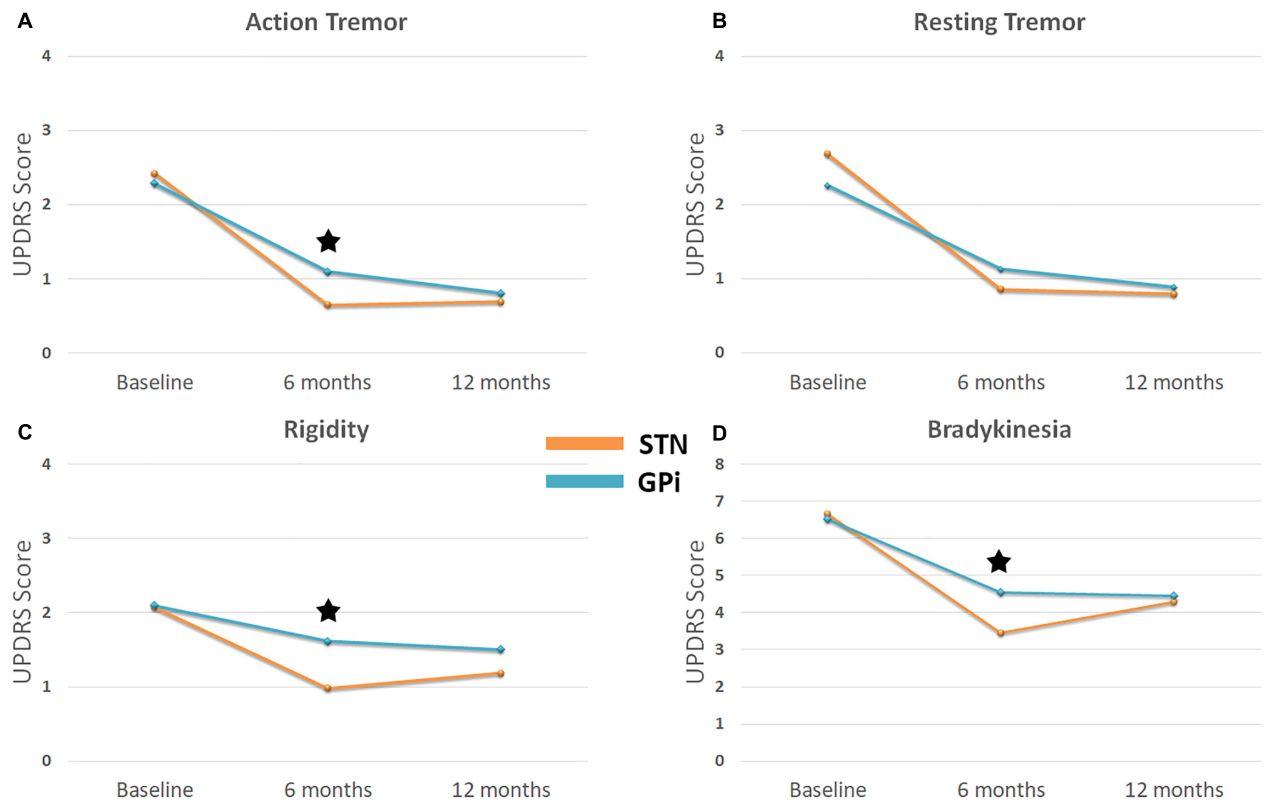

FIGURE 2 | Line graph illustrates outcomes for **(A)** action tremor **(B)** rest tremor **(C)** rigidity and **(D)** bradykinesia for STN DBS versus GPi DBS. Blue line represents STN DBS and orange line represents GPi DBS. Baseline represents UPDRS item scores before surgery. UPDRS item 20 applicable to contralateral arm was used for assessment of rest tremor, item 21 for action tremor, item 23 for rigidity and summation of items 23, 24, and 25 for bradykinesia. Scores at 6 and 12 months after DBS were obtained in during OFF medication – ON stimulation state. *Denotes a statistically significant difference between the two groups.

for the model. A summary of sub-group distribution between "optimal responders" and "suboptimal responders" are illustrated in **Figure 3** and the components of the regression model can be seen in **Supplementary Table 1**.

DBS Response for Bradykinesia and Rigidity: Comparisons Between Targets

The mean change of bradykinesia and rigidity are also depicted in **Figure 2**. For bradykinesia, STN DBS provided a 48 and 36% improvement while GPi DBS provided 30 and 32% improvement from baseline to 6 and 12 months, respectively. For rigidity, STN DBS provided a 53 and 43% improvement while GPi DBS provided 23 and 28% improvement from baseline to 6 and 12 months, respectively. STN DBS provided a greater decrease in bradykinesia and rigidity compared to GPi DBS at 6 months post-implantation ($p < 0.001$ and $p = 0.025$, respectively). There were no differences between the two groups at 12 months post-implantation.

Adverse Events

The surgery-related and device-related adverse events (AEs) for STN and GPi are summarized in **Table 2**. The most common AEs were DBS lead hardware issues and hemorrhage. The majority of hardware issues were short or open circuits discovered during the post-operative programming period. None of the hemorrhages required acute surgical intervention and all patients improved with conservative management.

DBS Programming Parameters

The anatomical coordinates for the active contacts relative to the mid-commissural point (MCP) for the STN group were 11.3 ± 2.1 (mm) lateral to midline; 3.3 ± 1.5 (mm) anterior to MCP; 4.6 ± 2.3 (mm) ventral to intercommissural plane. The anatomical coordinates for the GPi group were 20.8 ± 1.6 (mm) lateral to midline; 0.8 ± 1.5 (mm) anterior to MCP; 4.8 ± 1.3 (mm) ventral to intercommissural plane.

The stimulation settings (mean ± SD and range) at one-year follow-up after implantation for the STN group were voltage (2.65 ± 0.6, 1.0–4.0), pulse width (97.9 ± 22.1, 60–150), and frequency (156.6 ± 25.7, 100–200). The stimulation settings (mean ± SD and range) at one-year follow-up after implantation for the GPi group were voltage (2.7 ± 0.8, 1.0–4.0), pulse width (88.2 ± 14.7, 60–120), and frequency (162.4 ± 25.3, 130–210).

In the *t*-test comparisons of suboptimal responders vs. optimal responders for AT and RT, we found the z coordinate of the active contact for RT optimal responders in the STN was statistically

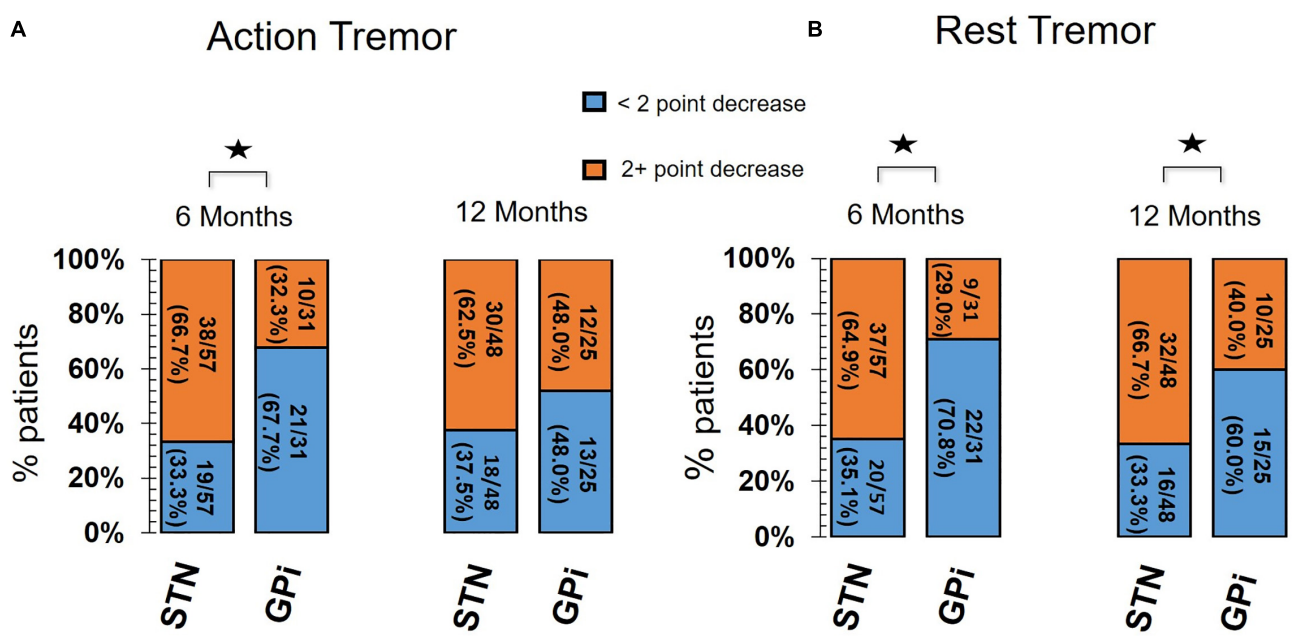

FIGURE 3 | Bar chart for Optimal Responders versus Suboptimal Responders of **(A)** action tremor and **(B)** rest tremor. Orange segment of each bar represents number of Optimal Responders with ≥2 point drop in tremor score compared to baseline (before surgery). Blue segment of each bar represents number of Suboptimal Responders with <2 point drop in tremor score compared to baseline. The percentage or proportion of patients who were either optimal or suboptimal responders to STN DBS and GPi DBS for action tremor and rest tremor are shown at 6 and 12 months follow-up. UPDRS part III item 20 (for arm contralateral to DBS) was used for assessment of rest tremor. UPDRS part III item 21 (for arm contralateral to DBS) was used for assessment of action tremor. The STN DBS group had significantly greater number of optimal responders compared to suboptimal responders in the GPi DBS group for action tremor at 6 months and rest tremor at 6 and 12 months. *Denotes a statistically significant difference between STN and GPi groups.

more dorsal with t (Mostofi et al., 2019) = −2.4 (p = 0.02) compared to suboptimal responders. However, these findings were not significant when corrected for multiple comparisons. The remaining comparisons pertaining to AT in STN group and AT and RT in the GPi group were not significant.

The composite data can be seen in **Figure 4** and individual coordinate data can be seen in **Supplementary Table 2**.

TABLE 2 | Summary of adverse events at one year follow-up.

STN		GPi	
Adverse event	**Number of events**	**Adverse event**	**Number of events**
DBS lead hardware problem	2	DBS lead hardware problem	4
Infection	1	Infection	1
Intracranial hemorrhage	5	Intracranial hemorrhage	2
Lead migration	1		
Seizure	3		
Twiddler's syndrome	1		
Total events (%)	13		7

STN, subthalamic nucleus; GPi, globus pallidus internus.The number of events do not necessarily reflect unique patients as some patients experienced multiple adverse events and thus were counted in multiple columns.

DISCUSSION

Action tremor in patients with PD can be particularly disabling as it can directly interfere with voluntary motor tasks. It has been hypothesized that the disruption of the cerebello-thalamo-cortical network may be involved in the underlying pathogenesis of tremor (Elble, 2013). Neuromodulation of the thalamus via VIM DBS evolved as a powerful treatment for essential tremor and PD tremor. VIM DBS does not, however, address other parkinsonian symptoms such as bradykinesia and rigidity. VIM DBS has been proposed as a possible target for AT in PD, however, our study findings indicate that STN and GPi DBS are both reasonable options to address many of the cases of moderate AT in patients with PD. In our cohort, one out of 88 patients required subsequent VIM DBS implantation suggesting that severe cases of PD tremor may benefit from VIM DBS to relieve the tremor adequately.

While previous studies have revealed that DBS therapy can effectively control tremor in PD, no study has examined the individual effects of DBS on AT and RT. Many surgical centers select STN as the target of choice for medication refractory PD tremor. Yet, a recent meta-analysis of randomized controlled trials did not detect a difference between STN and GPi in the tremor outcomes for patients with PD (Wong et al., 2018). It should be noted, however, the outcomes for the meta-analysis combined assessment of AT and RT, and there was no assessment of unique factors influencing tremor suppression. Here, we

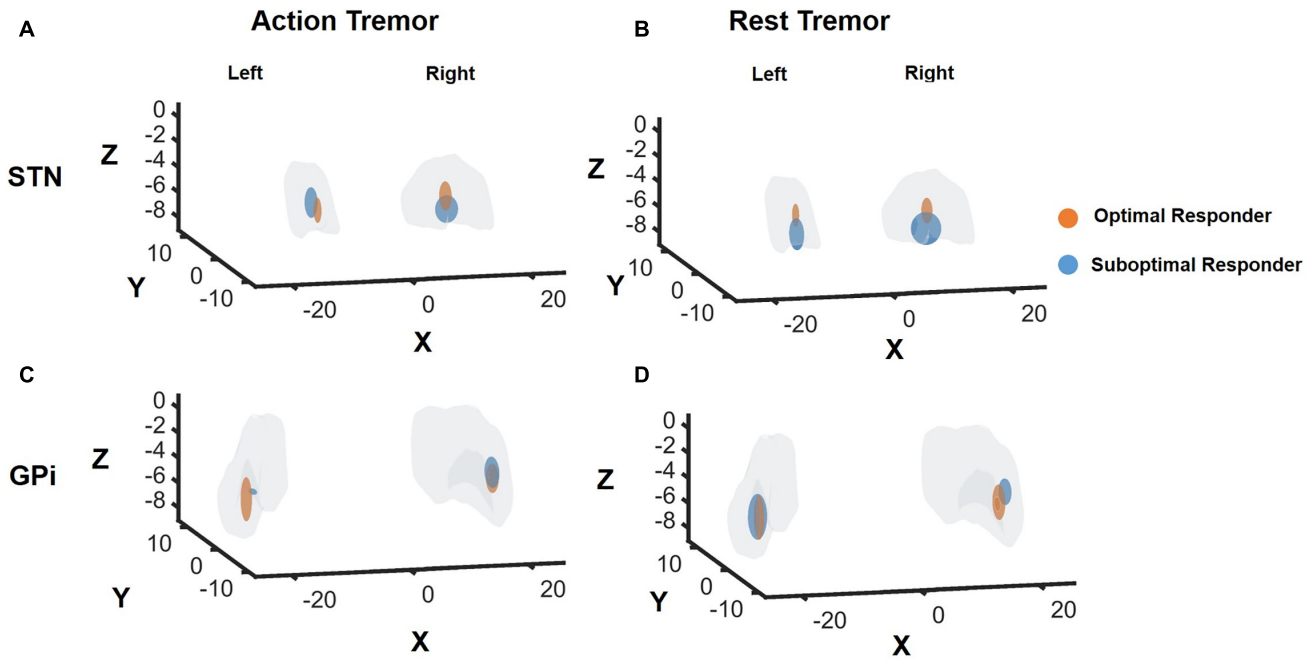

FIGURE 4 | DBS contact locations in Optimal Responders versus Suboptimal Responders for STN and GPi DBS groups. Response for rest tremor and action tremor was individually analyzed. OR, responder, SR, suboptimal responder. "Optimal responders" were defined as patients experiencing >2 point decrease in the UDPRS Part III item 20 and 21 for rest and action tremor, respectively. "Suboptimal responders" were defined as <2 point decrease in the UDPRS Part III item 20 and 21 for rest and action tremor, respectively. The gray region in panels **(A,B)** represents the STN while the gray region in panels **(C,D)** represent the GPi. The orange bubble represents the "optimal responders," and the blue bubble represents "suboptimal responders." The size of the bubble is not electric field or volume of tissue activated. The size of the bubble represents the variance within each subgroup. While there were no significant differences between the two subgroups for action tremor control regardless of the target and rest tremor control with GPi DBS; however, rest tremor control with STN DBS suggested the optimal contact was slightly dorsal in location as seen along the *z*-axis.

present a longitudinal single-center comparative analysis of a large dataset of PD DBS patients managed with both DBS targets. In the primary analysis there was no statistical difference and are consistent with several previous randomized controlled trials (Weaver, 2005; Weaver et al., 2012; Sako et al., 2014; Odekerken et al., 2016; Mansouri et al., 2017).

Although there were no overall differences in tremor outcomes between the two targets, we noted there was a temporal effect of DBS therapy on tremor. We observed that AT outcomes following STN and DBS were better than GPi at 6 months, but this effect disappeared by 12 months follow-up. This suggests that STN and DBS may be more effective in suppressing AT in the early postoperative period and that GPi DBS may require more time to appreciate the maximum benefit. There is increasing evidence to support the role of GPi in the pathogenesis of tremor. A functional imaging study revealed that the pathogenesis of PD tremor could be explained by a "dimmer – switch" model (Helmich et al., 2011). The efferent fibers from the GPi may trigger the tremor circuitry (analogous to a light switch) and dentato-rubro-thalamic (DRT) fibers may control the tremor intensity (analogous to a light dimmer). Hu et al. also found that GPi stimulation could paradoxically induce tremors in PD possibly due to stimulation spread to involve the pallido-thalamic outflow fibers (Hu et al., 2018). The temporal differences in DBS outcomes may be related to connectivity differences between the STN and GPi within the tremor circuit. Functional connectivity analyses suggest that the STN has both afferent and efferent connections with the cerebello-thalamo-cortical network whereas the GPi primarily has efferent connectivity (Helmich et al., 2012). When interpreted alongside physiology data, this has led to the proposal that the cerebello-thalamo-cortical network is the primary tremor generator and input from the basal ganglia contributes varying degrees of tremor modulation (Helmich et al., 2012, 2013; Helmich, 2013). Future DBS tractography studies, including larger samples of PD tremor will hopefully further elaborate on the role of GPi in RT and AT, specifically in the setting of PD. These studies will need to approach PD tremor from both the local nuclei effect as well as a network level perspective.

In the RT assessments, the between-group comparisons were not significant through 12 months of follow-up, however, one nuance in the data was that the percentage of "optimal responders" in the STN group was higher than GPi at both 6 and 12 months but there were no differences when AT outcomes was in consideration. These findings suggest that the RT circuitry is likely distinct and traverses the STN compared to the AT circuitry.

Analysis of postoperative lead localization and anatomical coordinates suggested that a dorsal STN location was more

likely to optimally control RT, which may be related to modulation of DRT fibers traversing the posterior subthalamic region or fiber connectivity to the motor and premotor cortex (Plaha et al., 2006; Accolla et al., 2016; Eisinger et al., 2018; Mostofi et al., 2019). Analysis of AT outcomes, however, did not reveal a specific subregion within the STN. Also, we could not find a "sweet spot" for optimal tremor response in GPi, and this may have been due to small sample size.

Exploration of the factors that impacted the optimal vs. suboptimal tremor responders revealed a higher RT severity score at baseline increased the odds of prominent tremor suppression following DBS. While these results may suggest DBS has greater effects when the baseline tremor score is higher, we believe our findings are more possibly related to Weber's law. According to the law the smallest discernible change in tremor amplitude is proportional to the initial baseline tremor amplitude (Elble, 2018). Thus, clinical raters are more likely to discern a 2-point drop (e.g., from a 4-to-2) in tremor score when collected using the tremor assessment item of the UPDRS as compared to a drop in someone with less baseline tremor (e.g., a 2-to-0).

Looking beyond tremor, previous target-based comparisons of DBS outcomes have revealed no major differences in the cardinal features of PD, including bradykinesia and rigidity when using either the STN or GPi target (Anderson et al., 2005). Like tremor outcomes, we observed a temporal difference in the DBS effects. We found that STN DBS led to superior rigidity and bradykinesia improvements in the early postoperative period compared to GPi DBS, but these differences were not sustained at one-year follow-up. This would again suggest that clinicians should be patient when programming the GPi target.

Our study had several limitations. First, the evaluation of AT was based on the UPDRS part III item 21 score, which combined postural and kinetic tremor. This score cannot differentiate between a re-emergent postural tremor and pure postural tremor. These differentiations can have important clinical implications as the underlying pathophysiology between the tremor subtypes are not identical (Jankovic et al., 1999; Dirkx et al., 2018). The score is also designed around a 4-point scale, limiting the resolution to more finely characterize important differences in tremor severity. Second, we recognize that medication intake can affect approaches to DBS programming and the total dosage requirement for dopaminergic medications may respond differently across various targets. However, levodopa responsiveness for tremor was given due consideration in our analysis and tremor scores were measured while off medications. Thus, the clinical measures in this study are unlikely to be affected by medication effect. Third, tremor assessments were not blinded, we did not include assessments longer than one year and we did not include VIM DBS for comparisons. Fourth, we did not assess the individual impact of RT and AT on the quality of life after DBS surgery. Fifth, as a common obstacle of longitudinal studies, a small percentage of our patients were lost to follow up at the 12-month time. All 88 patients in this study were retained at 6 months but 15 of the 88 patients in our study were lost to follow up by the 12-month visit. Finally, we do not have a gold standard test to determine co-pathology in patients within the cohort (PD plus essential tremor).

In conclusion, findings from this single-center cohort indicate that tremor control with STN and GPi DBS in PD is comparable regardless of whether RT and AT outcomes are individually assessed or combined. Clinicians should be aware that it may take longer to achieve a similar tremor outcome when utilizing the GPi target. The nuance of a possible higher rate of RT suppression with STN may suggest that the circuitry for RT traverses the STN and that the circuitry may be distinct from the AT network. Prospective larger multi-center studies with longer follow-up periods will be needed to confirm these findings.

DATA AVAILABILITY STATEMENT

Requests to access the datasets should be directed to aparna.shukla@neurology.ufl.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Florida. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and VV participated in study design, data acquisition, data analysis, and manuscript preparation. KN-F participated in data acquisition and data analysis. RE participated in data acquisition and data analysis and manuscript preparation. EL and AD participated in data acquisition. KF, AZ, and MO participated in manuscript preparation. AW participated in study design and manuscript preparation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.578615/full#supplementary-material

Supplementary Table 1 | Logistic Regression Analyses for Rest and Action Tremor Scores at 6 and 12 months (GPi and STN).

Supplementary Table 2 | The mean of coordinates for optimal contact in the two subgroups of responders.

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Case Report of Dual-Site Neurostimulation and Chronic Recording of Cortico-Striatal Circuitry in a Patient With Treatment Refractory Obsessive Compulsive Disorder

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Psychiatric disorders are increasingly understood as dysfunctions of hyper- or hypoconnectivity in distributed brain circuits. A prototypical example is obsessive compulsive disorder (OCD), which has been repeatedly linked to hyper-connectivity of cortico-striatal-thalamo-cortical (CSTC) loops. Deep brain stimulation (DBS) and lesions of CSTC structures have shown promise for treating both OCD and related disorders involving over-expression of automatic/habitual behaviors. Physiologically, we propose that this CSTC hyper-connectivity may be reflected in high synchrony of neural firing between loop structures, which could be measured as coherent oscillations in the local field potential (LFP). Here we report the results from the pilot patient in an Early Feasibility study (https://clinicaltrials.gov/ct2/show/NCT03184454) in which we use the Medtronic Activa PC+ S device to simultaneously record and stimulate in the supplementary motor area (SMA) and ventral capsule/ventral striatum (VC/VS). We hypothesized that frequency-mismatched stimulation should disrupt coherence and reduce compulsive symptoms. The patient reported subjective improvement in OCD symptoms and showed evidence of improved cognitive control with the addition of cortical stimulation, but these changes were not reflected in primary rating scales specific to OCD and depression, or during blinded cortical stimulation. This subjective improvement was

correlated with increased SMA and VC/VS coherence in the alpha, beta, and gamma bands, signals which persisted after correcting for stimulation artifacts. We discuss the implications of this research, and propose future directions for research in network modulation in OCD and more broadly across psychiatric disorders.

Keywords: neurostimulation, cortico-striatal circuitry, obsessive compulsive disorder, ventral capsule/ventral striatum, supplementary motor area, neural oscillations, synchrony, local field potential

INTRODUCTION

Obsessive compulsive disorder (OCD) is a chronic and severe psychiatric condition characterized by recurrent and intrusive thoughts, images, or fears which produce marked distress or anxiety (obsessions), and the performance of repetitive mental or physical rituals in response to that anxiety (compulsions). Individuals with OCD experience frequent and significant social impairments (Koran et al., 1996). Roughly 40% of individuals living with OCD report being unable to work (Mancebo et al., 2008). Standard treatments include exposure and response prevention therapy (ERP; e.g., Foa et al., 2005), and pharmacological interventions (e.g., Fineberg and Gale, 2005). Unfortunately, 30–60% of individuals will fail to respond adequately to treatment. Even those who do respond to treatment are often left with some level of residual symptoms (Pallanti et al., 2002; Foa et al., 2005; Dougherty et al., 2018).

For those treatment refractory individuals, neurostimulation, and in particular deep brain stimulation (DBS), is an option. Current neurostimulation therapies arose from the success of psychiatric neurosurgery procedures in which areas of the internal capsule were lesioned, with modern versions of those surgeries having open-label response rates as high as 80% (Brown et al., 2016; Dougherty et al., 2018; Rasmussen et al., 2018; Spatola et al., 2018). Given the irreversible nature of lesion surgeries, neurostimulation was proposed as a reversible option, which has greater customizability than the one-size-fits-all lesion surgeries (Nuttin et al., 1999). Early approaches in the internal capsule evolved into the current ventral capsule/ventral striatum target (VC/VS; Greenberg et al., 2010; Karas et al., 2019; for reports using different names for a similar target see: Luyten et al., 2016; Raymaekers et al., 2017). The VC/VS target is located at a putative junction of the anterior commissure, internal capsule, and striatum (Greenberg et al., 2010). Positive outcomes seen in early open label studies (Greenberg et al., 2010) led the VC/VS target to receive Humanitarian Device Exemption (HDE) approval for OCD in 2009 (approval H050003).

Response and symptom improvement rates with VC/VS DBS are promising, but there is much room for improvement. Reported (Luyten et al., 2016) and non-reported (NCT00640133) randomized controlled trials, as well as open-label trials (Menchón et al., 2019) have shown response rates of around 67% (response is considered a 35% drop in Yale-Brown Obsessive Compulsive Scale – YBOCS). This means that over 30% of individuals did not respond. These studies also found median improvement in YBOCS of 40–60 percent, with a median score of 20 with active stimulation. Critically, a YBOCS of 20 represents a level of symptom severity that often prevents the individual from working (Mancebo et al., 2008). In a qualitative survey of patient perspectives on VC/VS DBS, the majority of patients (86%) cited incomplete or unreliable symptom relief as their primary dissatisfaction with VC/VS DBS (Klein et al., 2016). Therefore, there is a need to advance neurostimulation to produce a more consistent response, and a higher level of effectiveness.

Improving Neurostimulation for OCD: Potential for Targeted Network Disruption Through Dual-Site Stimulation

Obsessive compulsive disorder is thought to be a network disorder. There is some consensus that dysfunction of the cortico-striatal-thalamo-cortical loops (CSTC loops; e.g., Alexander et al., 1986; Parent and Hazrati, 1995), of which VC/VS (and the striatum, more generally) is a hub (Alexander et al., 1986; Obeso et al., 2008; Krack et al., 2010; Lapidus et al., 2013; Dougherty et al., 2018), is involved in the etiology of OCD (see Dougherty et al., 2018; Robbins et al., 2019 for reviews). Structures outside these loops (e.g., amygdala) also likely play key roles in OCD in at least some patients (Milad and Rauch, 2012; Gürsel et al., 2018; Hazari et al., 2019; Robbins et al., 2019). That said, CSTC loop dysfunction almost certainly plays at least a partial role in OCD. Further, individuals with OCD show deficits in cognitive domains (e.g., cognitive flexibility; Robbins et al., 2012; Shin et al., 2014; Voon et al., 2015; Vaghi et al., 2017) that are thought to involve CSTC loop function (Haber, 2003; Robbins et al., 2012, 2019; Vaghi et al., 2017).

The dominant narrative of CSTC dysfunction in OCD emphasizes CSTC hyper-connectivity (e.g., Dougherty et al., 2018; Calzà et al., 2019). There are many functional neuroimaging studies showing heightened connectivity between regions within CSTC loops (Graybiel and Rauch, 2000; Maia et al., 2008; Milad and Rauch, 2012; Brennan and Rauch, 2017; Dougherty et al., 2018). These have been considered to be further supported by robust results showing striatal hyper-activations in OCD (Robbins et al., 2019), but it is important to recognize that activity and connectivity are entirely separate constructs. A given region may have radically disrupted connectivity without any change in its overall level of activity. In that vein, some studies have linked OCD pathology to hypo- rather than hyper-connectivity within CSTC loop components (Göttlich et al., 2014; Posner et al., 2014; Vaghi et al., 2017). A recent meta-analysis concluded that there is evidence of general aberrant activity in CSTC loops, but that that disconnectivity was not in any specific direction- hypo or hyper (Gürsel et al., 2018). Hyper- versus hypoconnectivity seems to be, in part, a function of which functionally distinct CSTC loop the regions are in Harrison et al. (2009); Göttlich et al. (2014),

Posner et al. (2014), and Vaghi et al. (2017), as well as the specifics of the experiment and patient population (Göttlich et al., 2014; Robbins et al., 2019). Despite differences, one common thread through the literature is the presence of a complex pattern of aberrant brain network communication in individuals with OCD. VC/VS DBS is believed to alter this pathological CSTC circuit function. For example, it alters cerebral glucose use in individuals with OCD (Rauch et al., 2006; Dougherty et al., 2016), and those alterations correlate with depressive (but not OCD) symptoms (Dougherty et al., 2016). Other groups have reported changes in cortico-striatal connectivity on functional MRI (Figee et al., 2013) or improvement in CSTC-related cognitive function after VC/VS DBS (Widge et al., 2019).

Thus, it may be possible to make VC/VS DBS more effective by identifying ways of more strongly disrupting targeted CSTC loops. Physiologically, this may mean disruption of abnormal oscillatory synchrony in the local field potential (LFP). LFP oscillations are argued to underlie many processes, including working memory, and even cognition in general (e.g., Miller et al., 2018). Oscillatory activity can be synchronous, or coherent, between brain regions, and this synchrony has been proposed to be a primary means by which regions in a circuit communicate (Fries, 2005, 2015). If this model holds and oscillatory synchrony is an index of communication between brain regions, then there may be CSTC hypersynchrony in individuals with OCD. High theta and beta subthalamic nucleus (STN) to cortical coherence has been reported in an individual with OCD (Wojtecki et al., 2017; using cortical MEG), but the synchrony theory has not been investigated within CSTC circuitry. In this way, establishing whether CSTC hypersynchrony exists in OCD may be a critical next step in understanding the disorder, improving treatments, and identifying useful biomarkers.

Similarly, disruption of oscillatory synchrony may be a mechanism of clinical DBS (Widge and Miller, 2019). For instance, in Parkinson's disease, there is increased beta band activity in the STN, that beta power decreases with active DBS (Wingeier et al., 2006; Bronte-Stewart et al., 2009), and this decrease is in turn correlated with symptom improvement (Kühn et al., 2006, 2008; Ray et al., 2008). DBS in Parkinson's specifically alters network-level LFP synchrony. For example, De Hemptinne et al. (2015) found a reduction in phase-amplitude coupling in the cortex with STN DBS in Parkinson's patients, while Oswal et al. (2016) reported a reduction in cortico-STN coherence. In animal models, optogenetic neurostimulation increased oscillatory synchrony between brain regions, which was in turn causally linked to both changes in behavior and neurotransmission (Padilla-Coreano et al., 2019). To the degree that CSTC hyper-connectivity is reflected in hyper-synchrony, new stimulation methods to disrupt that synchrony may significantly improve the effectiveness of DBS (Widge and Miller, 2019).

Therefore, we proposed that delivering frequency mismatched stimulation to multiple areas within a CSTC circuit would disrupt OCD-related hypersynchrony/hyperconnectivity more effectively than single site simulation. Stimulation resets the phase of neural oscillations (e.g., Rosanova et al., 2018). Stimulating two regions at mismatched frequencies should thus disrupt synchrony, by preventing the phase of the oscillations in the two regions from aligning. The supplementary motor area (SMA) is a particularly promising second target for this mismatched stimulation. While traditionally associated with the motor CSTC loop (e.g., Nakano et al., 2000; Obeso et al., 2008), the SMA (and medial prefrontal cortex, more generally) also participates in decision-making linked to limbic/associative CSTC loops (Milad and Rauch, 2012; Dougherty et al., 2018). Further, transcranial magnetic stimulation (TMS) of the SMA is an effective treatment for individuals with severe OCD (Mantovani et al., 2010; Gomes et al., 2012; Carmi et al., 2018, 2019), implicating this area in the neuropathology of the disorder. Given the CSTC hyperconnectivity hypothesis, we hypothesized that OCD symptoms would be reflected in heightened coherence between these two regions. Further, we hypothesized that mismatched stimulation would break this hyper-coherence between VC/VS and SMA.

Here, we report the first patient in an early feasibility study[1] combining VC/VS DBS with frequency mismatched stimulation of SMA in an effort to disrupt CSTC synchrony in treatment refractory OCD. The patient first received open-label VC/VS only stimulation, followed by a blinded phase of combined cortical and VC/VS stimulation, and finally an open-label combined stimulation phase. During the course of the study, daily LFP recordings from VC/VS and SMA were taken, allowing for the first known chronic recording of a cortico-striatal circuit in human. Using these recordings, we tested the hypersynchrony hypothesis, as well as the hypothesis that frequency mismatched stimulation could disrupt that hypersynchrony. These results are an important proof-of-principle toward understanding the mechanism of action for OCD neurostimulation, identifying biomarkers, and improving treatment.

Patient History: Diagnoses, Symptoms, and Previous Treatment

The patient was a male in his 20s, who had previously received VC/VS DBS for treatment refractory OCD. Prior to the initial DBS surgery, the patient's YBOCS was 29. He reported onset of OCD symptoms at approximately age 12–13, primarily of a mental ritualizing/obsessional type. Obsessions have included his symptoms themselves, counting, and symmetries. The patient had a past history of object-touching/rearranging compulsions, but at the time of his first course of DBS, he reported only mental rituals. Further, his OCD symptoms had sometimes been body-focused in ways that raised questions of body dysmorphic disorder (BDD).

Prior to beginning the first course of DBS, the patient was also diagnosed with treatment-resistant depression, with a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) of 36. He reported substantial low mood and anhedonia, for the prior several years, combined with substantial anxiety. Symptoms also included difficulty concentrating when not using stimulants, low energy, some psychomotor slowing, and profound emotional numbing. The patient denied frank suicidality but had frequent thoughts/wishes of being dead. He had also previously carried the diagnosis

[1]https://clinicaltrials.gov/ct2/show/NCT03184454

of bipolar disorder, with past clinicians stating there were brief periods of hypomania. However, clinicians at the time of his first DBS surgery felt that symptoms previously labeled as hypomania were more correctly attributable to OCD/anxiety related racing thoughts. There were no identifiable distinct episodes of impulsivity, goal-directed activity, or decreased need for sleep.

The patient had been receiving weekly or biweekly cognitive behavioral therapy (CBT) and exposure with response prevention (ERP) for five years prior to the onset of his first course of DBS, conducted in a private practice. At the time of surgery, the patient continued that therapy with the same clinician, and was able to display numerous mindfulness and distress tolerance techniques.

The patient had also tried numerous serotonergic and dopaminergic medications: Paroxetine (four weeks), citalopram (2 weeks), mirtazapine (unknown time frame), fluoxetine (several weeks), lorazepam (unknown time frame), clomipramine (unknown time frame) were all trialed and discontinued due to intolerability of side effects. At the time of surgery the patient's medications included: Fluvoxamine (400 mg), lithium (900 mg), amphetamine salt (20 mg), levomefolic acid (22.5 mg), lamotrigine (300 mg), olanzapine (27.5 mg) and levothyroxine (150 mcg). Additionally, the patient had undergone a course of rTMS for depression that he had not found helpful. At the time of his first DBS surgery, the patient had been undergoing bi-weekly maintenance electroconvulsive therapy (ECT) for depression, and had received around 50 sessions over the course of 2 years. The patient had found ECT to give him a slight mood lift. Despite these treatments, the patient continued to experience significant functional impairment, unable to attend community college, maintain significant employment, or live independently.

Roughly 3 years prior to enrollment in the present study the patient began his first course of bilateral VC/VS DBS treatment for OCD and depression. He showed initial improvement reaching his lowest YBOCS, 14, about 6 months after implantation. The patient's MADRS dropped significantly as well, with his lowest score of 18 recorded over 2 years after surgery. However, this improvement was not sustained. Generally, his YBOCS was in the mid-to-high 20 s, and his MADRS in the high 20 s, to low 30 s. By the time of enrollment in the present study, his YBOCS and MADRS were back to baseline levels (27 and 37, respectively). Given that the patient was still experiencing significant functional impairment, a multidisciplinary review committee (Widge and Dougherty, 2015) felt that the patient met criteria for inclusion in the present study (full criteria are at https://clinicaltrials.gov/ct2/show/NCT03184454).

MATERIALS AND METHODS

All study procedures described below were reviewed and approved by the Institutional Review Board at Massachusetts General Hospital. The study was conducted under an Investigational Device Exemption from the US Food & Drug Administration (FDA).

Surgery and Electrode Placement

The patient was implanted with bilateral electrodes targeting the VC/VS and SMA. VC/VS electrodes were implanted first, followed by SMA electrodes through the same burr hole. For VC/VS, the patient's previously implanted leads (Medtronic model 3387 lead) were first removed, as we sought to use larger contacts to more efficiently activate capsular white matter and reach fibers running in the dorsal capsule. Using standard stereotactic surgery procedures, and coregistration of MRI and CT images, Medtronic model 3391 leads were implanted bilaterally targeting VC/VS. We sought to place contact 0 within the gray matter of the ventral striatum, 2 mm anterior to the posterior border of the anterior commissure. The lead trajectory was aligned with the internal capsule, so that contact 3 would be in the capsular white matter immediately adjacent to the caudate nucleus. Before securing the lead, we tested bipolar stimulation at up to 6 V (130 Hz, 150 μs pulse width) between all pairs of contacts, without adverse effects. There was no intraoperative hedonic or mirthful response.

Cortical paddles (Medtronic model 3986, Resume 4-contact paddle lead) were placed under direct visualization through the burr holes used to place the VC/VS electrodes. The surgeon (ZW) retracted the underlying cortex inferiorly and placed the paddles on the dorsal surface of the superior frontal gyrus (SFG). In this first patient, cortical lead placement was purely empirical, targeting the SFG just anterior to the motor strip, guided by the cortical landmarks visible to the surgeon. As with the deep leads, we performed test stimulations (50 and 130 Hz, 150 μs) at up to 4V through the cortical electrode to verify lack of adverse events. Before securing the electrodes, we recorded local field potentials (LFP) from both the deep and surface leads in each hemisphere through the intraoperative monitoring system (NeuroOmega, Alpha-Omega Systems, Nazareth, Israel; see Data Collection section below for more details). DBS and paddle electrodes were then secured using sutures on the dural edge, and burr holes were sealed with cranioplasty material. Final lead placement was confirmed by intraoperative x-ray, and post-operative CT scan. See **Figure 1** for final lead locations.

In a subsequent surgery on the following day, two infraclavicular pulse generators (IPG; Medtronic Activa PC + S) were implanted bilaterally in the patient's chest. The PC + S system was selected for it's sensing/recording capabilities (discussed below). Given that the IPGs were only able to deliver pulses at one frequency to leads attached to the same device, the two VC/VS electrodes were attached to one device, and cortical electrodes were attached to the second device.

Study Phases and Stimulation Parameters

Over the course of almost 2 years, the patient progressed through several phases of a single-blind randomized cross-over study (see **Figure 2** for timing of each study phase). In the VC/VS optimization phase (study days 0 to 172, as measured by the days since operation), he only received VC/VS stimulation. We identified the initial most effective contact and titrated VC/VS stimulation voltage according to the algorithm in Widge and

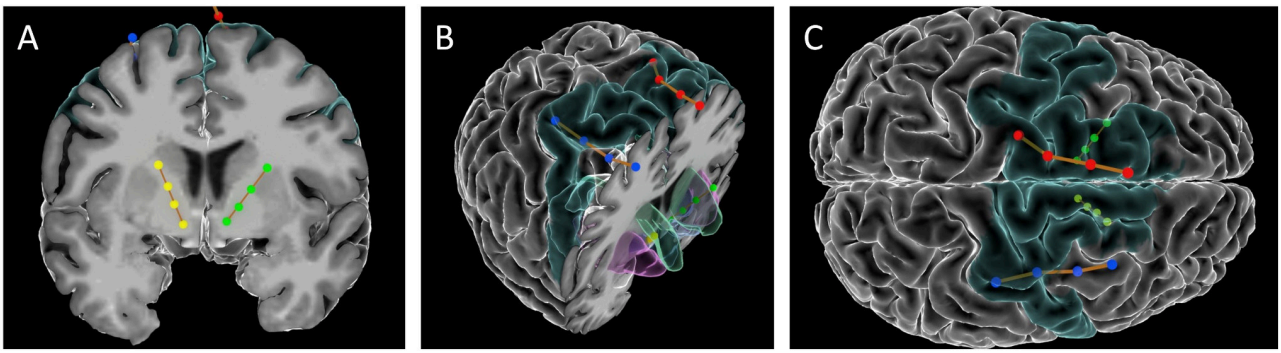

FIGURE 1 | Images of the DBS and paddle leads rendered with the Multi-Modality Visualization Tool (Felsenstein and Peled, 2017; Felsenstein et al., 2019). Position of left (red) and right (blue) SMA leads, and left (green) and right (yellow) VC/VS leads. Brodmann Area 6 is colored in turquoise. **(A)** coronal slice showing position of VC/VS leads (subcortical regions not colored). **(B)** Angled view with cortical coronal slice. Caudate nucleus colored in green, nucleus accumbens (Nacc) in blue, and putamen in pink. **(C)** Superior view (left on top) showing cortical lead positions. Note: the right VC/VS lead is in the caudate nucleus and NAcc whereas the left VC/VS lead is more laterally placed in the putamen. No adverse effects of lead placement were observed with the patient.

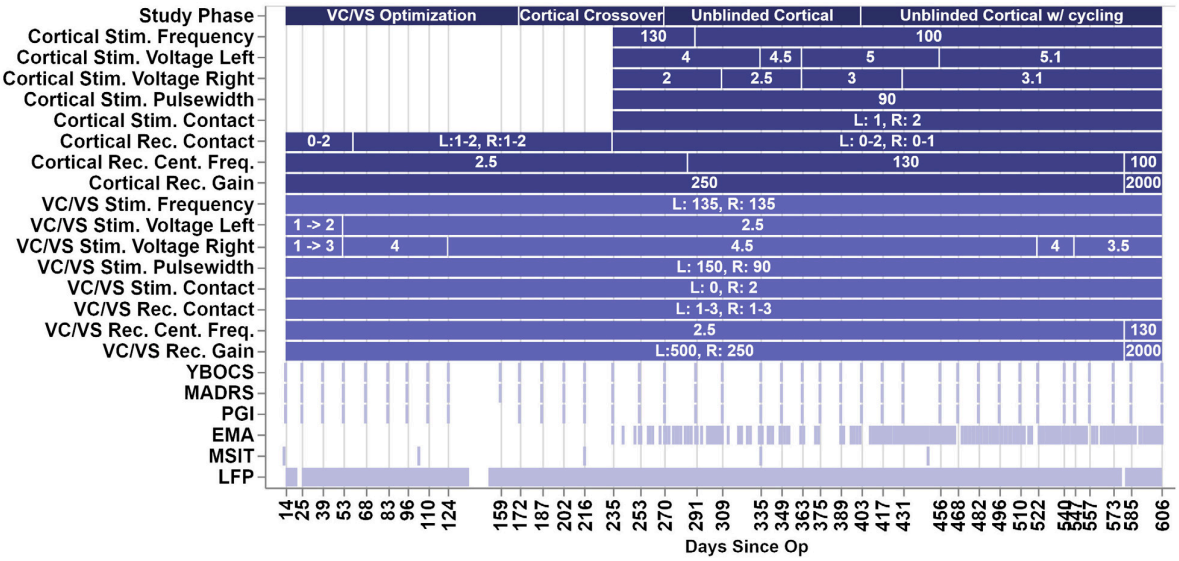

FIGURE 2 | Figure depicts the timeline of study phases, changes in stimulation or recording parameters, and collection of clinical measures and LFP recordings. The *x*-axis values are days since the operation, and the ticks/labels denote days of clinical programming sessions. Note that there was no chronic cortical stimulation until day 235.

Dougherty (2015). This also served as a baseline period in which cortical-striatal synchrony was measured in the absence of combined, mismatched stimulation. The original protocol called for a 2-week baseline phase after IPG implant, and preceding the VC/VS optimization phase, in which the pattern of LFP oscillations in the absence of stimulation could be established. However, on the day after the IPG was implanted, while recovering in the hospital, the patient reported depression and suicidality. He stated that this was due to withdrawal of his prior DBS therapy, that he was certain it would not be tolerable, and that he could not maintain his personal safety for any period of time. Consistent with the study protocol's directives that suicidality was a reason to escape a patient from any given phase/procedure, his VC/VS leads were thus activated early. Thereafter, the patient declined to permit deactivation of VC/VS stimulation, even if only for a few moments, making stimulation-off recordings impossible to obtain.

In the blinded cortical crossover phase (days 172–270) the patient had biweekly clinical visits with the unblinded programmer (DDD). During one of these sessions (day 235), cortical stimulation was activated, unknown to the patient or to the researchers obtaining rating scales. At the onset of this phase (day 172), we performed an acute cortical optimization in which we identified cortical stimulation parameters. During the cortical optimization, the VC/VS electrodes remained on, using the same contact as previously programmed for clinical therapy, but set to a frequency of 135, 55, or 15 Hz. For each of those VC/VS frequencies, we programmed the ipsilateral cortical

stimulation to a corresponding (slightly mismatched) frequency of 130, 50, or 10 Hz, respectively. The 5 Hz difference between frequencies was selected because this was the only spacing that could be achieved consistently at all three frequency bands given the limits of the pulse generator (at higher frequencies, only steps of 5 Hz were possible).

We then tested each contact of the cortical electrode, in a monopolar configuration, at 2, 4, and (if tolerated) 6 V. At each setting, the patient rated the change in his mood, anxiety, and overall energy level on a 1–10 scale. The settings producing the best clinical effect were retained, but the cortical electrodes/IPG remained inactive until the actual crossover at day 235. During the cortical optimization procedure, no evidence of seizure activity was detected by clinicians. This is unsurprising, as chronic epicortical stimulation has been trialed in psychiatric patients in multiple studies without epileptic complications (Kopell et al., 2011; Williams et al., 2016). In the open label, unblinded cortical phase (days 270–606) the blind was broken on the cortical stimulation while the patient continued to receive combined stimulation. The full course of the study ranged from day 0, or the day of surgery, to day 606, at which point the battery for the VC/VS IPG reached the cut-off for minimum battery life required to take recordings.

VC/VS stimulation parameters can be seen in **Figure 2**. The patient received constant unipolar stimulation at contact 0 (left hemisphere) and contact 2 (right hemisphere). VC/VS stimulation frequency was 135 Hz. VC/VS stimulation pulsewidth was 150 and 90 μs for left and right hemispheres, respectively. VC/VS stimulation voltage was gradually increased to 2.5 and 4.5 V for left and right hemispheres, respectively, during the VC/VS optimization phase.

Cortical stimulation parameters can be seen in **Figure 2**. From day 235 until day 403, the patient received constant unipolar stimulation at contact 1 (left hemisphere) and contact 2 (right hemisphere) of the cortical paddles. Cortical stimulation frequency was 130 Hz during the blinded cortical phase, until approximately 2 weeks after the patient was unblinded (from day 235 to 291). Due to patient complaints of what he described as "overstimulation," the stimulation frequency was reduced to 100 Hz at day 291, where it remained for the remainder of the study. Complaints of "overstimulation" also resulted in the patient beginning day-night cycling of his cortical stimulation (turning it off at night) at day 403. See section "Clinical outcomes with deep brain and combined stimulation" for a more detailed description of the patient's feelings of overstimulation. Cortical stimulation pulsewidth was 90 μs. Voltage ranged from 4 to 5.1 V for the left hemisphere, and from 2 to 3.1 V for the left hemisphere, limited in both cases by anxious distress at higher voltages.

Impedances were measured during clinical visits, and were within normal ranges. Mean (SD) impedance was 777.46 (18.54) Ω for the left VC/VS lead, 761.12 (42.89) Ω for right VC/VS, 757.64 (22.25) Ω for left cortical, and 1144.46 (79.22) Ω for the left cortical lead. There were no dramatic shifts in impedance throughout the study, and changes in impedance did not correspond to changes in power spectra.

Data Collection

Clinical Outcome Measures

Clinical sessions occurred approximately every 2 weeks (see **Figure 2**). Stimulation settings were adjusted only during these sessions. The primary outcome variable was the YBOCS (Goodman et al., 1989). Key secondary outcomes were MADRS (Montgomery and Åsberg, 1979) and patient global impression of improvement (PGI-I; Yalcin and Bump, 2003). All were collected during the biweekly clinical sessions.

Ecological Momentary Assessment (EMA)

Midway through the present study, the patient enrolled in a separate study. The purpose of that study was to use data from the patient's smartphone to obtain a more continuous measure of functioning than the sporadic clinical ratings. Among other measures, this study collected ecological momentary assessments (EMAs; Shiffman et al., 2008). Data collection for the EMA study began 151 days following surgery, with the first EMA collected 235 days following surgery. The EMA contained eight questions regarding the patient's motivation and ability to perform tasks (e.g., "In the past 24 h; it was difficult for me to get anything done," or "It was difficult for me to complete my morning routine"). These prompts were derived from the patient's report of his primary symptoms. Questions were scored on a scale from 0 to 4, with 0 indicating the highest level of functioning (e.g., "extremely easy") and 4 indicating the lowest level of functioning (e.g., "extremely difficult"). The scores for the eight questions were averaged to create a summary EMA score. The patient was prompted to take the EMA at least once a day but could choose not to participate.

Multi-Source Interference Task (MSIT)

During several clinical sessions (on days 13, 104, 216, 335, and 448, see **Figure 2**) the patient performed the Multi-Source Interference Task (MSIT; Bush et al., 2003; Bush and Shin, 2006). Considered to measure cognitive control, the MSIT produces robust subject-level behavioral and neural effects (Bush et al., 2003, preprint; Bush and Shin, 2006; González-Villar and Carrillo-de-la-Peña, 2017; Widge et al., 2019), which can be modulated through DBS of CSTC circuitry (Basu et al., preprint; Widge et al., 2019).

During an MSIT trial three numbers (between 0 and 3) were presented on the screen. Two of these numbers had the same value, and the other was different (e.g., 020 or 233). The patient's task was to identify, via button press, the identity of the number that was unique, not its position. Trials were either congruent or incongruent. In congruent trials (e.g., 020), the unique number was in the same position as it's corresponding keyboard position, and the other numbers were always '0', which was never a valid response. In incongruent trials (e.g., 233) the unique number was in a different position than its corresponding position, and the non-unique numbers were always one of the other valid responses, such that incongruent trials contained multiple types of interference (position and response). Congruent and incongruent trials were presented together in a pseudo-randomized fashion, such that no more than two trials in a row ever shared the same condition or correct response finger. The

patient performed 8 blocks of 48 trials each, for a total of 384 trials per run of the MSIT. The task was run using the Psychophysics Toolbox (Kleiner et al., 2007).

We analyzed MSIT response time (RT), as task accuracy is very high, and previous effects of DBS on MSIT performance have been shown in response time data. We grouped MSIT runs based on the stimulation phase/condition: VC/VS only stimulation with non-optimized settings (non-optimized VC/VS), VC/VS only stimulation after settings had been optimized (optimized VC/VS), and combined VC/VS and cortical stimulation (combined). Note that we only have MSIT runs during 100 Hz cortical stimulation. Trials were removed from analysis based on the criteria used in Widge et al. (2019). Namely, error and post-error (i.e., trials following an incorrect response) trials, as well as trials with RTs with a likelihood of less than 0.005 based on a fitted gamma distribution. We excluded 130 trials (0.07% of total trials), leaving 1790 trials in the analysis. Following Widge et al. (2019), we analyzed trial-wise RT in a generalized linear model (GLM) using a gamma distribution and identity link function, with conflict (congruent and incongruent) and stimulation condition (non-optimized VC/VS, optimized VC/VS, and combined) condition as the fixed effects. Collinearity between day since operation and stimulation condition was high. Further, adding day to the model containing conflict condition and stimulation condition (i.e., adding day to RT $\sim$ conflict condition + stimulation condition) did not add significant explanatory power ($F = 2.32$, $p = 0.13$), whereas doing the same for stimulation condition (i.e., adding stimulation condition to RT $\sim$ conflict condition + day since operation) did add significant explanatory power ($F = 24.23$, $p < 0.0001$). For these reasons we opted not to include day since operation in the reported model.

Conflict adaptation, or Gratton effect (Gratton et al., 1992), has been shown to be modulated by CSTC connected regions (Sheth et al., 2012). The patient failed to show the typical effect (slower RT when switching from a low conflict to a high conflict condition versus no switch), and therefore we did not examine changes in this effect across treatment.

Intraoperative Local Field Potential (LFP) Recordings

As stated previously, the high resolution intraoperative monitoring system (NeuroOmega, Alpha-Omega Systems, Nazareth, Israel) was used to record LFPs intraoperatively, after the electrodes had been implanted. We recorded simultaneously from all cortical and striatal contacts, with separate recordings for the left and right hemispheres. Two recordings per hemisphere were taken. Each recording was 2.25–2.5 min, with a sampling rate of 1000 Hz. LFP recordings were referenced against a needle electrode in the scalp.

Daily Local Field Potential (LFP) Recordings

Daily timer triggered recordings were taken by the cortical and VC/VS Activa PC + S devices throughout the course of the study. Recordings were taken every 6 h, yielding four recordings per day. Recordings were from a pair of contacts (bipolar montage) not used for stimulation. Recordings were 1 min long, at a sampling rate of 200 Hz (see **Figure 2** for other recording parameters). Recordings were downloaded at least every 2 weeks. Note on **Figure 2** that there are brief periods during the course of the study with missing LFP data, the largest of which occurred when the patient took an extended vacation. Given the potential for drift, the internal clocks of the cortical and VC/VS IPGs were re-synchronized with the programming device at each data download.

Saline Bath Testing and Artifact Subtraction

The recording/sensing capabilities of the Activa PC + S system have been utilized in preclinical (e.g., Connolly et al., 2015) and clinical (e.g., Swann et al., 2017; Huang et al., 2019; Veerakumar et al., 2019) studies. However, while the sensing capabilities in the PC + S system were designed to minimize the influence of stimulation artifacts, small artifacts remain (Stanslaski et al., 2012). Additionally, these original tests focused on measuring LFPs in the spectral domain; Stanslaski et al. (2012) state that results do not transfer easily to time domain, making phase-related analyses less reliable. For example, Swann et al. (2017) found broadband stimulation artifacts, as well as narrow band artifacts (with stimulation off) that were influenced by the sampling rate of recordings. Stimulation artifacts have caused some recent PC + S studies to analyze only stimulation-off recordings (e.g., Huang et al., 2019; Veerakumar et al., 2019).

Given that the recording and artifact removal capabilities of the PC + S device were not designed for our configuration (two IPGs delivering different frequency stimulation at the same time; Stanslaski et al., 2012), we specifically characterized the artifacts in our configuration in the absence of brain signal. We tested the recording and stimulation setting configurations used in the experiment in a saline preparation. We rejected the resulting artifact from the patient recordings (see LFP preprocessing and analysis below).

Saline testing used two Activa PC + S IPGs, with one electrode per IPG (Medtronic model 3387 and 3391). Settings were tested by taking simultaneous recordings, with the recording and stimulation settings used for the patient's VC/VS leads in one IPG, and the settings used for the patient's cortical leads in the other. Due to limited availability of leads, we were able to mimic only one hemisphere of the brain with a cortical and a VC/VS lead at one time. That is, this testing captured intra-hemispheric but not cross-hemispheric artifacts. Each lead had 4 contacts and were immersed in a saline bath. Each IPG was grounded through an alligator clip that was taped to the IPG body on one end via a metal foil and a resistor on the other end that was suspended in the same saline bath as the leads. Each IPG was connected via an antenna to a Nexus-D telemetry head which was in turn connected to a laptop (**Figure 3**). The recording settings on the IPGs were changed using a sensing programmer (SP) while the stimulation settings were changed using a clinician programmer (CP). Before starting any recordings, we first measured the impedances of both the electrodes with the CP. We ensured good contact on all leads, with impedance below 1000 Ω on at least 3 of the 4 contacts. We verified impedances again between recordings.

We manipulated frequency (cortical only), pulsewidth (150 μs for left VC/VS channel, 90 μs for other channels), configuration of the recording contacts (whether or not recording contacts directly flanked the stimulation contact), centering frequency,

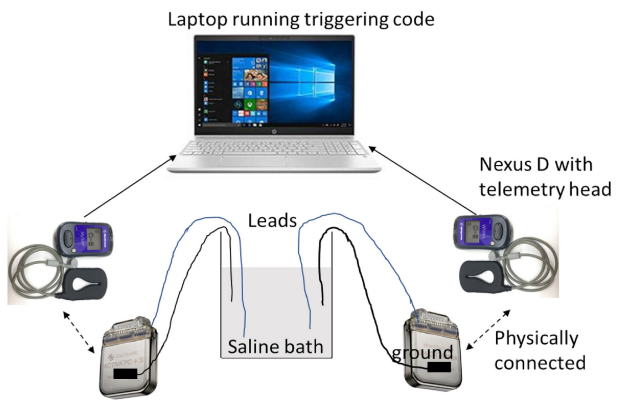

FIGURE 3 | Schematic of saline bath preparation.

and gain (see **Figure 2** for list of possible values). Sampling rate (200 Hz), and VC/VS channel frequency (135 Hz) did not vary over the course of the patient experiment, and thus were not varied in the saline test. To reduce the number of tests, only configurations used in the study were used in the saline test. We also took baseline (stimulation off) recordings, in which we assessed the change in the signal while varying only recording settings.

We took at least two recordings per setting configuration, on two separate days. Each recording was 2 min in length. We used custom written code in MATLAB to manually trigger recording in both the IPGs. Before sending the trigger command, we changed the recording settings (centering frequency, recording contact pair, gain) using the SP and the stimulation settings (stimulation current, frequency, pulse width, and lead contact) using the CP.

The saline bath recordings were preprocessed and power and synchrony were calculated using the same steps and criteria used for the patient recordings. See the LFP preprocessing and analysis section below for these criteria, and for a description of the methods used for artifact subtraction.

Intraoperative LFP Preprocessing and Analysis

We calculated cortical-striatal synchrony for the left and right side, as a function of VC/VS depth. For the purposes of clarity/brevity and alignment with previous studies exploring cortical-striatal connectivity, we use the term cortical-striatal here, though at least one of the contacts is not technically in the striatal gray matter (but in VC/VS, more broadly). Data from the four contacts on each lead were first bipolar referenced, yielding 3 pairs. Intraoperative recordings were then epoched into one second segments, and bad epochs were identified and removed by visual inspection for artifacts. Epochs for the two recordings (from a given hemisphere) were concatenated.

We used the debiased weighted phase lag index (WPLI) as the measure of cortical-striatal synchrony. This measure was selected as a way to minimize stimulation artifacts in the daily LFP recordings from the device. Volume conduction of stimulation artifacts could create artificial synchrony between brain regions. We selected the debiased weighted phase lag index (WPLI) because it is less sensitive to this artifactual synchrony caused by volume conduction (Vinck et al., 2011). The WPLI, and other similar measures, use the principles proposed by the imaginary part of coherency (Nolte et al., 2004), which operates on the assumption that volume conduction has essentially no time lag (e.g., Stinstra and Peters, 1998), and therefore effects due to volume conduction will have zero phase lag. By using the imaginary components of the cross-spectral density, which are themselves phase shifted, phase synchrony with zero phase lag is removed (Nolte et al., 2004). The WPLI builds on the phase lag index (PLI; Stam et al., 2007), which is a measure of the asymmetry of the phase leads and lags between two signals, by weighting the contribution of phase asymmetries based on the magnitude of the imaginary component of the cross-spectral density (Vinck et al., 2011). Given that the WPLI can be positively biased (Vinck et al., 2011), the debiased estimator or squared WPLI was used.

To calculate WPLI each epoch was decomposed to its time-frequency representation (TFR) using Morlet wavelet convolution, with wavelet base frequencies from 5 to 50 Hz, in 32 logarithmically spaced steps, and the number of cycles characterizing a wavelet ranging from 3 to 7, in 32 logarithmically spaced steps. WPLI was calculated between the ipsilateral cortical and VC/VS leads.

Daily LFP Preprocessing and Analysis

Local field potentials from the two recording contacts were bipolar re-referenced by the device internally prior to download from the IPG. All other LFP pre-processing and analysis was conducted using the MNE-Python suite (Gramfort et al., 2013).

Cortical and VC/VS recordings were temporally aligned using each IPG's internal timestamp, which was reset during each data download session to reduce the amount of temporal drift. Given the reliance on the accuracy of the two devices' timestamps, which do not have millisecond level precision, there is some uncertainty regarding the synchrony of the timing of the cortical and VC/VS signals. However, the temporal offset of the signals remains consistent within each pair of 1-min recordings. Phase synchrony is defined as a consistent phase difference, and thus can be calculated regardless of a constant shift/offset between two recordings. Only the portions of the recordings that overlapped temporally between the cortical and VC/VS IPGs were used in analysis. Therefore, while timer triggered recordings were each 1 min, the portion of the recording used in analysis was slightly less than 1 min in length. Recordings were band pass filtered between 5 and 50 Hz, in an effort to reduce the influence of stimulation artifacts. Additionally, given variations in the scale across recordings, each recording (within a channel) was normalized by scaling the band passed data to the interval from −1 to 1.

Spectral Analysis

Single recordings (5–50 Hz bandpass, normalized) were decomposed to their time-frequency representation (TFR) using Morlet wavelet convolution, and then averaged within

the approximately 1-min recording to arrive at the power spectral density (PSD) for a given recording within each channel (VC/VS left, VC/VS right, cortical left, and cortical right). TFRs were calculated with wavelet base frequencies of 5–50 Hz, in 32 logarithmically spaced steps, and the number of cycles characterizing a wavelet ranging from 3 to 7, in 32 logarithmically spaced steps. These same TFR parameters were used for the synchrony analysis.

We then subtracted the artifact signal from the recording. This was done by subtracting the PSD from the saline bath recording matching the recording/stimulation settings used in the patient recording (PSD averaged across at least two saline recordings) from the PSD of a given channel for the corresponding 1-min patient recording.

Finally, for analysis of changes in power across the course of the study, we averaged the PSDs within each channel across the recordings for a single day to arrive at the average PSD for each day for the VC/VS left and right, and cortical left and right channels.

Cortical-Striatal Synchrony: Weighted Phase Lag Index

To calculate the WPLI the time-aligned, band-pass filtered, normalized recordings were epoched into one second segments. Within recording, each epoch was then decomposed to its TFR as above. WPLI was calculated between the ipsilateral cortical and striatal leads (separately for left and right hemispheres), then averaged across time to get the WPLI at each base frequency and hemisphere for a single minute recording. WPLI was calculated using the spectral connectivity function in the MNE python suite, with the wpli2_debiased option.

We then subtracted the artifactual WPLI from the left and right hemisphere WPLI of a given recording, by subtracting the WPLI across frequency from the saline bath recording matching the recording/stimulation settings used in the patient recording from the WPLI values for that 1-min patient recording.

To assess changes across the study, the WPLI from recordings on a single day were then averaged to get the average WPLI for that day for the left and right hemispheres.

Clinical Outcomes and WPLI Correlations

Based on our initial hypotheses, we explored the relationship between the clinical outcome measures (YBOCS, MADRS, PGI, EMA) and cortical-striatal synchrony (WPLI) in each frequency band. We calculated the mean WPLI (left and right hemispheres averaged) within each frequency band (theta, alpha, beta, gamma) for the nearest recording day that occurred prior to the day of the corresponding clinical outcome measurement. The day prior was used for clinical outcomes (YBOCS, MADRS, PGI), as on many occasions there were also stimulation settings changes that occured on the day the measure was taken (i.e., the recordings for that day reflected the stimulation settings, not the symptom burden over the prior week). In cases where the EMA did not occur on a clinical session day, the recordings from the day the EMA was taken were used to calculate WPLI. We then correlated the WPLI in each band to the clinical measures. Given multiple comparisons for each clinical outcome, a Bonferroni corrected p-value of 0.0125 was used to determine significance.

Random Forests Using LFP Features to Predict Clinical Outcomes

We conducted five-fold cross validated (using five equally sized groups) random forest regressions to predict each clinical outcome measure (YBOCS, MADRS, PGI, EMA) using features of the LFP recordings, as well as some recording and stimulation settings features. The number of dependent data points for each regression depended on the instances of the given outcome (total of 39 for YBOCS and MADRS, 38 for PGI, and 215 for EMA).

We created power and WPLI features from the LFP recordings. Power and WPLI for each recording, in each band (theta, alpha, beta, or gamma) were either averaged across a full day of recording (full day), or binned into the time of day they occurred (night: 12:00am to 6:00am; morning: 6:00am to 12:00pm; afternoon: 12:00pm to 6:00pm; evening 6:00pm to 12:00am). Within each of those groups, features were then created based on whether recordings contributing to the features were from the day prior (for clinical outcomes; day of for EMA only days) to the day a given outcome measure was taken, or were the average of the recordings across all the days in the 2 weeks prior the outcome measure. The total number of LFP features was 280. Features also included 12 recording and stimulation parameters that varied throughout the experiment (for a total of 292 features): cortical stimulation (on vs. off), cortical stimulation frequency, cortical and VC/VS (left and right separately) stimulation voltage, and left and right cortical recording channel names. Missing values were possible, as there was not always a recording that occurred during a given time of day when only a single day of data was used. Missing values were imputed using the mean from that feature.

We used the scikit-learn package in Python (Pedregosa et al., 2011) to perform the random forest analyses. The random forest was conducted using 2000 estimators, with 2 samples required to split the group (a low sample to split was chosen because of the low number of instances of the clinical outcomes). All possible features were used at each split. The model was calculated first with all the features, and then again using only the top 5 features (based on importance scoring) from the first model. We report model accuracy, R^2, and feature importances for the model using the top five features only. Model accuracy is 100 minus the mean absolute percentage error (MAPE) in prediction of the outcome variable on the held-out test set. R^2, or coefficient of determination, is essentially a measure of whether the model created using the training set is performing better than a constant model (i.e., using the training set mean) for predicting the values in the test set. R^2, in this case, ranges from -1 to 1, with an R^2 of 1 indicating perfect prediction, $R^2 > 0$ indicating the model is performing better than the constant model, and an $R^2 < 0$ indicating that the model is performing worse than the constant model at predicting the test set values. Feature importances are a normalized estimate of predictive power for each feature, based on the fraction of samples a feature contributes to, combined with decrease in error by splitting. Reported values for all measures

are calculated as the average of the values for each of the five cross-validated test sets.

RESULTS

Clinical Outcomes With Deep Brain and Combined Stimulation

Changes in clinical outcomes over the course of the study are displayed in **Figure 4B** (with the timing of study events, for reference in **Figure 4A**). The patient's OCD symptoms changed modestly throughout the study (**Figure 4B**). The patient's YBOCS was 27 at the pre-surgery baseline, at which point he was already receiving VC/VS DBS (he had a YBOCS of 29 prior to his first course of DBS). His mean YBOCS during the VC/VS optimization phase was 25.13 (SD = 2.13), dropping 13.34% from his score prior to any DBS. With the addition of cortical stimulation, his YBOCS dropped another point (M = 24.25, SD = 1.92), dropping a further 3% from his initial YBOCS of 29 (i.e., 16.38% change). YBOCS consistently fell below the criteria for severe OCD (YBOCS < 24) during his last four clinical sessions. There was no difference in mean YBOCS between the blinded and unblinded cortical phases. During acute cortical optimization the patient reported that with the addition of cortical stimulation he felt that he was more easily able to focus attention away from the OCD thoughts, and that it was as if the OCD was on the other side of a door or barrier, trying to get through, but that he was able to keep it behind the barrier. These subjective self-reports did not, however, translate to YBOCS improvement with chronic cortical stimulation.

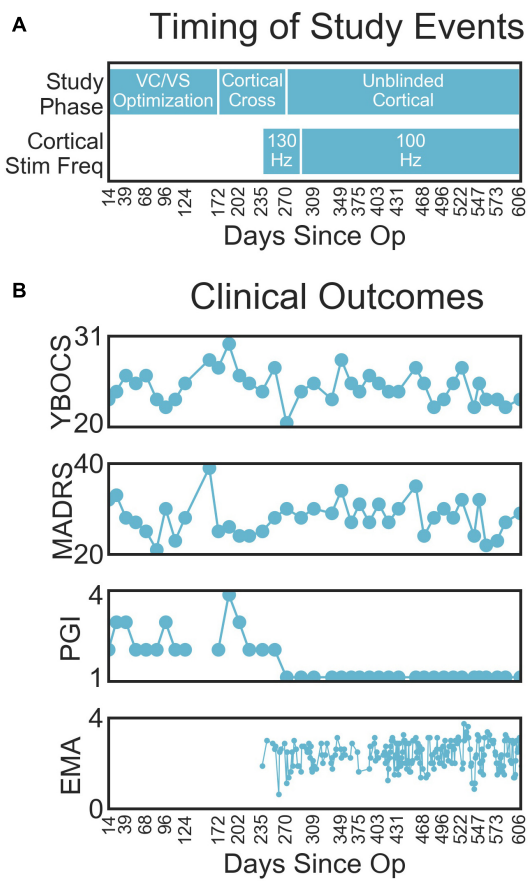

FIGURE 4 | (A) Timing of important study events, for reference. **(B)** Clinical outcomes (from top to bottom YBOCS, MADRS, PGI, EMA) by days since operation.

The patient's depressive symptoms appeared to improve with VC/VS stimulation, but did not improve further with the addition of cortical stimulation. By the end of his first course of VC/VS DBS, the patient continued to suffer from severe depression (MADRS > 34), with a MADRS of 37 at his pre-surgery baseline. During the VC/VS optimization phase, the MADRS dropped almost ten points (M = 27.33, SD = 4.61, 26.14% drop from baseline), with the patient no longer meeting criteria for severe depression. The MADRS rose slightly with the addition of cortical stimulation (M = 28.58, SD = 3.24, 22.76% drop from baseline).

The change in formal rating scales did not meet the standard criteria for YBOCS (35% drop) or MADRS (50% drop) response. Despite this, the patient felt that he was much improved with the addition of cortical stimulation. During the VC/VS optimization phase the patient's PGI-I averaged somewhere between minimally and much improved (M = 2.47, SD = 0.64). With the addition of cortical stimulation, the patient consistently rated his symptoms as very much improved (PGI-I = 1).

At the time of this writing, the patient continues to live with family, does not maintain significant employment or volunteer activities, and has not returned to complete his education.

The patient did not experience any significant side-effects from either the VC/VS or cortical stimulation. He did report experiences of being "overstimulated" with the 130 Hz cortical stimulation. Due to these, his cortical stimulation was changed to 100 Hz at day 291, and he began cycling his cortical stimulation off at night beginning at day 403. The patient described this experience as an overfocused, anxious, or agitated state, with the patient also using terms like "racing thoughts" and "tunnel vision" to describe the feeling. The attending clinicians did not believe these represented a hypomanic state, given that they were not accompanied by impulsivity, euphoria, or pleasure-seeking. In theory, this "overstimulation" could be akin to the anxiety effects reported from VC/VS stimulation, except that VC/VS-related anxiety tends to have a very acute onset and the patient's "overstimulation" feelings arose gradually. Moreover, even prior to this study, the patient's obsessions often focused on his current mood state and his stimulation settings, i.e., the possibility that his settings were incorrect and that he might feel bad as a result. Thus, some of this might not reflect actual side effects, but his usual obsessional content. Indeed, the patient only began reporting feelings of overstimulation after being unblinded to the cortical stimulation, indicating that it may be more psychological than physiological.

Multi-Source Interference Task (MSIT)

Both conflict condition (congruent and incongruent; f = 117.76, p < 0.0001) and stimulation condition (VC/VS non-optimized, VC/VS optimized, and combined; f = 1231.32, p < 0.0001)

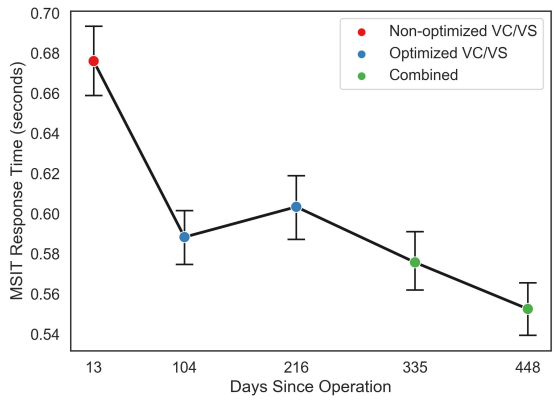

FIGURE 5 | Mean response time (in seconds) for each MSIT run as a function of day since operation the patient performed the task, collapsed across congruent and incongruent trials. Color of points indicates the stimulation phase: VC/VS only prior to setting optimization, VC/VS only after optimization, and combined VC/VS and cortical (100 Hz) stimulation.

contributed significantly to the final model. RT was faster for congruent (M = 0.507 s, SEM = 0.004) than for incongruent (M = 0.691 s, SEM = 0.004) trials ($\beta = 0.18$, $z = 34.36$, $p < 0.001$), replicating the robust subject-level effects seen in the literature.

RT also differed as a function of stimulation condition (see **Figure 5**). RT was faster when the patient was receiving optimized VC/VS stimulation (M = 0.596 s, SEM = 0.005) compared to non-optimized VC/VS stimulation (M = 0.676 s, SEM = 0.009; $\beta = -0.08$, $z = -10.33$, $p < 0.001$). RT was fastest during combined stimulation (M = 0.564 s, SEM = 0.005), differing from both non-optimized ($\beta = 0.11$, $z = 14.54$, $p < 0.001$) and optimized ($\beta = 0.03$, $z = 5.60$, $p < 0.001$) VC/VS only stimulation.

Daily LFP Recordings: Power and Cortical-Striatal Synchrony With Single-Site and Combined Stimulation

Intraoperative Cortical-Striatal Synchrony

A prominent alpha WPLI peak was detected intraoperatively using the high resolution OR rig (**Figure 6**). Alpha WPLI was more pronounced in the right hemisphere at each VC/VS depth. Right hemisphere alpha WPLI was relatively constant across VC/VS depth, whereas left hemisphere alpha WPLI was stronger more dorsally (near the head of the caudate). There was also a small gamma band WPLI peak, particularly in the left mid and dorsal striatum.

Saline Bath Test and Artifact Subtraction Results

When separated by the "cortical" stimulation frequency, there are noticeable artifacts in the "cortical," but not "VC/VS," saline recordings (**Figure 7A**). The spectrum of these artifacts differs depending on cortical stimulation frequency. For the patient recordings (**Figures 7B,C**), spectra also differ as a function of cortical stimulation frequency, particularly in the cortical recordings. These fluctuations largely remain after artifact subtraction, though the theta/beta peak appears to be much reduced. The 10 Hz peak in the cortical/right lead (**Figure 7C**, bottom right), at 130 Hz cortical stimulation is over-corrected, i.e., the saline artifact was larger than the same peak in the actual recording. Given this, 130 Hz cortical recordings showing a pronounced decrease in power in the 10 Hz range will not be interpreted as reflecting changes in brain signal.

While there are some marked artifacts in the power spectra, the synchrony spectra appear relatively artifact-free, as expected from a measure that is insensitive to volume conducted artifact (**Figure 8A**). In the patient recordings (**Figure 8B**), there are differences in WPLI with the type of cortical stimulation, which largely remain after artifact subtraction (**Figure 8C**). Contrary to our initial hypothesis, cortical-striatal synchrony increased with cortical stimulation, especially for 130 Hz stimulation. There is overcorrection in the lower frequencies of the right hemisphere, 0 Hz stimulation recordings (**Figure 8C**, top plot), therefore this will not be interpreted as hyposynchrony in the absence of cortical stimulation.

Daily LFP Spectral Analysis: Power Changes Over Time

VC/VS power spectra were relatively constant across stimulation settings, with a consistent peak in the theta range, and no other discernible peaks in the higher frequency bands (**Figure 9B**,

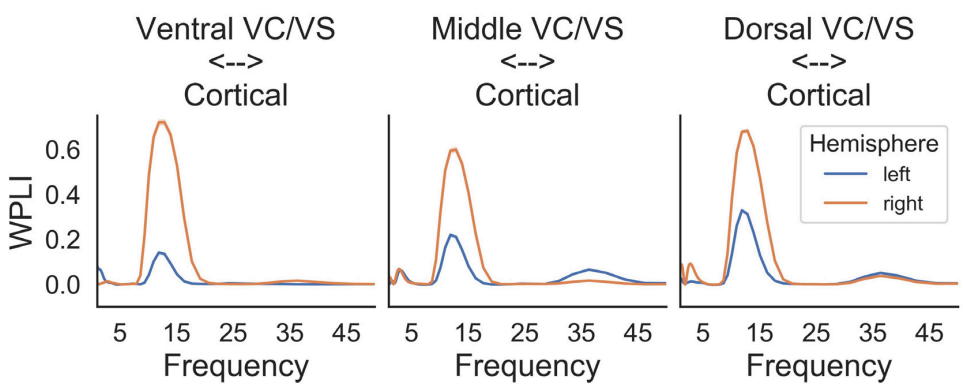

FIGURE 6 | Intraoperative WPLI as a function of VC/VS depth.

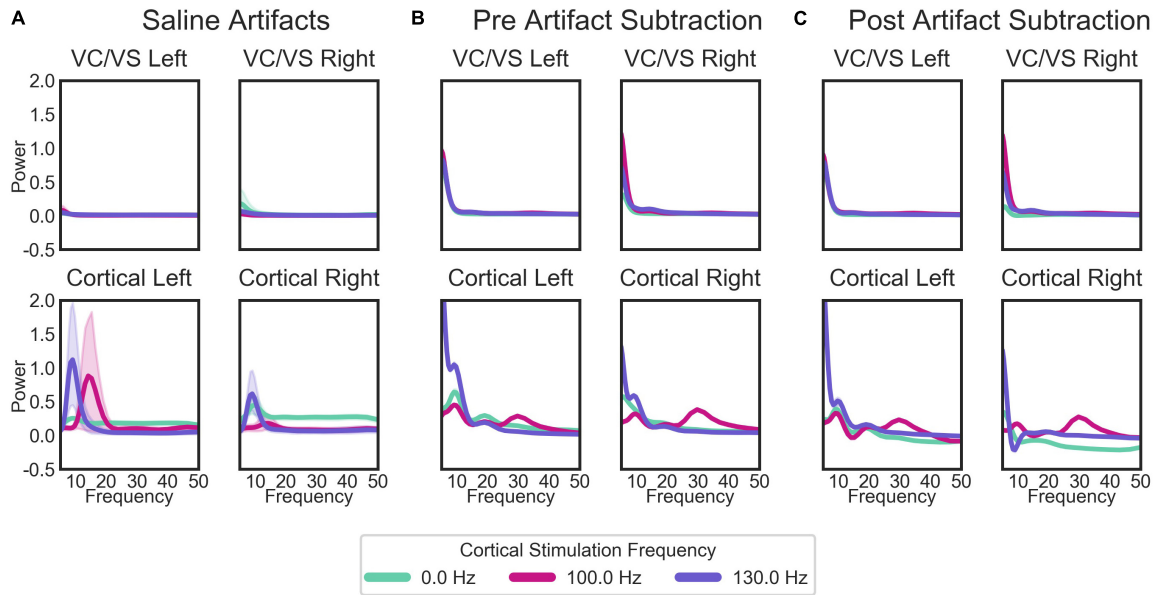

FIGURE 7 | Average PSDs for: **(A)** the saline bath test (artifact) recordings; **(B)** the patient recordings prior to the removal of artifacts; and **(C)** the patient recordings after the subtraction of artifacts. For the patient recordings **(B,C)**, each plot represents the recordings from each of the patient's four leads, labeled by the brain region (cortical or VC/VS) and hemisphere. Plots in **(A)** (saline recordings) are labeled by which region and hemisphere a given recording matched in terms of recording and stimulation settings. Lines in each plot are the average PSD for all recordings, separated by the cortical stimulation frequency. Cortical stimulation frequency of 0 Hz indicates that no cortical stimulation was on during that recording. Lines represent means for all saline bath **(A)** or patient **(B,C)** recordings in each group. Error bands represent 95% confidence intervals, calculated from 1000 bootstrapped samples.

upper panels, **Figure 9A** displays the timing of study phases for reference). Additionally, spectra were largely consistent across the left and right hemispheres.

Cortical power spectra, on the other hand, changed with study phases. Prior to turning on the cortical stimulation full-time, power for the cortical leads was relatively consistent across frequency and time (with some minor fluctuation in the theta band, **Figure 9B** lower panels). At day 235, when 130 Hz cortical stimulation was turned on, there was a dramatic shift in cortical power spectra. Interestingly, this shift resulted in increased power in the theta range, with an overall shift that looked much like the spectra of the DBS-on VC/VS recording. This change at approximately 5 Hz corresponds to the difference in frequencies between the cortical (130 Hz) and VC/VS (135 Hz) leads. The spectra shift again at day 291, when cortical stimulation is changed from 130 to 100 Hz. This shift results in the end of the increased theta power seen with 130 Hz stimulation, and some subtle banding in the alpha and beta/low gamma bands. These may correspond to the 35 Hz difference between the cortical and VC/VS stimulation.

There were also large shifts in cortical power spectra from day 172 to 202 and 216 to 235, which were more pronounced in the left hemisphere. No recording or stimulation parameter changes occurred at those times, other than the acute cortical optimization at day 172. Inspection of the non-normalized recordings indicated that the voltage values for those recordings were greatly increased relative to other recordings (by almost 100 fold). This may reflect a physical change in the contacts due to being stimulated for the first time, e.g., removal of accumulated protein deposits. However, the fact that these changes (including shifts in the scale of recordings) disappear between day 202 and 216, and then reappear between day 216 to 235, may indicate that there is also a neural component.

Daily LFP Cortical-Striatal Synchrony: Weighted Phase Lag Index

Consistent with our initial hypothesis, cortico-striatal synchrony changed more strongly than power across the study phases (**Figure 9C**). There were minimal differences between the left and right hemispheres. However, there does appear to be lower theta synchrony in the right hemisphere in the absence of cortical stimulation, which is not present in the left hemisphere. Given that this low theta synchrony only emerged after artifact subtraction (see **Figure 8**), and does not appear in the left hemisphere, its significance is uncertain.

Prior to the addition of cortical stimulation, WPLI was fairly equal across all frequency bands. This is in contrast to the intraoperative recordings (**Figure 6**), which showed WPLI peaks in the theta and alpha/low beta ranges. It is possible that this is a function of differences in the resolution of the recordings, but it may also indicate changes in synchrony when VC/VS stimulation is on (as is the case for the daily PC + S recordings) versus off (as is the case for the intraoperative recordings). Those changes would be consistent with our hypothesis that DBS disrupts cortico-striatal synchrony. The patient declined even temporary interruption of VC/VS stimulation, and thus we are unable to disentangle these possibilities at this time.

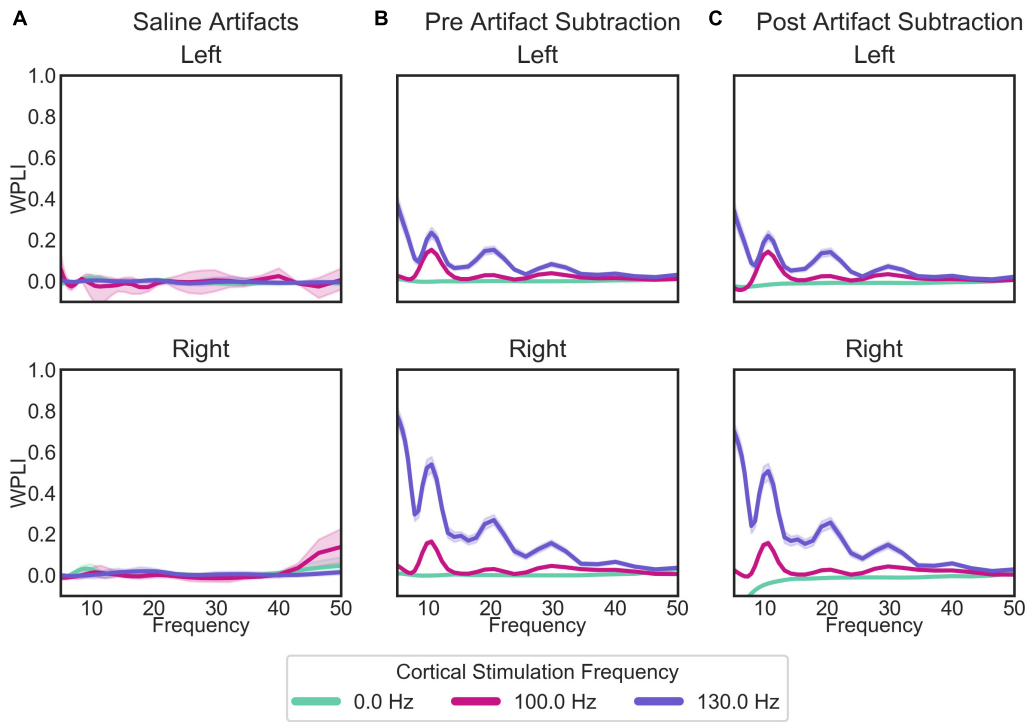

FIGURE 8 | WPLI across frequency for: **(A)** the saline bath test (artifact) recordings; **(B)** the patient recordings prior to the removal of artifacts; and **(C)** the patient recordings after the subtraction of artifacts. Plots of patient recordings **(B,C)** indicate the cortical-striatal WPLI for the left and right hemispheres, with colored lines indicating the cortical stimulation frequency at the time of recording. Saline test plots **(A)** indicate whether the recording and stimulation settings for the IPGs matched those of the left or right hemisphere of patient recordings. Error bands represent 95% confidence intervals, calculated from 1000 bootstrapped samples.

There is a dramatic increase in WPLI in the theta, alpha, beta, and low gamma bands when cortical stimulation is turned on full-time at 130 Hz (day 235). When stimulation is reduced to 100 Hz (day 291) this increase abates, although WPLI in the alpha, beta, and low gamma bands remains high relative to the other frequencies. Given the absence of WPLI artifacts in saline testing, these synchrony changes likely reflect true physiologic change. Contrary to our initial expectation, there was an increase in synchrony with combined VC/VS and cortical stimulation, and this increase was greatest when cortical stimulation was 130 Hz.

Relationship of Power and Cortical-Striatal Synchrony to Clinical Outcomes

Clinical Outcomes and WPLI Correlations

We correlated WPLI in each band (theta, alpha, beta, and gamma) to the clinical measures (**Figure 10**). Raw p-values are reported here; only p-values below the Bonferroni threshold of 0.0125 were considered significant. YBOCS improvement was correlated with higher WPLI in the theta band, but this did not reach significance ($r = -0.30$, $p = 0.06$) and may be driven by outliers. Improvement in MADRS was significantly correlated with lower WPLI in the gamma band ($r = 0.40$, $p = 0.01$). PGI correlations echoed the YBOCS, with improvement associated with increased WPLI in the alpha ($r = -0.63$, $p < 0.001$), beta ($r = -0.46$, $p = 0.004$), and gamma ($r = -0.47$, $p = 0.003$) bands. There were no significant correlations between EMA and WPLI in any band.

Random Forests Using LFP Features to Predict Clinical Outcomes

Table 1 contains the results of the random forest regressions predicting the clinical outcomes using LFP features. The models predicting MADRS ($R^2 = -0.14 \pm 1.39$) and EMA score ($R^2 = -0.01 \pm 0.40$) failed to perform better than a constant model. While average R^2 for the model predicting YBOCS was positive, the 2 SD confidence interval included 0. We therefore concluded that the model did not meet performance criteria ($R^2 = 0.23 \pm 0.28$). This was likely due to a lack of variability in YBOCS scores across the course of the study; the mean predicted YBOCS scores with 94% accuracy, calculated as the average across the 5 cross validated test sets. In line with the correlation results, the model predicting PGI did perform better than the constant model ($R^2 = 0.77 \pm 0.37$), and was able to predict PGI of the test sets with 92% accuracy. Cortical-striatal synchrony in the gamma and theta bands appeared as important features in the model.

DISCUSSION

We examined targeted CSTC network disruption with combined cortical (SMA) and VC/VS neurostimulation in one patient

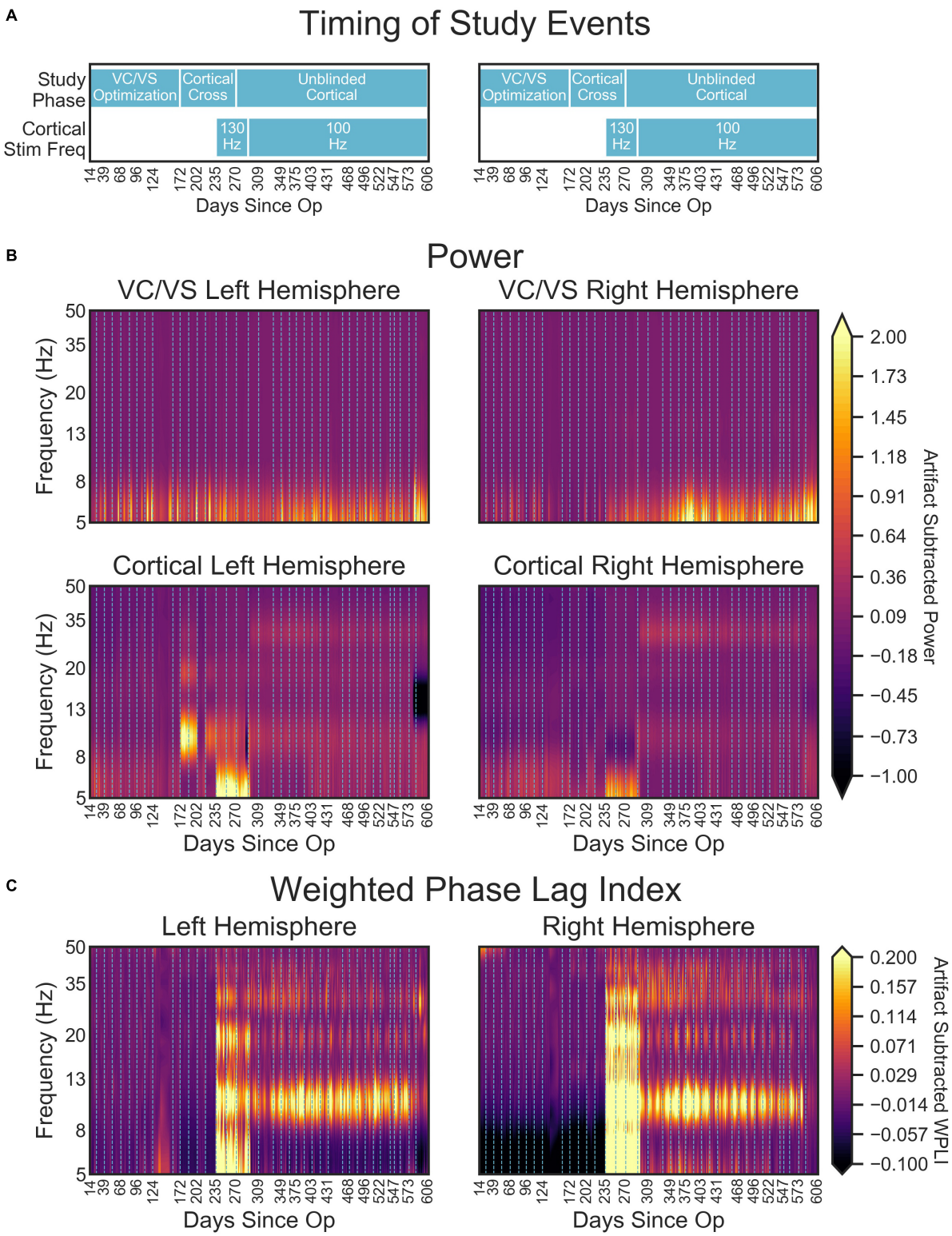

FIGURE 9 | (A) Timing of important study events for reference. **(B)** Heatmaps denoting the artifact corrected power (5–50 Hz) across the course of the study. **(C)** Artifact corrected cortical-striatal synchrony (WPLI) across the frequencies tested, as a function of days since operation. To better show subtle changes in WPLI, the range used for the color map is –0.1 to 0.2. Dotted lines on heatmaps **(B,C)** indicate clinical sessions, during which stimulation and recording settings changed and clinical outcomes were taken (see **Figure 2** above for timing of important settings changes). Areas with missing LFP recordings have been interpolated (e.g., between days 138 and 151).

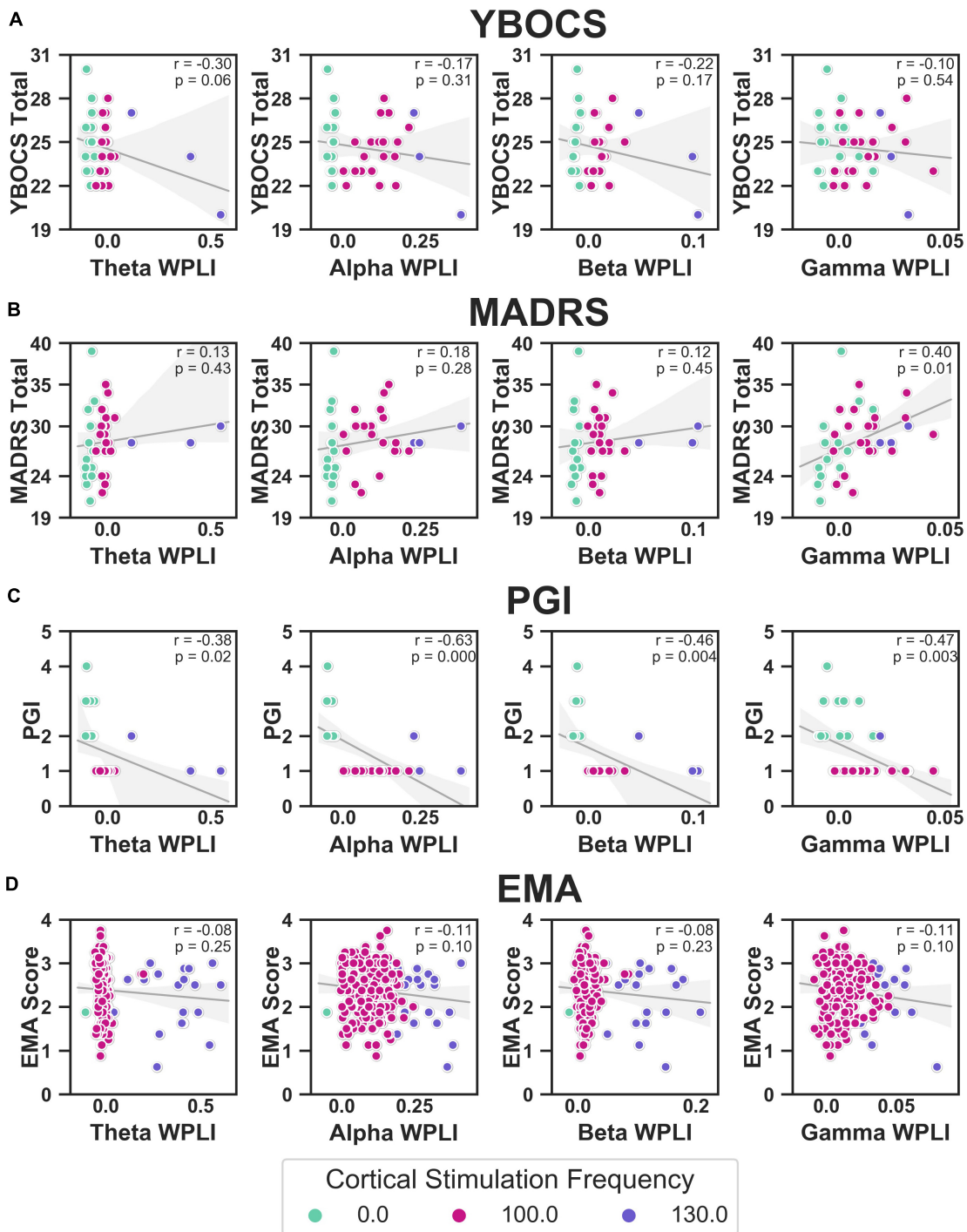

FIGURE 10 | Correlations between YBOCS **(A)**, MADRS **(B)**, PGI **(C)**, and EMA **(D)** and WPLI in the theta (leftmost column), alpha (second from the left), beta (second from the right), and gamma (rightmost column) bands. Data points are colored by the cortical stimulation frequency. Linear regressions (gray lines) were fit to the full data set for that measure (i.e., not separated by cortical stimulation frequency), with the error bands indicating the 95% confidence interval. Pearson correlations were also calculated, and the corresponding *r* and *p*-values are displayed.

with treatment refractory OCD in a blinded crossover study. Chronic recording of the cortical-striatal circuit for almost 2 years allowed us to test the hypothesis that frequency mismatched stimulation would disrupt CSTC hypersynchrony, leading to a greater improvement in symptoms with combined stimulation compared to VC/VS stimulation alone. The patient

TABLE 1 | Baseline accuracy indicates prediction accuracy for a constant model (i.e., using the mean to predict values), averaged across the 5 test sets.

Measure	Baseline accuracy	Model accuracy	Model R^2	Top feature properties				Top feature importance's
				Measure	Band	Recording time of day	Recording time period	
YBOCS	93.75%	94.25%	0.23 (±0.28)	SR Power	Gamma	Full Day	14 days prior	0.2870
				CL Power	Theta	Night	14 days prior	0.1945
				Left WPLI	Theta	Morning	1 day prior	0.1798
				SL Power	Theta	Evening	1 day prior	0.1723
				SL Power	Gamma	Evening	1 day prior	0.1665
MADRS	89.26%	89.06%	−0.14 (±1.39)	CL Power	Theta	Afternoon	14 days prior	0.2276
				Avg WPLI	Gamma	Evening	1 day prior	0.2165
				Right WPLI	Gamma	Full Day	1 day prior	0.2157
				Right WPLI	Gamma	Morning	14 days prior	0.2047
				Right WPLI	Gamma	Morning	1 day prior	0.1354
PGI	54.96%	91.80%	0.77 (±0.37)	Avg WPLI	Theta	Full Day	14 days prior	0.2360
				CL Power	Gamma	Afternoon	14 days prior	0.2250
				CR Power	Gamma	Evening	14 days prior	0.2051
				Left WPLI	Gamma	Morning	14 days prior	0.1922
				Right WPLI	Theta	Morning	1 day prior	0.1417
EMA	76.10%	77.48%	−0.01 (±0.40)	CL Power	Alpha	Evening	Day of	0.2240
				SR Power	Beta	Full day	Day of	0.2083
				CL Power	Alpha	Afternoon	14 days prior	0.1992
				Left WPLI	Gamma	Night	Day of	0.1849
				Avg WPLI	Theta	Afternoon	Day of	0.1836

Model accuracy indicates the accuracy of the model using only the top five features. Model R^2 (±2 SD), is the average test set coefficient of determination of the final model. R^2 values > 0 indicate that the model is performing better than a constant model, and values < 0 indicate the model is performing worse. The top five features (from an initial model using all possible features) are broken apart here into their component parts. The measure column indicates which LFP measure the feature contains (SL power, striatal left power; SR power, striatal right power; CL power, cortical left power; CR power, cortical right power; left WPLI, right WPLI, or average of left and right WPLI); Band indicates the frequency band of the feature; Recording time of day indicates which time of day the recordings contributing to the feature were from (morning, afternoon, evening, night, or the full day); Recording time period indicates how many days of recordings preceding the day the clinical measure was taken were used in the analysis (14 days preceding, one day prior to outcome measure day- YBOCS, MADRS, PGI, or day of the outcome measure day - EMA only). Top feature importances indicates the feature importance (normalized estimate of the predictive power of each feature) of each of the top features, averaged across the 5-fold cross-validated models.

is the first known case of chronic SMA stimulation, and of chronic combined cortical and VC/VS stimulation. The patient experienced no significant side-effects or adverse events with the addition of cortical stimulation. While this will need to be confirmed in future patients, these findings are a first step in establishing the safety of a combined cortical-subcortical approach to neurostimulation.

The patient experienced positive effects with acute combined cortical-striatal stimulation. Specifically, he reported an increase in the ability to divert focus away from OCD thoughts, which he did not feel with VC/VS-only stimulation. Throughout the study, the patient described cortical stimulation as the "icing on the cake" to traditional DBS. These positive effects did not translate into improvement in clinical outcomes with chronic combined stimulation, however. The patient did not respond to his initial course of standard DBS at the VC/VS target. Cortical and combined stimulation did not rescue this non-response. The patient's YBOCS dropped 13% from baseline with striatal stimulation, and 16% from baseline with the addition of cortical stimulation. The patient's MADRS dropped 26% with VC/VS stimulation, and 23% from baseline with the addition of cortical stimulation. While a single case cannot define a therapy's potential, the lack of response to chronic combined stimulation was surprising, given the positive acute effects.

Despite the lack of significant movement in formal rating scales, the patient felt as though his symptoms had greatly improved with the addition of combined stimulation, as measured by the PGI. However, it should be noted that the shift to "very much improved" occurred in the session where the patient was unblinded to the cortical stimulation. In this way, the most parsimonious explanation of subjective improvement with cortical stimulation is a placebo effect. Additionally, despite subjective feelings of improvement, at the time of this writing the patient continued to show significant impairment in functioning, as well as moderate OCD and depressive symptoms. Nevertheless, the patient's feelings of improvement may be important, given that they represent a change from previous treatments, and that the PGI-I has been shown to be related to more objective measures of symptom improvement in larger samples (e.g., Yalcin and Bump, 2003). Overall satisfaction with DBS therapy, despite a lack of response to the treatment has

been described before (e.g., Denys et al., 2020). It is possible that this effect represents changes in overall mood, or the limitations of the YBOCS in terms of sensitivity to change at extremes of pathology (van Westen et al., 2020). It is also possible, however, that this is simply a subjective sense of, "I had brain surgery, so it must be doing something." Regardless, overall satisfaction with the treatment even in the absence of response may serve a protective function, as it may represent a decrease in hopelessness, which is correlated with long-term adverse outcomes such as suicide (Papakostas et al., 2005; Beck et al., 2006).

The patient's cognitive control, as measured by performance on the MSIT, also appeared to improve with combined stimulation. In line with previous research showing improved performance with VC/VS DBS (Basu et al., preprint; Widge et al., 2019), the patient's response speed improved when he was receiving optimized VC/VS stimulation. With the addition of cortical stimulation he showed an additional quickening of response time, compared to optimized VC/VS stimulation alone. It should be noted, though, that the patient did appear to show an effect of time, such that he improved as day since operation increased (see **Figure 5**). Our study design meant that stimulation condition and day since operation were highly collinear. Therefore, we are unable to dissociate the improvement seen with stimulation condition from an improvement with time. However, Widge et al. (2019) found no differences in RT between multiple MSIT runs conducted an average of 88 min apart. It is unlikely that such effects would emerge at much longer time delays, such as those seen in our study. Therefore, differences between VC/VS only stimulation and combined stimulation may reflect an additional boost to cognitive control with the addition of cortical stimulation. This finding tracks with our finding of subjective symptom improvement with combined stimulation, and the possibility that the YBOCS may not have been sensitive enough to detect changes in our patient's OCD pathology. Namely, there may have been subtle shifts in some of the cognitive deficits thought to underly OCD (e.g., Robbins et al., 2012; Shin et al., 2014; Voon et al., 2015; Vaghi et al., 2017) which resulted in the subjective improvement felt by the patient, but which were too subtle to produce significant changes in traditional rating scales. This finding also tracks with prior studies implicating medial prefrontal cortex in the cognitive deficits seen in OCD (Haber, 2003; Cocchi et al., 2012; Robbins et al., 2012; Vaghi et al., 2017; Robbins et al., 2019).

This study represents the first chronic recording of the cortical-striatal circuit in a human. Using these recordings we were able to measure cortical-striatal synchrony continuously for nearly 2 years. In line with our initial prediction, frequency mismatched stimulation did in fact alter cortical-striatal synchrony. However, this alteration was in the opposite direction of our initial prediction - frequency mismatched stimulation actually increased cortical-striatal synchrony. Further, the increase in synchrony was greater when the two frequencies were closer together (130 and 135 Hz), versus when they were farther apart (100 and 135 Hz). While there were power changes with acute cortical stimulation, synchrony changes only emerged with chronic stimulation. These findings remained even after the removal of stimulation artifacts. Additionally, the increase in cortical-striatal synchrony (in the alpha, beta, and gamma bands) was associated with an increase in the patient's subjective feelings of improvement, with LFP features (especially synchrony) predicting PGI with 92% accuracy in a random forest regression. Synchrony was not significantly related to either OCD or MDD symptoms. Importantly, given the n of 1 and the absence of baseline and stimulation off recordings, any conclusions regarding changes in synchrony are extremely tentative. Future research is needed to elucidate the influence of combined (and arguably, single-site) stimulation on the synchrony of neural oscillations, and its relationship to symptom improvement.

If the finding holds, one possibility for the unexpected increase in synchrony with combined stimulation is that neural elements may have imprecise or broadly tuned frequency responses, or responses that become insensitive to mismatch at high driving currents (Fröhlich, 2015). At the relatively high stimulation intensities used in clinical DBS, a small mismatch between driving frequencies may essentially be zero mismatch from the biological system's perspective. Another possibility is that the DBS frequency may entrain the endogenous frequency, as was observed for narrowband gamma in Swann et al. (2016). Finally, rather than causing disruption (by forcing two oscillators out of phase), it may be that the separation between frequencies can actually entrain activity at the difference between the two driving frequencies, an effect that some have proposed could be exploited therapeutically (Grossman et al., 2017).

Subjective symptom improvement with increases in cortico-striatal synchrony was not in line with our initial hypothesis that OCD arises from CSTC hypersynchrony. While this finding clearly requires replication, one explanation is that the hyperconnectivity hypothesis represents an oversimplified view of the neurobiology of OCD. As discussed previously, there is evidence of both hyper and hypoconnectivity (Gürsel et al., 2018), which may be partially a function of which CSTC loop (e.g., motor, associative, or limbic loops: Obeso et al., 2008; Krack et al., 2010; Milad and Rauch, 2012; Lapidus et al., 2013) the regions showing aberrant connectivity are in Harrison et al. (2009); Göttlich et al. (2014), Posner et al. (2014), and Vaghi et al. (2017). In this way, it is possible that our patient's specific pattern between VC/VS and SMA was one of hypoconnectivity, and combined stimulation did move his networks toward a more normal/healthy connectivity pattern.

Establishing an individual's specific pattern of connectivity, therefore, may be a critical step in developing personalized treatments for OCD. However, establishing this pattern does no good if there is no means of restoring the communication to "normal" levels. Neurostimulation, and in particular combined stimulation, offers a unique means of directly influencing connectivity between regions. Despite the direction, our results suggest that the communication between CSTC regions, as measured by phase synchrony, may be altered by neurostimulation. Further, our results indicate that these alterations can potentially be sustained across long periods of time, while the patient is receiving stimulation. Thus, this case

supports the possibility of using DBS to deliver personalized, network-level therapy.

Limitations, Lessons Learned, and Future Considerations

The results of the present study are limited in that it is difficult to assess whether changes in power and synchrony are a result of actual changes in brain signal, or are artifacts of stimulation. This is in part a result of the imperfect artifact rejection from the device recordings (Stanslaski et al., 2012; Swann et al., 2017), amplified in this case by the fact that some of our optimal stimulation contacts did not permit the use of the preferred "flanking dipole" recording configuration. Further, while we attempted to subtract the artifact signal from our recordings using saline bath test recordings, these methods were imperfect. Most notably, we did not have enough leads to test the full four lead configuration in saline, potentially missing artifacts that only emerge with that full configuration. Despite imperfections, we do feel that the process of establishing the signal in the absence of brain signal (which to our knowledge has not been reported before in the DBS literature) may be an important check when making claims about the effect of DBS on neural oscillations in the presence of potential stimulation artifacts. Further, effective artifact subtraction/removal will almost certainly be critical for developing closed-loop therapies, which are a critical next step in advancing neurostimulation (Bilge et al., 2018; Widge et al., 2018).

To the prior point, we believe this study is the first to report an attempt at multi-structure chronic recording through two implanted PC + S systems. One of our unpleasant surprises was that this implant configuration could not be combined with real-time data streaming. The two implanted neurostimulators exhibited cross-talk during streaming attempts, whether using the base PC + S system (Sensing Programmer) or the more advanced Nexus-D toolkit. Starting streaming sessions from a second IPG immediately ended the streaming from whichever IPG we had contacted first. It is unclear whether this will continue to be a limitation in future generations of sensing systems, which may benefit from continued advances in medical implant communication infrastructure. There is a move toward wireless programming even for clinical applications, which necessitates the development of devices that can flexibly switch bands to prevent cross talk.

One solution to the problem of stimulation artifacts is simply taking recordings with stimulation off. This is the approach that has been taken in previous studies (Huang et al., 2019; Veerakumar et al., 2019), and will be our approach moving forward. However, taking stimulation off recordings presents potential challenges/drawbacks. The first is the potential unblinding of the participant during a randomized protocol. There is also the potential that the changes in synchrony due to combined stimulation only occur while stimulation is on. One indication that this may be the case comes from studies showing that the beneficial effects of VC/VS DBS for OCD are not sustained when stimulation is turned off in a blinded fashion (Luyten et al., 2016), and from our own studies showing rapid cognitive change from DBS discontinuation (Widge et al., 2019). Therefore, we also plan to take recordings with stimulation on. While this brings us back to the issue of stimulation artifacts, we believe that having corresponding stimulation on and off recordings would only be beneficial.

The data from this specific patient are limited in that there were no baseline recordings taken prior to turning on VC/VS stimulation. Baseline recordings would have helped establish the level of cortical-striatal synchrony in our patient in the absence of an intervention. The original protocol called for 2-weeks of baseline recordings. However, as discussed previously, while recovering in the hospital the patient reported suicidality, which he attributed to cessation from his prior DBS therapy. From then on, the patient declined any deactivation of VC/VS stimulation, and as such, we were unable to obtain any recordings in the absence of stimulation. This is also the reason we were unable to obtain stimulation off recordings throughout the course of the study. Psychiatric DBS patients generally tolerate turning the device off [e.g., 14 out of 14 participants in Widge et al. (2019) tolerated having their stimulation turned off], so DBS on/off comparisons will likely be possible in the future, and will clarify the baseline, non-stimulation recording characteristics.

The results are also potentially limited in the specific patient selected as the first participant. Given that the patient did not respond to his initial course of VC/VS DBS, the approving physicians felt that there was hope of improvement with the addition of combined stimulation. In hindsight, the lack of response to prior VC/VS DBS may instead have been an indication that the patient would also be more likely to be a non-responder to other types of neurostimulation. Further, the presentation of the patient's OCD symptoms is particularly challenging, in that his compulsions are largely mental and thus difficult to target for exposure. It is very hard to distinguish some of these compulsions from ruminative preoccupation. This pattern may have made it less likely that the patient would respond to treatment, and is an important caution for DBS patient selection generally.

Moving forward, we also plan on implementing EMA style assessments of OCD and other symptoms, which are an important way of capturing more frequent variability in symptoms [see Walz et al. (2014) for a review of their use in anxiety disorders]. We will also attempt take corresponding LFP recordings in an effort to more successfully model changes in symptoms using the features of the LFP. The EMA used in the present study was limited in that it did not specifically measure OC symptoms, but instead was an assessment of motivation and the ability to perform daily tasks. Further, the EMA only began being collected mid-way through the study, meaning that important baseline levels were not established. For the next patient, we plan to collect a wide range of baseline questionnaires and EMAs prior to initiating treatment. Theoretically, it should also be possible to then titrate future EMAs to just the areas in which the patient shows the most impairment, making the

EMAs more user friendly. As previously discussed, there are significant nuances and (likely) individual differences in the complex pattern of aberrant connectivity in individuals with OCD. Therefore, establishing an individual's specific pattern of connectivity may help improve neurostimulation therapies for psychiatric disorders through targeting brain regions which show dysfunctional connectivity. While there are almost certainly others, we see two methods of implementing this type of targeting. The first is the use of diffusion tensor imaging (DTI) and tractography. This type of MRI was not possible in the first patient due to his chronic indwelling hardware, but we anticipate collecting it in future patients. Using the patient's tractography between certain CSTC seed regions, we may be able to more specifically target both sub-cortical and cortical electrodes. The second is the through measuring cortical-striatal synchrony intraoperatively, in real-time. Electrodes (especially cortical) could be placed in areas showing the most pronounced synchrony patterns (either high or low synchrony, depending on the patient).

CONCLUSION

Psychiatric disorders, including OCD, are network disorders. We have shown that those networks can potentially be safely manipulated with multi-site continuous stimulation, and measured over periods of years with currently available technologies. Although the patient was not relieved of his psychiatric symptoms to the extent expected, our results are important safety and feasibility evidence toward a more network-oriented and personalized approach to DBS.

DATA AVAILABILITY STATEMENT

Preprocessed data and analysis script are available at: https://github.com/tne-lab/Olsen-et-al-2020. Raw data and preprocessing scripts can be made available upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Massachusetts General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AW conceived, developed, and supervised all aspects of the study, with significant input from DD. SO wrote the manuscript with support from AW and IB and performed the final data analysis with significant input from MTB, IB, and AW. AW, DD, CC, and TD performed the clinical care aspects of the study. ZW performed the study surgical procedures. MTB, IB, AK, MJB, AR, AG, and EH carried out the study procedures and collected the data. IB performed the saline bath test study. MTB conceptualized and created the data analysis procedures. IB, AK, MJB, AR, AG, and EH provided the data analysis support. NP and AR performed the MRI analysis and developed the MMVT software. JB conceived of and carried out the separate study of which the ecological momentary assessments are reported here. ME, IS, KF-H, and JS performed the data collection and some analysis of the ecological momentary assessment study. All the authors contributed to the article and approved the submitted version.

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A Pilot Study on Data-Driven Adaptive Deep Brain Stimulation in Chronically Implanted Essential Tremor Patients

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Deep brain stimulation (DBS) is an established therapy for Parkinson's disease (PD) and essential-tremor (ET). In adaptive DBS (aDBS) systems, online tuning of stimulation parameters as a function of neural signals may improve treatment efficacy and reduce side-effects. State-of-the-art aDBS systems use symptom surrogates derived from neural signals—so-called neural markers (NMs)—defined on the patient-group level, and control strategies assuming stationarity of symptoms and NMs. We aim at improving these aDBS systems with (1) a data-driven approach for identifying patient- and session-specific NMs and (2) a control strategy coping with short-term non-stationary dynamics. The two building blocks are implemented as follows: (1) The data-driven NMs are based on a machine learning model estimating tremor intensity from electrocorticographic signals. (2) The control strategy accounts for local variability of tremor statistics. Our study with three chronically implanted ET patients amounted to five online sessions. Tremor quantified from accelerometer data shows that symptom suppression is at least equivalent to that of a continuous DBS strategy in 3 out-of 4 online tests, while considerably reducing net stimulation (at least 24%). In the remaining online test, symptom suppression was not significantly different from either the continuous strategy or the no treatment condition. We introduce a novel aDBS system for ET. It is the first aDBS system based on (1) a machine learning model to identify session-specific NMs, and (2) a control strategy coping with short-term non-stationary dynamics. We show the suitability of our aDBS approach for ET, which opens the door to its further study in a larger patient population.

Keywords: deep brain stimulation, neural decoding, essential tremor, machine learning, adaptive deep brain stimulation, closed-loop deep brain stimulation

1. INTRODUCTION

Deep brain stimulation (DBS) is an established clinical treatment for refractory stages of Parkinson's disease (PD), dystonia, and essential tremor (ET) (Krauss et al., 2004; Rodriguez-Oroz et al., 2005; Baizabal-Carvallo et al., 2014). In a standard clinical context, DBS parameters (as amplitude, frequency, pulse width, and electric field shape) are periodically determined by a trained expert for each patient. This recurring yet infrequent adaptation, accounts for post-surgical transient states and disease progression. However, it is insufficient for adapting to behavioral contexts and neurophysiological changes occurring on much shorter timescales. Furthermore, patients undergoing such continuous DBS (cDBS) therapy are prone not only to chronic motor and neuropsychiatric side-effects like speech disorders, dysarthria, depression, and emotional disinhibition (Bin-Mahfoodh et al., 2003; Appleby et al., 2007; Ondo et al., 2007; Witt et al., 2008, 2012; Fakhar et al., 2013; Castrioto et al., 2014; Little et al., 2016), but also to transient side-effects, including paresthesia, other speech disturbances, and gait ataxia (Kuncel et al., 2006; Appleby et al., 2007; Aldridge et al., 2016; Reich et al., 2016).

1.1. Closed-Loop Adaptive DBS

As an alternative to cDBS strategies, adaptive DBS (aDBS) systems use motor state surrogates to provide an online adaptation of DBS parameters. Such strategies decrease stimulation when it is not required, and thus may ameliorate DBS-induced side-effects (Little et al., 2013, 2016; Khobragade et al., 2015).

1.1.1. Surrogates of Motor Performance

A key component of an aDBS system is a reliable motor state estimate, which can be quantified using inertial measurement units (IMU) or surface electromyography (Graupe et al., 2010; Herron et al., 2016). Alternatively, motor state surrogates can be extracted from brain signals, thus disregarding the necessity of external sensors (Little and Brown, 2012; Hoang et al., 2017; Panov et al., 2017). These motor state surrogates, termed neural markers (NMs), can be measured from local field potentials (LFP) of subcortical (Little et al., 2013; Priori et al., 2013) or cortical areas (Whitmer et al., 2012; Cao et al., 2017; Swann et al., 2018). A well-known example of NMs extracted from LFPs is the power of the beta-band (12–30 Hz), which—despite unclear causal relation and action mechanisms—is correlated with PD symptoms, such as bradykinesia and rigidity (Kühn et al., 2008, 2009; Whitmer et al., 2012; Blumenfeld and Brontë-Stewart, 2015; Neumann et al., 2017). Likewise, cortical band-power features have also been found to correlate with motor symptoms' severity in PD and ET (Weiss et al., 2015; Kondylis et al., 2016). The aforementioned studies follow a top-down approach for the identification of NMs by following *a priori* pathophysiological group-level knowledge about the disorder. While these surrogates facilitate the understanding of underlying neural dysfunctions, their informative value for controlling an aDBS system may be limited when it comes to an individual patient, because the heterogeneous phenotype of the diseases indicates that a global NM suited for all patients may not exist (Johnson et al., 2016). Such an NM seems even more elusive in a more semiologically complex disease, as PD, where research has been focused on symptom-wise NMs identification.

In contrast to top-down approaches used in the field of brain-computer interfaces (BCI) can be used to determine subject-specific NMs using machine learning (Blankertz et al., 2011; Tangermann et al., 2012; Neumann et al., 2019), thus improving motor state characterization of individual users (Meinel et al., 2016). Initial work in this direction has been presented by Connolly et al. (2015), who implemented machine learning methods to decode stages of PD in an animal model based on band-power and cross-frequency features. In more recent studies, Tan et al. (2019) and Yao et al. (2020) have argued in favor of a bottom-up approach for identification of NMs and discussed the implications that this may have on an aDBS system, however, their study was only implemented offline and thus, the suitability of such approach in a real scenario remains an open issue.

1.1.2. Strategies of Closed-Loop Control for aDBS

Pioneering studies of aDBS for PD animal models utilized control strategies triggered by action potentials in the motor cortex or internal globus pallidus (Rosin et al., 2011). Later studies in human patients implemented uni-dimensional power-band features driving threshold-based controllers, yielding symptom suppression comparable to cDBS strategies, while having a significantly shorter effective stimulation time, as shown by Little et al. (2013, 2015). Likewise, Rosa et al. implemented a proportional control strategy based on the same oscillatory NMs, obtaining similar results in terms of symptom suppression and reduced net stimulation (Rosa et al., 2015). These studies stand out among the first approaches on aDBS systems for humans. In more recent contributions, Velisar et al. (2019) have improved upon them by utilizing fixed dual-threshold control implementing hysteresis which accounts for fast variations in the control signal.

These threshold-based and proportional control strategies generally disregard any state transition information or the temporal evolution of the symptoms and of the corresponding NMs, since the next control signal is determined based on just a single NM state measurement (the NM at the current time point). However, the temporal history of the NMs might contribute important information. For example, several authors have suggested temporal dynamics of beta-band power embedded in beta-burst characterization as potential source of dynamics-aware information (Tinkhauser et al., 2017; Moraud et al., 2018; Piña-Fuentes et al., 2019). Likewise, dynamics-aware control strategies have also been explored. For example, model predictive control for ET in an aDBS system based on IMU information (Haddock et al., 2017), coordinated-reset in PD patients and animal models (Adamchic et al., 2014; Wang et al., 2016), phase-dependent burst stimulation (Cagnan et al., 2016), or context-triggered strategies based on event-related desynchronization (Herron et al., 2017). These studies are an important indication for considering patient-specific temporal dynamics for control of aDBS systems.

1.2. Developing aDBS Systems for ET Patients

Developing novel aDBS systems is a challenging endeavor. For example in PD, the characterization of robust NMs by itself is a difficult task, mainly due to PD's phenotype hetereogenity and the difficulty of measuring axial symptoms and their delayed suppression upon DBS. Furthermore, the temporal dynamics in PD are non-trivial due to the DBS *washout*—a decaying clinical effect of DBS therapy observed after stimulation withdrawal—which affects different symptoms at different timescales (Cooper et al., 2013). In contrast, ET has several characteristics that renders it a simpler scenario for aDBS development, compared to PD. Notably, ET symptoms are generally restricted to kinetic and postural tremor, and the DBS washout effect is negligible. Finally, as the prevalence of ET is significantly greater, it is easier to investigate: a recent meta-study found that ET affects nearly 5% of the population over 65, compared to <2 % of the same demographic diagnosed with PD (Alves et al., 2008; Louis and Ferreira, 2010).

With our contribution, we present a proof-of-concept study of a novel closed-loop aDBS system with model-free control. To the best of our knowledge, it is the first system that implements (1) characterization of NMs based on machine learning and (2) a dynamics-aware control. As such, it addresses the major challenges found in aDBS. We provide results for three ET patients, totaling five experimental sessions, demonstrating the feasibility of our approach.

2. METHODS

The proposed aDBS system is grounded on two main functional building blocks: (a) the estimation of ongoing tremor intensity based on individual spectral features extracted from ECoG signals, processed by a machine learning algorithm *(in section 2.1 NM identification based on machine learning methods)*; and (b) a model-free control strategy, that adapts the stimulation amplitude based on temporally local statistics of tremor prediction *(in section 2.2 control signal generation robust to non-stationary dynamics)*. In the following subsections, we will describe both functional building blocks and the specific methods used to implement them[1]. At the end of the section, a brief description of the Fahn-Tolosa-Marin (FTM) rating scale is provided, which is a clinical assessment tool that characterizes tremor intensity in patients and which we would also use for supporting the assessment of tremor.

2.1. NM Identification Based on Machine Learning Methods

The appearance of ET has been linked to dysfunctions in the cortico-thalamic-cerebellar loop. Specifically, anomalies in the connectivity and band-power activity of the motor cortex have been identified as physiological surrogates of the disease (Raethjen and Deuschl, 2012; van Wijk et al., 2012; Neely et al., 2014). Therefore, we propose to use the band-power of ECoG signals recorded from the primary motor cortex (M1) as information source to learn patient-specific NMs for the proposed data-driven tremor estimation.

Let $\boldsymbol{y} \in \mathbb{R}^{N_e}$ be a vector containing average tremor intensity measured at N_e time windows, as characterized from an IMU. We propose to find a linear projection vector $\boldsymbol{w} \in \mathbb{R}^{N_f+1}$, where N_f is the number of frequency bins of the ECoG signal, such that

$$\widehat{\boldsymbol{y}} = \boldsymbol{w}^{\mathsf{T}}\boldsymbol{X} \tag{1}$$

with $\widehat{\boldsymbol{y}} \in \mathbb{R}^{N_e}$ denoting the predicted tremor intensity at N_e time windows, and $\boldsymbol{X} \in \mathbb{R}^{N_f+1\times N_e}$ a matrix containing the spectral power of selected frequency bins computed from N_e time windows recorded from an ECoG electrode placed over M1, and a row containing only ones, for bias estimation. Tremor intensity $\boldsymbol{y}$ is an autocorrelated process since contiguous time points are not necessarily independent; however, for the sake of simplicity in our proof-of-concept system, we assume that the measurements of $\boldsymbol{y}$ have sufficient temporal distance such that the samples are independent and identically distributed. Under this assumption, the weights $\boldsymbol{w}$ can be estimated by solving the optimization problem $\arg\min_{\boldsymbol{w}} ||\boldsymbol{y} - \widehat{\boldsymbol{y}}||^2$.

This ordinary least mean square regression problem can be solved analytically, resulting in a weight vector $\boldsymbol{w} = (\boldsymbol{X}\boldsymbol{X}^{\mathsf{T}})^{-1}\boldsymbol{X}\boldsymbol{y}$.

2.2. Control Signal Generation Robust to Non-stationary Dynamics

In the closed-loop study by Little et al. (2013), thresholds on NMs to switch DBS on or off had been determined manually. Similarly, the proportional control strategy by Rosa et al. (2015) uses pre-estimated band-power ranges to determine a linear mapping to DBS amplitude. These approaches were successful (even in experiments involving freely moving PD patients) and are referents in the field.

Those fixed mappings between observed NMs and amplitude, however, presuppose the underlying neural system as a stationary process. Nonetheless, this assumption is problematic in aDBS: The dynamics of band power NMs are context-dependent and change upon, e.g., sitting, walking, or during transitory movement states (Bulea et al., 2014; Haddock et al., 2017). In addition, they are co-modulated by other processes, such as the circadian rhythm or medication intake (Pollok et al., 2012). Therefore, we propose a time-varying mapping of $\widehat{\boldsymbol{y}}$ to the DBS-amplitude, based on local *high* and *low* tremor intensity states, derived from moving statistics of the estimated tremor. Specifically, we define an increase or decrease in DBS amplitude Δu by

$$\Delta u = \begin{cases} u_i, & \text{if } \widehat{\boldsymbol{y}} > \delta_h^t \\ u_d, & \text{if } \widehat{\boldsymbol{y}} < \delta_l^t \\ 0, & \text{otherwise} \end{cases} \tag{2}$$

where $u_i \in \mathbb{R}^+$ and $u_d \in \mathbb{R}^-$ are scalars that respectively indicate an increase or decrease in stimulation amplitude, and $\delta_h^t, \delta_l^t \in \mathbb{R}^+$ are the corresponding time-varying thresholds at time point t.

[1]All methods were implemented using the publicly available MNE python (Gramfort et al., 2013) and scikit-learn (Pedregosa et al., 2011).

We use the Bollinger bands method (Bollinger, 2001) to compute δ_h^t and δ_l^t. It is widely used in financial analysis for detecting trends in assets pricing, characterizing relative high and low states. In our case, the same principle is used to detect whether the current tremor estimation delivered a relative *high* or *low* intensity state, based on a short term history of the estimated tremor $\widehat{y}$. Specifically, $\delta_h^t = a_N\left(\widehat{y}_t\right) + Kstd_N\left(\widehat{y}_t\right)$ and $\delta_l^t = a_N\left(\widehat{y}_t\right) - Kstd_N\left(\widehat{y}_t\right)$, where $K \in \mathbb{R}^+$ is a scaling constant, $a_N\left(\widehat{y}_t\right)$ is the moving average of $\widehat{y}$ computed in the time interval $[t-N, t]$, and $std_N\left(\widehat{y}_t\right)$ defines the standard deviation of $\widehat{y}$ in the same period of time.

2.3. Binary and Graded aDBS

We propose two approaches for determining the control signals u_i and u_d, inspired by the threshold-based aDBS and proportional aDBS systems used in Little et al. (2013), Rosa et al. (2015), and Velisar et al. (2019):

In the data-driven *binary aDBS* (**b-aDBS**), only DBS "on" and "off" states are considered, i.e., $u_i = -u_d = A_{cDBS}$, where A_{cDBS} corresponds to the patient-specific DBS amplitude optimized by a trained expert for clinical cDBS therapy.

In the data-driven *graded aDBS* (**g-aDBS**), a granular control of the DBS amplitude is provided by $u_i = -u_d = 0.5\,V$, which is the minimum voltage change Δu implementable in the available hardware platform.

In both cases, the stimulation amplitude is restricted to the interval $[0, A_{cDBS}]$.

2.4. Clinical Assessment of Tremor

In a standard clinical context, the FTM is used for assessing the tremor intensity in ET patients and the corresponding efficacy of DBS or standard pharmacological treatment. We will use the FTM scale as one of the assessment criteria for our developed systems. The FTM assessment is divided into several items that evaluate axial symptoms, motor activities (such as drawing or water pouring), as well as tremor intensity in specific limbs. These items are scored with integer numbers from 0 (no tremor), up to 4 (tremor amplitude >2 cm). For more details about the FTM scoring system, we refer the reader to the original publication (Fahn et al., 1993).

3. EXPERIMENTAL SETUP

3.1. Patients

This study was conducted under supervision of the University of Washington Institutional Review Board following the set of ethical principles outlined in the Declaration of Helsinki regarding human experimentation. Experiments were conducted in five sessions performed with three right-handed patients diagnosed with ET: one session with patient 1 (S_1^1), and two sessions each with patient 2 (S_2^1, S_2^2), and patient 3 (S_3^1, S_3^2). All patients were unilaterally implanted with DBS electrodes in the left ventral intermediate nucleus and with an four-electrode linear ECoG strip (re-purposed Medtronic Resume II spinal cord stimulation electrode with four contacts) over the hand area of the left M1. The ECoG strip was positioned using steady state evoked potentials obtained from the median nerve to identify the hand sensorimotor cortex. The canonical ventral intermediate nucleus coordinates are targeted based on the anterior and posterior commissural points (AC/PC) rectification of MRI and corrections based on patient anatomy. X is left-right, Y is anterior-posterior, and Z is superior-inferior. Canonical target is: X = 0.55 × AC/PC distance lateral to midline; Y = 0.25 × AC/PC distance posterior to mid-commissural point (half the distance between AC and PC); Z is at a plane defined by the line between AC and PC. Additionally, the location of the internal capsule and the width of the third ventricle is examined. The electrode is positioned at least 3 mm from the border of the internal capsule, which is usually about 10.5 mm + 1/2 the width of the third ventricle, roughly corresponds the X as calculated above. DBS lead and ECoG strip location were confirmed with post-operative CT scan.

Signal acquisition and DBS was performed with the implantable Medtronic Activa PC + S, an investigational neurostimulator approved for use in this research through both an FDA investigational device exemption. The ECoG recording electrode configuration was determined in a different study as the most effective for achieving volitional control of DBS, with the same patient population here presented (Houston et al., 2018).

Excepting stimulation amplitude, DBS parameters were kept unchanged from clinical decisions, and thus vary between subjects, as found in **Table 1**. The same table shows the time elapsed between implantation surgery and execution of the corresponding experimental session, and amount of data collected per session.

3.2. Session Design

Figure 1 shows an overview of the implemented system and its individual components, as described in the previous section. In the following, the training and testing stages of the system will be explained.

3.2.1. Training Data Collection

Training data was collected during a cDBS parameter optimization procedure carried out for a parallel study (please refer to Haddock et al., 2018 for further information). Patients sat at rest in a chair with hands in their laps; for each *trial*, the experimenter prompted patients to move the dominant hand to a patient-specific tremor-eliciting *posture*, where it was held during a 10 s interval, followed by a 30 s *rest* period. For the

TABLE 1 | Information about experimental sessions: Months since implantation (MSI), therapeutical cDBS parameters (amplitude, frequency, and pulse width), total amount of *rest* and *posture* trials, and the resulting time segments utilized for training the tremor decoding model.

	MSI	cDBS parameters	Rest-posture trials	N_e
S_1^1	22	2.5 V, 140 Hz, 90 μs	22	220
S_2^1	13	3.9 V, 130 Hz, 90 μs	20	200
S_2^2	16	4.1 V, 130 Hz, 90 μs	20	200
S_3^1	5	2.9 V, 140 Hz, 60 μs	20	200
S_3^2	12	3.1 V, 140 Hz, 60 μs	30	83

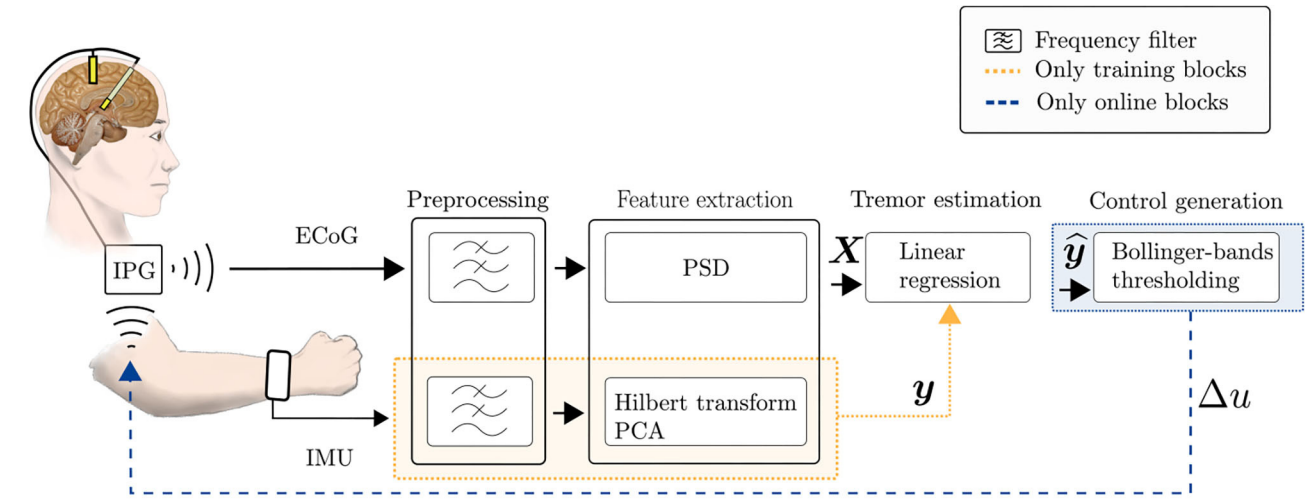

FIGURE 1 | Scheme of the implemented data-driven aDBS system, for training and online stages. Firstly, ECoG data and IMU data are collected for training the tremor estimation model. During the online stage, the tremor estimated by the trained linear regression model of Equation (1) is used for generating the DBS control signal in Equation (2).

tremor-eliciting *posture*, patients were instructed to conduct the "arms extended" and "wing-beating" postural tests of the TETRAS test (Elble et al., 2016). If these tests did not generate sufficient tremor, patients were asked to hold a posture they knew to be especially troublesome while untreated. Specifically, for S_1 and S_3, the "wings" posture was most effective, while for S_2 imitating the act of holding a screwdriver to a fixed point was most effective.

Even though different DBS configurations were applied throughout the stage, only trials performed during DBS-off were used as training data. From these trials, only *posture* segments were used. Restricting our analysis to the posture condition only is not a useful distinction in a clinical aDBS. However, for this pilot study, we want to prioritize NMs that do not represent voluntary movements. In a scenario where one would consider both, posture and rest conditions, then the derived labels y would be structured as two large clusters of tremor activity corresponding to these conditions. The tremor would vary within each of them, but the largest variation might be between them. So if both conditions are considered, any NM that we extract to capture variations in tremor, might be related to tremor itself (and would be an appropriate feedback signal for the aDBS system), or might be related only to posture and rest conditions but unrelated to any pathology. The latter, of course, would be unsuitable as a feedback signal for the control system because the tremor label would have acted just as a label of rest/posture conditions, and not as a label of pathological tremor.

The total amount of rest-posture trials collected during this stage can be found in **Table 1**.

3.2.2. Online Stage—Posture Prompt

Following the training run, the b-aDBS and g-aDBS approaches were applied online. Analog to the training stage, a computer screen prompted patients to remain at *rest* during 20 s, and then to hold that same patient-specific tremor-inducing *posture* during 30 s before going back to the rest position. In total, 12 rest-posture trials were collected for each controller type during this online stage.

3.2.3. Online Stage—Clinical Assessment

In the final phase of the experimental sessions, the clinical efficacy of the aDBS strategies was compared to cDBS and DBS off, using parts A and B of the FTM scale (Fahn et al., 1993). The FTM tests were captured on camera and the videos were evaluated offline by two blinded clinical experts. Due to time constraints, the FTM assessment could not be performed for all aDBS conditions. As previous studies indicate a similar clinical outcome of binary aDBS and cDBS (Herron et al., 2016), we decided to perform the video recordings for g-aDBS only and not for b-aDBS. Due to logistic constraints, this clinical assessment was performed only for sessions S_2^1, S_3^1, and S_3^2.

3.3. Signal Acquisition and Pre-processing

LFP data was recorded from a single ECoG channel with a sampling rate of 422 Hz. Data was streamed at 400 ms intervals from the Activa PC + S unit to an RF receiver connected through USB to an external computer, where all relevant computation was conducted. Angular velocity and linear acceleration were recorded in three orthogonal spatial directions at 100 Hz using the IMU contained in an *LG G smartwatch* fastened onto the subject's right wrist, resulting in six IMU channels. Since ECoG and IMU data were acquired with different systems at different sampling rates, signals had to be aligned with respect to a common timestamp. This alignment was updated with the beginning of each rest-posture trial. IMU signals were band-pass filtered with a 5-th order butterworth filter in the band corresponding to pathological tremor, i.e., $[4 - 7]$ Hz. This frequency band was fixed for all sessions, however, we confirmed in the offline analysis that the pathological tremor for all patients was found in this frequency band (not shown).

The aligned IMU and ECoG signals were segmented into ten continuous, non-overlapping 1 s epochs per trial, such that up to 220 epochs were available per patient. An artifact rejection stage was applied, removing segments containing ECoG signals with a peak-to-peak amplitude $\geq$ 3 mV. For training data, segments belonging to the transient stages of movement—i.e., transitions between rest and posture conditions, and vice versa—were removed from the analysis. Such segments were identified by detecting epochs where any IMU channel showed a standard deviation of more than five times the IMU channel-wise average standard deviation across epochs, in the tremor frequency band.

Table 1 shows the final number of epochs N_e available for training of the tremor decoding model. Note that for S_3^2, ∼72 % of the epochs had to be rejected due to artifacts and inconsistent patient's pose during the posture condition. For the rest of the sessions, all data collected during *posture* was utilized.

3.4. Signal Characterization

3.4.1. Tremor Characterization

For obtaining tremor labels $\boldsymbol{y}$, the envelope of the band-pass filtered IMU signals was extracted as the magnitude of the Hilbert transform. Average channel-wise IMU power was computed for each of the epochs by averaging the envelope across time. The resulting $N_e \times 6$ matrix was subsequently standardized along the first dimension. Finally, principal component analysis (PCA) was performed and the signals were projected onto the principal component associated with the largest eigenvalue of the corresponding decomposition, thus yielding an unidimensional representation of tremor intensity, used as the ground truth label $\boldsymbol{y}$ for training and validating the regression model in Equation 1.

3.4.2. Neural Signal Characterization

For extracting neural features, the power spectral density (PSD) of the ECoG signal was computed for each epoch using the Welch method based on the fast Fourier transform computed with 256 coefficients. Only spectral features in the interval [3 − 25] Hz were considered for further analysis, resulting in fourteen 1.56 Hz-wide frequency bins. The motivation for limiting the analysis to this frequency band lies on the spectral properties of stimulation and muscle artifacts, which are sometimes detectable in the >25 Hz rhythms. Even though ECoG signals are rather robust to muscle artifacts compared to non-invasive recordings, such as electroencephalographic signals, the pilot character of our study called for a more conservative approach to the experimental setup, which further enforced this design decision. However, we think that limiting the spectral analysis to this band does not erode the significance of results obtained, since NMs found in the literature are also typically found in this frequency range.

3.5. Training of the Tremor Decoding Model

A subset of the 14 ECoG spectral features were used to construct a patient- and session specific training data set $\boldsymbol{X}$. The subset was determined using a top-down feature selection procedure, where the full spectral feature set was iteratively pruned until the regression model's performance ceased to increase. In each iteration, the least important feature, as characterized by the corresponding weight in $\boldsymbol{w}$ was removed and the linear model was re-trained with the remaining features. Using a chronological 5-fold crossvalidation procedure (without sample shuffling), the decoding performance was assessed using the Pearson correlation coefficient ρ between $\boldsymbol{y}$ and $\widehat{\boldsymbol{y}}$. If a performance increase with respect to the previous iteration was observed, the pruned feature was left out and the iterative procedure was continued. Otherwise, the pruning stopped.

3.6. Control Signal Generation

The moving statistics determining δ_h^t and δ_l^t were computed using a time window of 20 s and a standard deviation scaling constant $K = 2$. These hyperparameters were not optimized per patient but fixed prior to the study. A control signal was issued according to the rules defined in sections 2.2 and 2.3 every time a new data package was available, i.e., every 400 ms.

4. RESULTS

4.1. Spectral Feature Relevance

Figure 2 shows the average PSD calculated for training data and the corresponding correlation ρ between band-power in each frequency bin of the ECoG signals and labels $\boldsymbol{y}$. Furthermore, the features selected by the top-down feature selection procedure are highlighted in green. The spectra show a high inter-patient variability: for patient 1, the spectrum is characterized by a prominent beta peak, similar to patient 3, whereas patient 2 is dominated by an alpha-band component. There is also a pronounced within patient variability across sessions in terms of the absolute spectral power. The frequency band of prominent spectral peaks, however, is constant across sessions within subject, i.e., alpha-band for patient 2 and beta-band for patient 3.

Power band features revealing the strongest correlation with tremor intensity vary considerably between patients: for S_1^1, S_3^2, and S_2^1 the frequency bins with the strongest correlation are in the alpha- and theta-band, whereas for S_2^2 and S_3^1 the most informative frequency bins are found beyond 10 Hz, mainly in the higher beta-band.

In contrast, features selected for inclusion in the tremor prediction model were found all across the spectrum analyzed. The absence of spectrally compact features may be explained by the high redundancy of neighboring frequency bins and as the feature selection procedure typically selects one only out of multiple bins with redundant information.

Figure 3 shows a representative example of the robustness of the spectral features used for tremor decoding under different DBS conditions. Specifically, it depicts a segment of ECoG data recorded during the online phase of session S_1. The stimulation artifact is clearly visible, nevertheless, it does not impede measurement of low-frequency components due to saturation of the amplifiers or sub-harmonics of the stimulation.

4.2. Tremor Estimation Accuracy

Table 2 shows the average Pearson correlation coefficient between estimated and true tremor intensity[2]. They indicate the

[2]For S_1^1 no IMU data was available during the online stage and consequently, tremor decoding accuracy scores can not be reported. For S_3^2, no online stage was executed for b-aDBS due to time constraints.

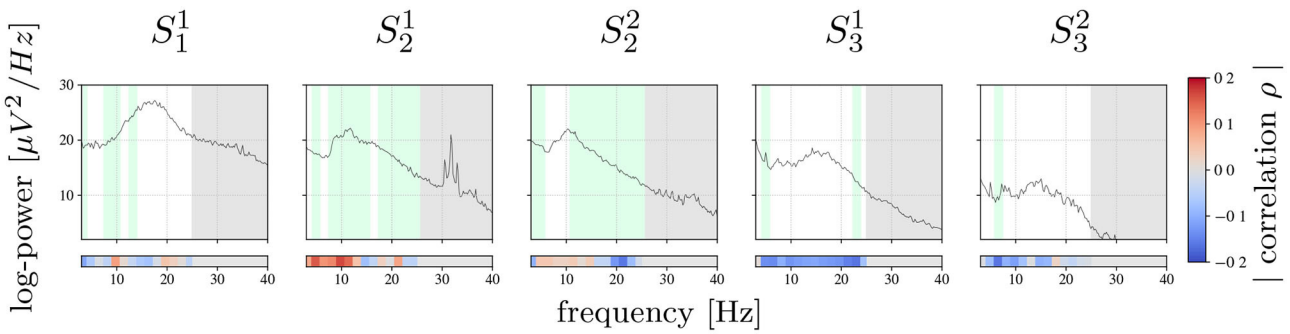

FIGURE 2 | Session-wise averaged PSD computed for training data. Bars on the bottom show the Pearson correlation achieved between each frequency bin and true tremor labels $\boldsymbol{y}$. Highlighted in green are the frequency bins selected by the feature selection algorithm. Marked with gray are frequency bins that were not used for the analysis.

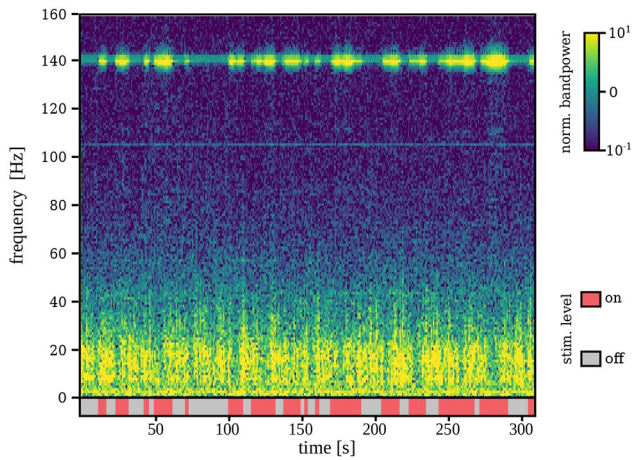

FIGURE 3 | Time-frequency representation of the ECoG signal during stimulation on and off for a representative example (S_1). Although stimulation artifacts are clearly visible, signal is not saturated and lower-frequency components are measurable even during stimulation on.

TABLE 2 | Average linear correlations between estimated and true tremor intensities.

	Training stage			Online stage	
	Theta-power (4–7 Hz)	**Data-driven**	**Informative band**	**b-aDBS**	**g-aDBS**
S_1^1	−0.06	0.39*	alpha	n/a	n/a
S_2^1	0.22*	0.21*	theta/alpha	−0.15	−0.10
S_2^2	0.16	0.22*	beta	0.05	0.12*
S_3^1	−0.14*	0.29*	theta/beta	0.29*	0.35*
S_3^2	−0.18	0.05	theta	n/a	0.20*

*Statistical significance (indicated by *) is defined at an uncorrected $p < 0.02$ obtained with a bootstrapping procedure with 1,000 label shuffles. Additionally, column informative band shows the frequency band with the largest correlations with tremor intensity, according to* ***Figure 2****.*

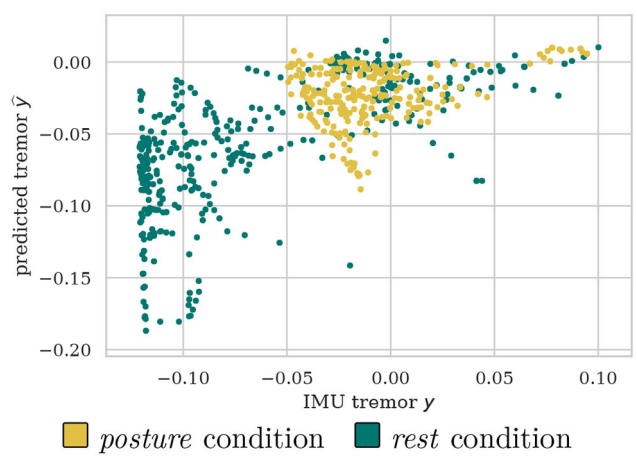

FIGURE 4 | Example scatter plot for S_3^1 of predicted vs. measured tremor intensities discriminated between *posture* and *rest* conditions.

tremor decoding accuracy during training and online stages. As a baseline, the average correlation between the theta-band power and true tremor intensity is also considered, which is a well-known NM for ET stemming from group-level studies (Kane et al., 2009). All scores derived from the training stage were computed using a 5-fold crossvalidation without shuffling. Statistical significance was defined at an uncorrected $p < 0.02$ for the probability that the score was obtained by chance under a bootstrapping procedure for 1,000 label shuffles.

It can be observed that the proposed data-driven tremor decoding model achieved a significant correlation in four out of the five sessions for the training stage. During the online stage, in three out of four sessions conducted, statistically significant decoding performance was obtained. Overall, the decoding performance of the data-driven model is superior to the fixed theta-band power, however, the correlation achieved is weak in all sessions analyzed. **Figure 4** shows a representative example of measured vs. estimated tremor, for session S_3^1.

4.3. Control Signals Distribution

Figure 5 shows an illustrative example of the control signal, including the Bollinger bands, as well as measured and predicted tremor. As expected, predicted and measured tremor intensity

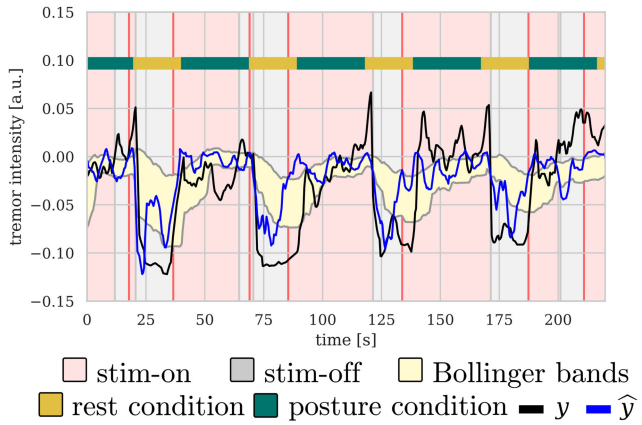

FIGURE 5 | Illustrative example of the control signal for b-aDBS computed during the online stage of S_3^1. There is a clear correlation between *posture* condition and tremor intensity, both predicted and measured, thus, triggering stimulation mainly during *posture* condition.

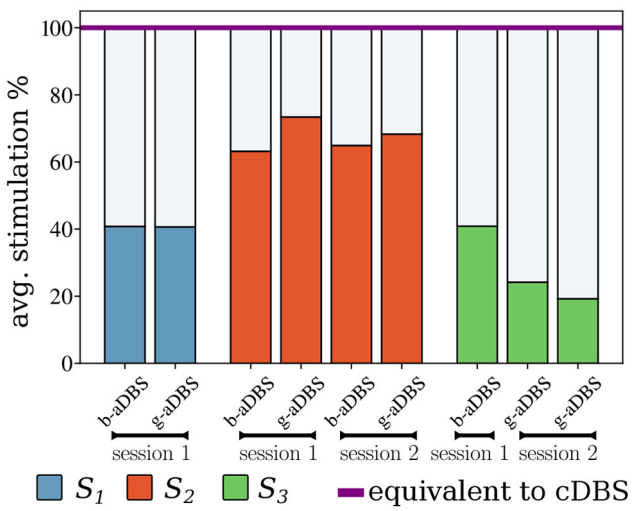

FIGURE 6 | Average time stimulated relative to the stimulation using the equivalent cDBS strategy.

increases during the *posture* condition, triggering the stimulation most of the times.

Figure 6 shows the average stimulation time during the online stages, compared to the equivalent cDBS strategy. It can be observed that for all types of controllers, the average time stimulated was considerably lower than that of the cDBS strategy. Furthermore, there is an indication for low intra-subject variability of average stimulation, whereas inter-subject variability might be larger. The total stimulation duration of b-aDBS and g-aDBS strategies was similar within patients.

4.4. Tremor Suppression in Online Stage

Figure 7 compares tremor intensity suppression ($1 - y$) between all stimulation strategies during online stages, under *posture* condition. Each box shows at the standardized mean difference of the pairwise comparison (top) and the p-values of the corresponding Mann-Whitney rank test (bottom). If standardized mean difference is negative, no values are shown. For S_3^2, no significant difference was established among all considered conditions, whereas for S_2^1 and S_3^1, adaptive strategies achieved superior tremor suppression than cDBS and improved upon DBS-off. For S_2^2, all stimulation strategies improved upon DBS-off, but no differences could be found among them. Even though, we expected aDBS to perform as good as cDBS, and better than DBS-off, cDBS only performed better than DBS-off in S_2^2, and even worse in S_3^1, suggesting a suboptimal setting of therapeutic parameters in cDBS. Overall, all significant differences reflect a small to medium size effect.

4.5. Clinical Tremor Assessment

Table 3 shows the FTM scores averaged for both clinical raters. Axial scores reported here comprises the sum of face, tongue, head, and trunk tremor scores. The scores for left/right upper/lower tremor comprises the sum of scores obtained during rest, posture, and action (finger to nose and toe to finger). For subtests with a discrepancy between clinical raters >1 point, we marked the averaged value (*) and provided both individual scores in parenthesis.

Considering the total FTM score per session, the proposed g-aDBS strategy did not lead to a worse FTM score than DBS off in none of the three sessions. The g-aDBS system achieved at least a moderate symptom suppression in two out of the three online sessions analyzed (S_2^1 and S_3^1). In these two sessions, cDBS and DBS off did not perform significantly different, while the g-aDBS score improved moderately by 2 points for S_2^1 and markedly by 3.5 points for S_3^1. For S_3^2, g-aDBS did not improve the symptoms compared to DBS off, while standard treatment cDBS reached an improvement of 2 points, indicating a moderate tremor amelioration.

A closer look at the subtests of FTM reveals that at least one point of improvement (mild tremor amelioration) between g-aDBS and the baselines cDBS and DBS off were obtained for axial and upper lateral scores for S_2^1. For S_3^1, handwriting, drawing, and pouring liquid with the right hand were the sub-tests for which g-aDBS achieved a mild improvement. Interestingly for S_3^2, g-aDBS did not worsen any symptom by more than one point (mild worsening). However, it improved drawing with the right hand by one point, compared to DBS off. In the other sub-tests, differences were at most 0.5 points, which is within the expected fluctuations over the course of a day (Pulliam et al., 2014) and indicates a marginal effect upon symptoms.

The b-/g-aDBS strategies were driven by NMs for right hand tremor (location of the IMU) extracted during *posture*. Consequently, it is important to analyze the specific scores for this item of the FTM individually: clinical raters assessed right hand postural tremor under DBS off for all the sessions as either absent (FTM score 0) or *slight* (FTM score 1 meaning an amplitude of <0.5 cm). These low tremor ratings may also offer an explanation for the low size effects shown in **Figure 7**.

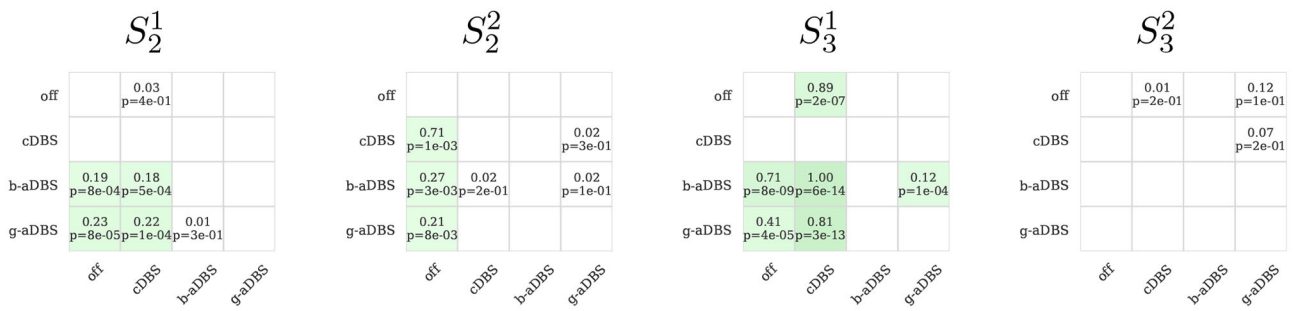

FIGURE 7 | Pairwise comparison of tremor intensity under different stimulation strategies during the online stage (only *posture* segments). In green, it is highlighted if the method in the y-axis achieved a greater tremor suppression compared to the corresponding method in th x-axis. In each box, top number indicates the effect size and bottom number the corresponding *p*-value obtained with the Mann-Whitney rank test, comparing the method on the y-axis against the corresponding method in the x-axis. Only positive effect sizes are shown. Green boxes indicate uncorrected $p < 0.05$. For the comparison, 1 s windows were used, extracted from the 30 s posture intervals of the 12 trials executed for the online stage.

TABLE 3 | Averaged scores of parts A and B of the FTM assessment for sessions S_2^1, S_3^1, and S_3^2.

	S_2^1			S_3^1			S_3^2		
Test	**cDBS**	**DBS off**	**g-aDBS**	**cDBS**	**DBS off**	**g-aDBS**	**cDBS**	**DBS off**	**g-aDBS**
Axial	1.5	1.5	0	0.5	0	0	0.5	0	0
Speaking	1	0.5	1	0	0	0	0	0	0
Handwriting	0.5	0.5	0.5	0	2.5	0.5	0.5	1.5	1
Left upper	4.5	3.5	3.5	2* (1/3)	1* (0/2)	1.5	1	1* (0/2)	1.5
Left lower	0	0.5	0.5	0	0	0	0	0.5	0.5
Left drawing	3	3	3	1.5	1	1	1.5	1	1.5
Left pouring	3	3	3	0.5	0.5	0	0	0	0.5
Right upper	3	4* (5/3)	3* (4/2)	3.5	3	3	2.5* (4/1)	3	3
Right lower	0	0	0	0	0.5	0.5	0.5	0.5	0.5
Right drawing	1.5	1	1	2	2	1	1.5	2	1
Right pouring	1	1	1	1	1	0	0.5	1	1* (0/2)
Total	19	18.5	16.5	11	11.5	7.5	8.5	10.5	10.5

Scores marked with a ∗ indicate a discrepancy of more than 1 point between the scores assigned by each of the clinicians, followed by the individual scores in parenthesis. Due to logistical constraints, FTM assessment is only available for g-aDBS.

Under cDBS, it was reported that in S_2^1 and S_3^2 tremor improved, while for S_3^1 no difference could be established. The evaluation of the g-aDBS strategy showed the same improvement as for cDBS, except for one of the clinical raters who stated that for S_2^1 tremor increased by 1 point to moderate (0.5–1 cm tremor amplitude).

5. DISCUSSION

We have presented a proof-of-concept study demonstrating the suitability of data-driven closed-loop aDBS strategies for treating ET patients. Our proposed system is based on session-specific, data-driven NMs obtained by a machine learning model, and a model-free control strategy accounting for non-stationary dynamics of the controlled system.

5.1. Using Machine Learning for Data-Driven Decoding of Tremor

Using our data-driven approach, tremor intensity could be decoded from spectral information contained in M1 ECoG signals, yielding a correlation value ranging from 0.21 to 0.39. This is a significant improvement compared to tremor decoding using solely theta-band power. Using the latter, a significant decoding performance was achieved in only two sessions. It is noteworthy that in one of the two sessions where theta-band power was informative about tremor intensity, a negative correlation was found. This not only evinces the poor generalization of NMs motivated by top-down approaches, but also shows the ambiguity in their information content. One observation confirmed by the D Agostinos K^2 test is that the kurtosis and skewness of tremor y and estimated tremor $\hat{y}$

deviate from a Gaussian distribution. This calls for caution when using the Pearson correlation coefficient, as in our case. However, the absence of long tails and outliers, and the fact that only the relative differences in correlation are important in our approach, makes this chosen decoding performance score an acceptable selection.

Furthermore, our decoding approach demonstrates that informative features are present in power of frequency bins found in the range of $[3 - 25]$ Hz and that the tremor estimation should not be limited to a single frequency band defined a priori. This result does not only confirm the necessity of data-driven NMs identification for ET, but also has important implications in the development of aDBS systems for more phenotypically heterogeneous disorders, such as PD, where patient and symptom specific characterization of the motor symptoms may improve aDBS even further.

We have also identified non-stationary dynamics contained in the NMs used. We have observed variations of global spectral features across sessions, as well as heterogeneity in the spectral feature information content, as described by the varying correlation scores between power in individual frequency bins and the tremor intensity, within patient, across sessions. Such variability in the feature information content and in tremor decoding performance within subject—for example S_3^1 and S_3^2—suggest an underlying mixture of processes that might correlate with tremor intensity, but that cannot be captured from spectral features extracted only from one contralateral ECoG channel in M1. Consequently, multimodal and multidimensional data-driven NMs should be explored.

5.2. Generation of Dynamics-Aware Control Signal

The model-free control strategy implemented in our system accounted for non-stationary dynamics of tremor estimation. Although, the number of patients included in the study is too small for a statistical analysis, the few sessions available indicated that accounting for non-stationary dynamics can allow to identify local tremor states. Their existence may explain symptom suppression achieved by our g-aDBS system in a wider variety of conditions during the FTM evaluation, compared to cDBS and DBS off.

Our control strategy does not account for non-stationary dynamics in the NMs space, but directly in the space where tremor estimation is found. However, different neural features may be governed by different non-stationary dynamics stemming from factors, such as the circadian rhythm, current physical activity, medication, and surgery-induced stun-effect. Therefore, accounting for non-stationary dynamics directly in the NM space might provide a more robust feedback signal. This should be subject to future studies, where a longer time horizon shall enable the study of multi-time scale dynamics as described above.

5.3. Clinical Assessment

From a clinical perspective, the g-aDBS strategy performed better than cDBS in two out of the three sessions assessed with the FTM scale. Unfortunately, one of the limiting factors in our study is that only the g-aDBS strategy, and not b-aDBS, was evaluated using the FTM scale. In general, the clinical evaluation of motor diseases, as PD and ET, requires a highly trained clinician and a lengthy assessment protocol. Such requirements play a major role in time-constrained situations as those encountered in typical experimental sessions.

An interesting observation regarding the FTM assessment under g-aDBS is that for S_3^1, the strongest symptom improvements were achieved for the right side of the body. Even though, the reduced number of sessions limits the interpretability of this observation, a possible explanation for this may be that the g-aDBS controller was triggered by NMs extracted from the left hemisphere, resulting in a right-sided biased symptom suppression. As a consequence, we suggest that NMs should be extracted bilaterally.

From the patients' perspective, they could clearly differentiate between no stimulation and active stimulation, but could not identify substantial differences between cDBS and g-aDBS. In b-aDBS, patients reported occasional paresthesias in their treated upper limb. This mainly occurred while stimulation was ramping up from 0 to the maximum amplitude due to the ramping rate required to keep b-aDBS effective (Meidahl et al., 2017).

5.4. Power Consumption Optimization

Our system achieved a reduction of at least 24% and as much as 80% of stimulation time. According to Khanna et al. (2015), the breakeven point of the Activa PC + S regarding power consumption in closed-loop mode is at a reduction of 6%. Therefore, our system allows a considerable reduction in power consumption well above this threshold. It is important to mention that modern systems, such as the Activa RC by Medtronic or Vercise by Boston Scientific, have rechargeable battery systems, where power consumption is not as critical as in older non-rechargeable systems. Another typical constraint when implementing aDBS in clinical grade systems is that the available platforms have low computational capacity, which limits the complexity of the algorithms that can be used. Fortunately, most computationally expensive parts of our system can be implemented by a fast Fourier transform (power spectrum estimation) and a linear projection (tremor estimation model). Both operations are relatively inexpensive and are easily implementable in simple embedded systems contained in modern DBS.

5.5. Limitations and Open Questions

5.5.1. Clinical Open Questions

The greatest limiting factor of our current contribution is the small sample size and partially conflicting outcome regarding the efficacy of the clinical cDBS condition used as control. Specifically according to the FTM scale, cDBS only performed better than DBS-off in one session, suggesting that cDBS suffered suboptimal therapeutic parameter settings, which may also define a ceiling for the effect of aDBS. This calls for a larger clinical study, where the efficacy of the proposed system can be drawn as a statistically sounding conclusion.

Another important item is clinical safety of our approach. Even though our patients did not report any side effects during treatment with aDBS (besides transient paresthesias) and we

think that our strategy does not represent any risk different from those encountered in existing aDBS strategies, the safety profile of our approach is still an open issue and should be further investigated with more patients.

5.5.2. Technical Open Questions

From a technical point of view, there are also several open questions to consider. First, we limited the training segments to *posture* condition only, this allowed us to obtain a model that effectively decodes tremor intensity during tremor-inducing conditions and should not contain discriminative information about the posture itself or movement onset. If *rest* segments would have also been included, our model would potentially learn to decode the motor task (going from *rest* to *posture* and viceversa). Although, detection of movement onset may provide additional information for controlling the system (Herron et al., 2017; Tan et al., 2019), our main goal was to obtain an aDBS system relying on symptom surrogates. This design decision limits the generalization of our approach to other postural conditions, which should be subject of further investigation.

Our system can account for spectral fluctuation of a specific NM in short and long term, since the Bollinger-bands consider a history of its activity. A large contextual change (e.g., falling asleep), however, may render the chosen NM uninformative and would limit our approach. In this case, an adaptation of the decoder (i.e., using a different NM) will be necessary. This shall be subject to future studies.

Finally, limiting the features to spectral power of M1 signals might reduce the decoding power of the underlying machine learning model. To improve upon this limitation, future systems shall include more complex features, for example as used by Yao et al. (2020) in their most recent work.

6. CONCLUSIONS

Our contribution offers the first data-driven aDBS system based on machine learning methods, accounting for short-term non-stationary dynamics, and allowing online patient-specific optimization in DBS therapy. As outlook, we foresee the clinical validation of the novel strategies presented here and the development of more advanced decoding techniques and control strategies to tackle the open challenges regarding non-stationary dynamics present in diseases, such as PD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Washington Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC-C, BF, HC, and MT conceived the methods and wrote the paper. SC-C and BF method implementation and contributed the analysis tools. SC-C, BF, SC, AH, and AK performed the experiments. SC-C, BF, SC, JH, AK, and MT analyzed the data. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Deep Brain Stimulation Impedance Decreases Over Time Even When Stimulation Settings Are Held Constant

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Objectives: To study whether and to what extent the therapeutic impedance and current change under long-term deep brain stimulation (DBS) with constant stimulation settings, which could inform the role of constant current stimulation.

Methods: Therapy impedance and current measurements were retrospectively collected from patients with Parkinson's disease (PD) undergoing DBS of the subthalamic nucleus (STN) or essential tremor (ET) undergoing ventral intermediate nucleus (VIM). Baseline and follow-up measurements were obtained for intervals of at least 6 months without changes in stimulation settings. The single longest interval of constant stimulation for each electrode was included. Temporal trends in impedance and current were analyzed as absolute and relative differences and as the rate of change.

Results: Impedance and current data from 79 electrodes (60 in STN, 19 in VIM) in 44 patients (32 with PD, 12 with ET) met inclusion criteria. The duration between baseline and follow-up measurements with constant stimulation settings was 17 months (median, with an interquartile range of 12–26 months) in the mixed group. Therapy impedance decreased by 27 ± 12 Ω/year (mean ± 2 standard errors; $p < 0.0001$), and therapy current increased at a rate of 0.142 ± 0.063 mA/year ($p < 0.0001$). Similar results were observed in the STN and VIM subgroups.

Conclusions: Impedance decreases gradually over time, even when stimulation settings are kept constant. The rate of decrease is smaller than previously reported, suggesting that changes in stimulation settings contribute to impedance drift. Stimulation-independent impedance drift is gradual but relevant to constant-current programming.

Keywords: impedance, current, voltage, DBS, STN, Parkinson's disease, VIM, tremor

Abbreviations: DBS, deep brain stimulation; mA, milliampere; Ω, Ohms; V, volts; Hz, Hertz; µs, microseconds; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus.

INTRODUCTION

Deep brain stimulation (DBS) has proven to be of significant therapeutic benefits for patients with Parkinson's disease (PD), essential tremor (ET), and dystonia (Vidailhet et al., 2005; Weaver et al., 2009; Follett et al., 2010; Williams et al., 2010; Deuschl et al., 2011). DBS has traditionally relied on constant-voltage therapy, in which the stimulation voltage is set and current delivery varies according to electrical impedance. However, constant current therapy has become increasingly used to provide more stable energy delivery (Okun et al., 2012). One of the major reasons for this is the downward drift in impedance over time (Satzer et al., 2014; Hartmann et al., 2015; Wong et al., 2018). The cause of this drift is unknown; gradual accumulation of cerebrospinal fluid around the electrode has been proposed as a potential mechanism (Satzer et al., 2014). Many factors are known to affect impedance; these include stimulation voltage, contact activity, target nucleus, and contact location concerning target nucleus (Cheung et al., 2013; Satzer et al., 2014, 2015; Wong et al., 2018). Electrode position is fixed after implantation, but stimulation settings are frequently adjusted due to disease progression and evolving patient needs. Impedance has been reported to immediately decrease after contact activation and higher stimulation voltages have been associated with lower impedance values (Satzer et al., 2014). While prior studies have employed multivariate analysis of impedance changes over time, stimulation settings have not been held constant in any of these studies. Since stimulation is associated with lower impedance, it is conceivable that a long-term increase in programmed energy delivery (compensating for disease progression) could entirely account for the observed downward impedance drift over time.

This study aimed to assess if impedance declines over time when stimulation settings are kept unchanged. Impedance has been associated with clinical response to DBS (Satzer et al., 2015). Changes in impedance over time may affect long-term benefits and motivate constant-current stimulation. Additionally, the presence or absence of stimulation-independent impedance drift can expand the understanding of the brain-electrode interface.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study was approved by the Institutional Review Board at the University of Chicago Medicine. All patients included in this study underwent DBS electrode placement (Medtronic, MN, USA) in the bilateral or unilateral subthalamic nucleus (STN) for PD or ventral intermediate nucleus of the thalamus (VIM) for ET. Patients with an interval of at least 6 months without changes in stimulation settings (voltage, pulse width, frequency, and active contact) between 2016 and 2019 were identified. Only patients undergoing constant-voltage monopolar stimulation were included. Data from the first 6 months following electrode implantation were excluded due to known early post-operative impedance fluctuation (Lempka et al., 2009). Stimulation settings, including therapy impedance (i.e., impedance measured from active contacts at the therapeutic stimulation settings) and current, were recorded from the initial and follow-up visits. Only one interval with stable stimulation settings was included per electrode; in the case of multiple such intervals, the longest interval was selected. In patients with bilateral DBS electrodes, each electrode was treated independently.

Outcome Measures and Predictors

Therapy impedance (Ohms, Ω) and current (milliampere, mA) were measured at the baseline visit (i.e., visit at the start of > 6-month interval) and follow-up visit (i.e., visit at end of >6-month interval). Time since baseline visit, DBS target (STN or VIM), and electrode laterality (left or right) were recorded. Patient demographics and fixed stimulation parameters were recorded as well.

Statistical Analysis

Data for several variables diverged from a normal distribution, and nonparametric statistical analysis was used unless otherwise specified. Subgroup composition by sex was compared between STN and VIM subgroups with the chi-squared test. Other demographic data and stimulation parameters were compared between STN and VIM subgroups with the Mann–Whitney-*U* test.

Relative change in impedance and current was calculated as value at follow-up minus value at baseline, divided by baseline value. Absolute and relative changes were compared to a hypothetical mean of zero with the Wilcoxon rank-sum test.

The rate of change of impedance and current over time was assessed with a mixed linear regression model. Impedance or current was used as the dependent variable; time, target, and laterality were analyzed as fixed effects; and a random effect for electrode was introduced to account for variation between electrodes.

An alpha level of 0.05 was used for all significance testing. Statistical analysis was performed with SAS University Edition (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Forty-four patients (32 with PD, 12 with ET) and 79 DBS electrodes (60 in STN, 19 in VIM) met the study criteria. Demographic information and stimulation parameters are reported in **Table 1**. The median length of the longest interval with constant stimulation parameters was 17 months (interquartile range of 12–26 months). There was no difference between the STN and VIM subgroups in the sex distribution, age at disease onset, age at DBS placement, length of study interval, voltage, or pulse width. The frequency was lower for STN electrodes (median 130 Hz, interquartile range 60–130 Hz) than VIM electrodes (median 130 Hz, interquartile range 130–180 Hz; $p = 0.004$), since 17 of 60 STN electrodes were programmed at 60 Hz whereas no VIM electrodes were programmed at low frequency, and several VIM electrodes were programmed as high as 180 Hz.

TABLE 1 | Patient demographics and stimulation settings.

	STN + VIM	STN	VIM	*p* (STN vs. VIM)
Patients/electrodes	44/79	32/60	12/19	-
Female[1]	13	10	3	0.73
Age at disease onset[1] (years)	54 (45–57)	54 (45–57)	48 (19–59)	0.37
Age at DBS placement[1] (years)	63 (58–69)	63 (58–69)	62 (57–71)	0.82
Longest interval without change in stimulation settings[1] (months)	17 (12–26)	17 (12–26)	11 (7–25)	0.28
Amplitude[2] (V)	3.0 (2.2–3.4)	3.0 (2.2–3.3)	3.1 (2.3–3.8)	0.22
Frequency[2] (Hz)	130 (130–130)	130 (60–130)	130 (130–180)	0.004
Pulse width[2] (μs)	60 (60–60)	60 (60–60)	60 (60–90)	0.08

Values are expressed either as counts or as median (interquartile range). [1]Statistics by the patient. [2]Statistics by the electrode. V, volts; Hz, Hertz; μs, microseconds.

TABLE 2 | Changes in impedance and current over the study period.

		STN + VIM	STN	VIM
Therapy impedance (Ω)	Baseline	719 (627–780)	719 (627–774)	727 (630–827)
	Follow-up	658 (575–738)	661 (574–739)	658 (582–718)
	p (baseline vs. follow-up)	<0.0001	<0.0001	0.004
Current (mA)	Baseline	3.691 (2.669–4.801)	3.628 (2.602–4.612)	4.219 (2.776–6.189)
	Follow-up	3.953 (2.924–4.924)	3.913 (2.926–4.739)	4.595 (2.882–6.526)
	p (baseline vs. follow-up)	<0.0001	<0.0001	0.02
Change in impedance (%)		−5% (−10% to −1%)	−5% (−9% to 0%)	−4% (−10% to −1%)
	p (vs. 0)	<0.0001	<0.0001	0.005
Change in current (%)		4% (0–9%)	5% (0–9%)	4% (1–9%)
	p (vs. 0)	<0.0001	<0.0001	0.02

Values are expressed as median (interquartile range). V, volts; mA, milliampere; Ω, Ohms.

Changes in Impedance and Current

Significant absolute and relative reduction in the impedance was found in the entire cohort ($p < 0.0001$) and in the STN ($p < 0.0001$) and VIM ($p < 0.01$) subgroups (**Table 2**; **Figure 1**). Significant increase in the absolute value and percentage change of current were also found in the entire cohort ($p < 0.001$) and in the STN ($p < 0.001$) and VIM ($p = 0.02$) subgroups (**Table 2**; **Figure 1**).

Changes in Impedance and Current Over Time

The linear mixed model analysis demonstrated a significant relationship between time, therapy impedance, and therapy current. Impedance decreased at a rate of 27 ± 12 Ω/year (mean ± 2 standard errors; $p < 0.0001$). Current increased at a rate of 0.142 ± 0.063 mA/year ($p < 0.0001$). The relationship of time, current, and impedance is illustrated in **Figure 2**. There was no significant effect of electrode laterality on impedance ($p = 0.96$) or current ($p = 0.56$). Current was 0.998 ± 0.847 mA lower for electrodes targeting STN compared to electrodes targeting VIM ($p = 0.02$). Target was not significantly related to impedance.

DISCUSSION

Impedance Drift With Constant Voltage

This is the first published study to examine DBS impedance over time when stimulation settings are kept constant. The longest interval without a change in stimulation settings was analyzed for each of 79 electrodes (60 in STN and 19 in VIM) in 44 patients (32 with PD and 12 with ET). Data collected within 6 months of electrode implantation were excluded due to early fluctuation in impedance (Lempka et al., 2009). Despite constant stimulation parameters, impedance still decreased by 27 ± 12 Ω/year, with a commensurate increase in the current of 0.142 ± 0.063 mA/year.

The rate of temporal impedance drift has previously been reported as −80 ± 8 Ω/year (Satzer et al., 2014). The lower rate in impedance decline observed in this study may indicate that changes in stimulation settings are partially responsible for impedance drift. Therapy voltage has been found to inversely correlate with electrode impedance, and contact activation has been associated with a more rapid decline in impedance (Satzer et al., 2014). This is consistent with data from animal studies showing a rapid decrease in impedance after acute stimulation, possibly due to oxidation at the brain-electrode interface (Lempka et al., 2009). Pulse stimulation has been used to restore lost signal-to-noise ratio in animal models (Johnson et al., 2005).

Relationships With DBS Targets

While the target nucleus was not significantly related to impedance, the current was 0.998 ± 0.847 mA lower for electrodes targeting STN compared to that targeting VIM. Stimulation frequency was lower among STN electrodes, but it is not immediately obvious how lower frequency would result in the lower current. Prior research has found higher impedance for STN electrodes, and while the relationship between current and time has not been assessed in prior studies, Ohm's law predicts that higher impedance would result in the lower current (Satzer et al., 2014). Anecdotally, ET-DBS patients tend to have higher voltage requirements, and higher voltage would correspond to higher current for VIM electrodes. While no significant relationship between target nucleus and voltage was observed in

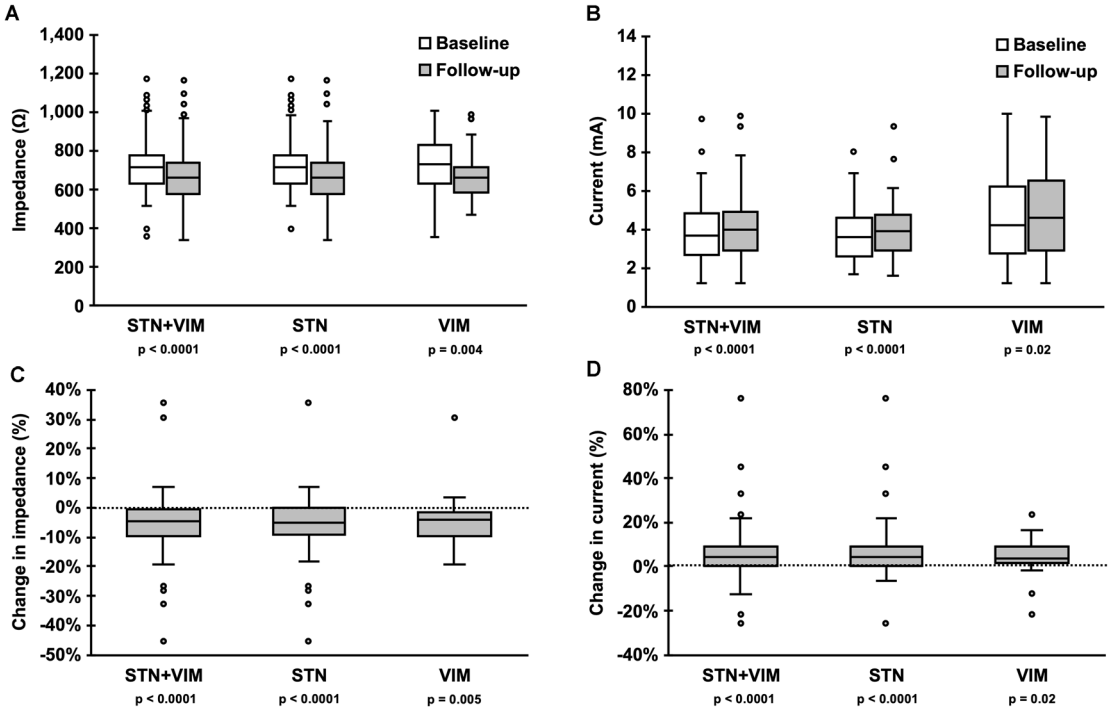

FIGURE 1 | Changes in impedance and current over the study period. Box-and-whisker plots of **(A)** impedance and **(B)** current at baseline (white) and follow-up (gray) measurements show a significant decrease in impedance, and a commensurate increase in current, for the entire cohort as well as the subthalamic nucleus (STN) and ventral intermediate nucleus (VIM) subgroups. Likewise, box-and-whisker plots of percent change in panel **(C)** impedance and **(D)** current show a significant decrease in impedance and increase in current for the entire cohort and the STN and VIM subgroups.

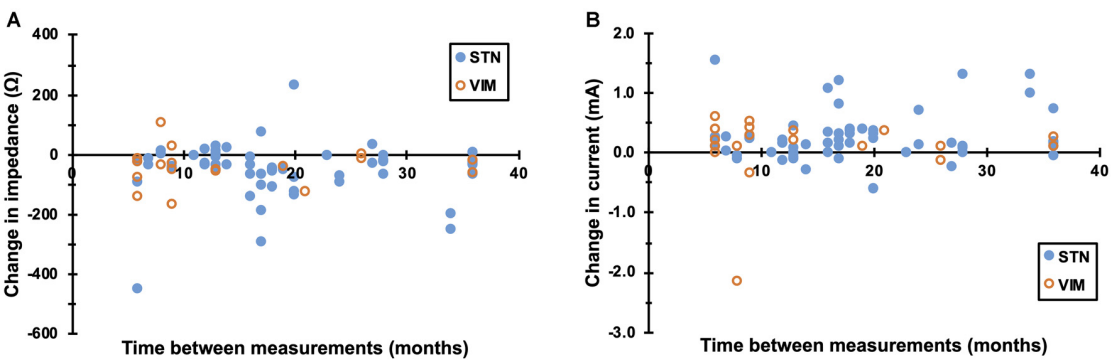

FIGURE 2 | Rate of change of impedance and current. **(A)** Therapy impedance decreased at a rate of 27 ± 12 Ω/year (mean ± 2 standard errors; $p < 0.0001$). **(B)** Likewise, therapy current at a rate of 0.142 ± 0.063 mA/year ($p < 0.0001$). Values from STN and VIM electrodes are indicated by closed and open circles, respectively. Note that absolute values of impedance and current were used for statistical analysis.

this study, the VIM subgroup was small, and the absence of a relationship between target, impedance, and voltage may simply reflect sample size.

Study Limitations

One potential confounder is the reason for the absence of stimulation setting changes during the study period. Programming changes are often made when therapy is suboptimal, losing effectiveness, or associated with stimulation-induced side effects. The patients in this cohort did not experience significant clinical worsening during the study period, and therefore the findings of this analysis may not be generalizable to all patients undergoing DBS therapy.

Another caveat in comparing these findings to prior studies is the consideration of electrode vs. therapy impedance. Electrode impedance is measured for each contact at a standardized test voltage and is easily compared between subjects, whereas

therapy impedance is measured between active contacts at the therapy voltage and has direct clinical relevance. Both types of impedance have been found to decrease over time (Satzer et al., 2014; Wong et al., 2018). The present study attempted to compromise between both types of impedance by recording therapy impedance exclusively from patients undergoing monopolar stimulation in periods without changes in stimulation setting.

This study was retrospective. The sample size was small, due to the strict inclusion criteria including an extended interval without a change in stimulation settings, although this trade-off was made to control for stimulation parameters, which varied in previous studies. Secondary analysis of data from larger prospective trials mandating fixed stimulation parameters could overcome these limitations.

Implications for DBS Therapy

In clinical practice, programmed voltage is expected to increase over time to compensate for disease progression. This study suggests that increases in stimulation magnitude may account for some variation in impedance over time but do not fully explain impedance drift. Stimulation-independent impedance drift (and the corresponding increase in current) appears to be a very gradual and mild phenomenon but still serves as a motivator for constant-current programming. The clinical significance of this change requires further study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Chicago Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TX: conception and design. TX, DS, and HY: analysis and interpretation. TX and MW: data collection. TX, DS, and HY: drafting the article. TX, DS, HY, MW, PW, MP, and MB: critical revision of the article. DS, HY, and MW: made equal contributions to the study. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Globus Pallidus Internus (GPi) Deep Brain Stimulation Induced Keyboard Typing Dysfunction

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Introduction: Typing on a keyboard requires complex collaboration between visuospatial/procedural memory, language, and motor function. The impaired ability to type, independent of motor deficits, apraxia, or aphasia has been coined "dystypia."

Case Presentation: A 68-year-old woman with a history of blepharospasm, oromandibular, and segmental dystonia underwent bilateral pallidal deep brain stimulation (DBS) because of a waning response to botulinum toxin therapy. Following DBS, she discovered she no longer "remembered" how to type fluidly and had to "hunt and peck" for letters on the keyboard. This issue persisted at a 2-year follow-up. The patient underwent serial typing tests with the DBS ON vs. OFF. Post-operative lead reconstruction was performed using Lead-DBS. The volume of tissue activation (VTA) modeling was combined with whole-brain tractography.

Results: Typing improved when the device was switched to the DBS OFF state. Cortical mapping revealed strong modulation of the right angular gyrus, left calcarine fissure, and left cuneus. There was also activation of bilateral supplemental motor areas and superior parietal gyri.

Discussion: Shared lesion topography analysis of dystypia cases in the literature has suggested the involvement of the superior longitudinal fasciculus (SLF). The SLF involves the superior parietal lobe, angular gyrus, supramarginal gyrus, and arcuate fasciculus. Our patient's connectivity pattern suggested SLF involvement. The improvement in OFF state typing and her imaging together suggested that the dystypia in her case was a stimulation-induced side effect.

Conclusion: Dystypia is a rare side effect of Globus Pallidus Internus (GPi) DBS therapy and may be associated with SLF involvement.

Keywords: deep brain stimulation, dystonia, dystypia, connectomics, stimulation induced side effect

INTRODUCTION

Typing on a keyboard is a complex coordinated function that requires network coordination between visuospatial procedural memory, language, and motor function (Ryu et al., 2012; Cook et al., 2013). The impaired ability to type, when manifested independently of motor deficits, apraxia, or aphasia, has been coined "dystypia" (Otsuki et al., 2002). Dystypia can be disruptive and impact activities of daily living especially given the heavy use of technology. In light of recent reports of swimming dysfunction following deep brain stimulation (DBS), we report a case of dystypia (keyboard typing dysfunction) as a potential side effect of DBS therapy (Waldvogel et al., 2020).

CASE PRESENTATION

A 68-year-old woman with a history of blepharospasm, oromandibular and segmental dystonia underwent bilateral pallidal DBS. Before DBS she had a waning response to botulinum toxin therapy. In the acute stage of her recovery from the DBS surgery, she reported "forgetting how to type on the computer." At baseline, she was proficient in typing as she did not have dystonia symptoms in the arm. Her previous occupation was administrative office work which involved copious typing. Within weeks following DBS implantation, she reported she no longer "remembered" how to type fluidly and had to "hunt and peck" for letters on the keyboard. This issue persisted into the 2-years of follow-up we have for her post-DBS. She did not have issues with any other motor tasks.

The clinicians performed the following testing to sort out the dysfunction and the relationship to DBS activation or inactivation (three conditions): (1) DBS ON; (2) 10 min following the DBS OFF condition; and (3) 20 min following the DBS OFF condition. Informed consent for testing and videotaping was obtained from the patient. Visuospatial testing (e.g., Trail Making B test, cube copy, clock drawing) and the neurological exam were performed in the DBS ON state and it was confirmed that there was no evidence of visuospatial neglect or aphasia. She performed three different 1-min online typing tests which were provided by the National Computer Science Academy (NCSA, Whitesboro, TX, USA). The tests can be viewed in the **Supplementary Video 1**. The three segments show DBS ON, 10-min washout, and 20-min washout. The testing duration was limited by the return of the patient's pre-operative dystonia symptoms.

A post-operative DBS lead location analysis was performed using the Lead-DBS advanced image processing pipeline (Horn and Kühn, 2015; Horn et al., 2019)[1]. The volume of tissue activation (VTA) was modeled and estimated based on the patient's most recent DBS programming parameters [Left Globus Pallidus Internus (GPi): 1 − C + 3.5 V, 150 μs, 120 Hz; Right GPi: 9 − C + 2.5 V, 150 μs, 120 Hz]. Whole-brain deterministic tractography was computed in DSI Studio using a diffusion MRI population-averaged template from the Human Connectome Project (HCP-1021; Yeh et al., 2013, 2018). The VTA was used as a seed for fiber tracking and resulting activated fiber tracks were calculated.

[1]https://www.lead-dbs.org/

RESULTS

Video testing of the patient's typing was performed at 2 years and 7 months post-implantation. The DBS programming settings at the time of testing were unchanged for the previous 2 years. This setting was reported to provide maximal benefit for her dystonia symptoms. Based on the latest settings, she reported complete or near-complete resolution of her dystonia symptoms except for her mild dystonic tremor in the right arm.

As the washout time increased (DBS OFF), she reported increased confidence in her typing abilities and less dependence on looking down at the keyboard. Her typing speed also increased from 0.6 words per minute (WPM) at baseline to 2.6 WPM and 3.8 WPM after turning the DBS OFF for 10 and 20 min, respectively. She felt typing improved OFF DBS but not back to her pre-DBS baseline.

The fiber tract activation pattern from the patient's DBS lead location analysis is shown in **Figure 1**. Cortical parcellation mapping revealed a strong modulation of the right angular gyrus, left calcarine fissure, and left cuneus. There was the activation of bilateral supplemental motor areas and the superior parietal gyri.

DISCUSSION

Several case reports have described "dystypia" in the absence of motor weakness, apraxia, and aphasia (Otsuki et al., 2002; Ryu et al., 2012; Cook et al., 2013; Thomas and Mestre, 2017; Sharma et al., 2019). Typically, dystypia has been reported in the setting of acute stroke. One case report described a patient with dystypia following bilateral subthalamic nucleus (STN) DBS (Lee et al., 2016). Post-operative imaging revealed prominent vasogenic edema in the frontal lobe surrounding the left STN DBS lead. In contrast to this case, Lee et al. (2016) attributed the dystypia to frontoparietal network dysfunction secondary to peri-electrode edema rather than a stimulation-induced side effect of STN DBS. The authors observed a marked improvement in dystypia following resolution of the peri-electrode edema. A recent literature review investigating the shared lesion topography of dystypia cases proposed involvement of the superior longitudinal fasciculus (SLF; Sharma et al., 2019). The SLF has been characterized to involve the superior frontal lobe, dorsal prefrontal region, superior parietal lobe, the angular gyrus, the supramarginal gyrus, and the arcuate fasciculus (Makris et al., 2005). A comparison to our patient's connectivity pattern also revealed the involvement of the SLF as a possible explanation for her dystypia.

We acknowledge several limitations of this study. First, we recognize our case is an N-of-1 observation and that these results should be interpreted with caution. However, the findings in our study highlight that there may be underrecognized stimulation-induced DBS related side effects. As these impairments appear to be task-specific and patient-specific, we appreciate the need for a larger, more robust exploration into stimulation-induced

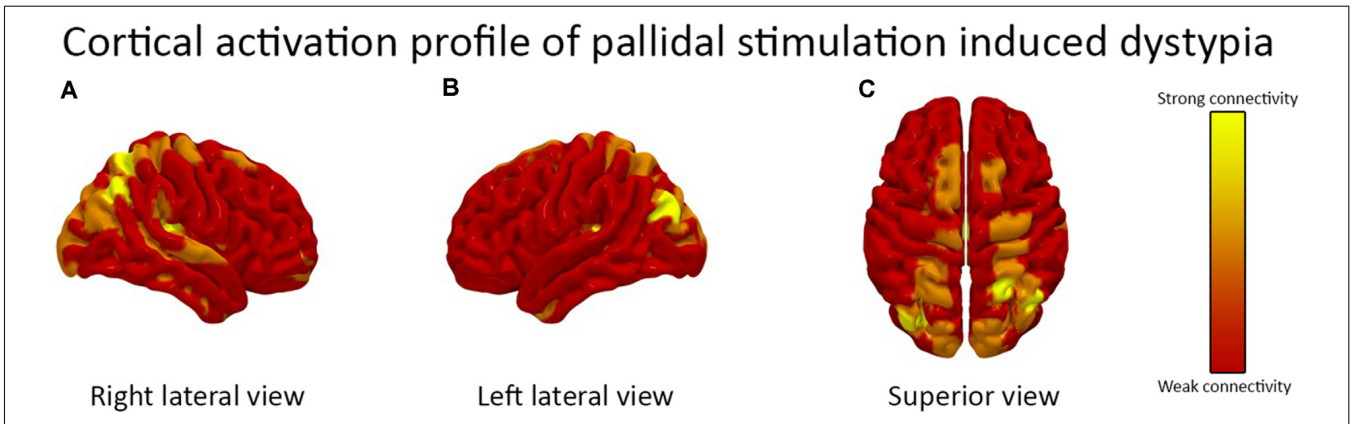

FIGURE 1 | The cortical activation pattern of bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) is demonstrated. The **(A)** right lateral view **(B)** left lateral view and **(C)** superior view are shown. The activation pattern is based on the patient's DBS device programming parameters. There was a strong activation of the right angular gyrus, left calcarine fissure, and left cuneus and moderate activation of bilateral supplemental motor areas and the superior parietal gyri.

side effects. Second, due to limitations in the MRI acquisition, our connectomic analysis utilized population-averaged template data rather than patient-specific data. Future studies should incorporate both approaches to see if there are any differences in connectivity results. Finally, we acknowledge the need in future cases for a comprehensive neuropsychological testing battery to further characterize dystypia.

Our findings suggest that dystypia is a rare stimulation-induced side effect of GPi DBS therapy and may be related to SLF involvement. This phenomenon appears different than GPi induced parkinsonism, however, comparative studies should be performed to observe if parkinsonism involves a common network pathway (Blahak et al., 2011; Schrader et al., 2011). Although the fundamental phenomenology between dystypia and parkinsonism is different, the examination of the active contacts, lead location, and fiber bundles stimulated by GPi DBS may reveal overlapping connectivity profiles or modulation of interconnected nodes along the same network. Recent reports of DBS-induced swimming dysfunction may share common underpinnings and this approach may be useful to better understand this phenomenon (Waldvogel et al., 2020). Finally, since the majority of centers have yet to formally assess for dystypia post-DBS, the prevalence of this DBS side effect remains unknown.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available. Requests to access the datasets should be directed to joshua.wong@neurology.ufl.edu.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW designed the study, acquired and analyzed the data, and drafted the manuscript. MA, LA, AW, AP, and MO revised the manuscript. IM designed the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Oxford, and Cambridge (movement disorders books). MO is an associate editor for the New England Journal of Medicine Journal Watch Neurology. MO has participated in CME and educational activities on movement disorders sponsored by the Academy for Healthcare Learning, PeerView, Prime, QuantiaMD, WebMD/Medscape, Medicus, MedNet, Einstein, MedNet, Henry Stewart, American Academy of Neurology, Movement Disorders Society and by Vanderbilt University. The institution and not MO receives grants from Medtronic, Abbvie, Abbott, and Allergan and the principal investigator (PI) has no financial interest in these grants. MO has participated as a site PI and/or co-investigator for several NIH, foundations, and industry-sponsored trials over the years but has not received honoraria.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fnhum.2020.583441/full#supplementary-material.

SUPPLEMENTARY VIDEO 1 | Pallidal deep brain stimulation (DBS)-induced dystypia. The patient in the video begins by taking a typing test with the DBS ON. Her hands are positioned off-center and she frequently looks down at the keyboard for visual confirmation of each keystroke before pressing down. She primarily uses her index finger to type and must pause to double-check her progress on the screen. After turning the DBS OFF for 10 min, her fingers are positioned over the "home row" keys and she can type more fluidly. She does not constantly look down at the keyboard. After turning the DBS OFF for 20 min, she incorporates all fingers into her typing and she spends most of the time viewing the screen.

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Researcher Perspectives on Ethical Considerations in Adaptive Deep Brain Stimulation Trials

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Interest and investment in closed-loop or adaptive deep brain stimulation (aDBS) systems have quickly expanded due to this neurotechnology's potential to more safely and effectively treat refractory movement and psychiatric disorders compared to conventional DBS. A large neuroethics literature outlines potential ethical concerns about conventional DBS and aDBS systems. Few studies, however, have examined stakeholder perspectives about ethical issues in aDBS research and other next-generation DBS devices. To help fill this gap, we conducted semi-structured interviews with researchers involved in aDBS trials (n = 23) to gain insight into the most pressing ethical questions in aDBS research and any concerns about specific features of aDBS devices, including devices' ability to measure brain activity, automatically adjust stimulation, and store neural data. Using thematic content analysis, we identified 8 central themes in researcher responses. The need to measure and store neural data for aDBS raised concerns among researchers about *data privacy and security* issues (noted by 91% of researchers), including the avoidance of unintended or unwanted third-party access to data. Researchers reflected on the *risks and safety* (83%) of aDBS due to the experimental nature of automatically modulating then observing stimulation effects outside a controlled clinical setting and in relation to need for surgical battery changes. Researchers also stressed the importance of ensuring *informed consent and adequate patient understanding* (74%). Concerns related to *automaticity and device programming* (65%) were discussed, including current uncertainties about biomarker validity. Additionally, researchers discussed the potential impacts of automatic stimulation on patients' *autonomy and control over stimulation* (57%). Lastly, researchers discussed concerns related to *patient selection* (defining criteria for candidacy) (39%), challenges of ensuring *post-trial access to care and device maintenance* (39%), and potential effects on *personality and identity* (30%). To help address researcher concerns, we discuss the need

to minimize cybersecurity vulnerabilities, advance biomarker validity, promote the balance of device control between patients and clinicians, and enhance ongoing informed consent. The findings from this study will help inform policies that will maximize the benefits and minimize potential harms of aDBS and other next-generation DBS devices.

Keywords: ethics, neuroethics, bioethics, interviews, neuromodulation, deep brain stimulation, ELSI, closed-loop

INTRODUCTION

Adaptive deep brain stimulation (aDBS) devices are part of the emerging field of personalized neurointerventions that are responsive to a patient's neural activity. In contrast to conventional DBS, the promise of aDBS systems is that they will identify neural activity associated with symptoms and adjust stimulation delivery in real time to alter neural activity and manage symptoms accordingly (Arlotti et al., 2016; Shute et al., 2016). The goal of aDBS systems is to deliver stimulation only when pathological brain activity is detected in order to prevent overtreatment, decrease side effects (e.g., hypomania), and battery depletion, which requires surgical replacement (Hosain et al., 2014; Beudel and Brown, 2016; Shukla et al., 2017). In addition to these safety advantages, aDBS may lead to better outcomes for patients because it adjusts automatically, thus avoiding the delay between suboptimal symptom management and adjustment of stimulation in a clinical encounter (Klein, 2020, p.336).

However, some have suggested that these defining features, which make aDBS promising, may also exacerbate certain neuroethics concerns (Klein, 2020, p.336; Aggarwal and Chugh, 2020, p.158). In particular, aDBS could exacerbate concerns about felt authenticity of affective states and patient agency due to the fact devices adjust stimulation automatically, which likely occur outside of a patient's conscious awareness (Gilbert et al., 2018, p.9; Gilbert et al., 2018, p.323–324; Goering et al., 2017, p.59–70). Moreover, advancements in aDBS technology depend largely on measuring and storing neural data for programming, raising novel challenges related to patient privacy. Addressing ethical concerns related to these defining features of closed-loop DBS may help to promote safety and efficacy, with potentially broader implications for other next-generation DBS devices containing with similar features.

In an effort to understand researchers' perspectives on the key neuroethics considerations related to the development of aDBS devices, we conducted interviews with researchers working in aDBS studies, who provided critical insights into the concerns raised by the capabilities and limitations of these devices. Drawing from these interviews, we identify pressing neuroethics issues and concerns, some of which apply to conventional DBS, but many of which are distinctive of or exacerbated by aDBS devices. We contextualize these findings within the existing neuroethics literature and discuss potential responses to these concerns as technologies with adaptive features become more prevalent in the future.

MATERIALS AND METHODS

We interviewed researchers ($n = 23$) involved in aDBS trials using a semi-structured, open-ended interview format. Understanding this stakeholder group's perspectives about ethical issues related to the development of aDBS systems is essential because these individuals possess expert knowledge about these devices, have direct experience developing and implementing them, and/or have expertise related to conditions with characteristics (e.g., treatment-resistance, severity of symptoms) that are similar to the intended users of these technologies. Thus, they are in an ideal position to identify ethical issues and inform resultant discussions related to these devices (Lázaro-Muñoz et al., 2019).

Participants were recruited from funded aDBS trials. Purposeful sampling with a snowball strategy was employed (Palinkas et al., 2015) in order to ensure recruitment of different project roles of researchers involved in aDBS trials (e.g., trial coordinators, neurologists, neurosurgeons, psychiatrics, and engineers) (See **Table 1**). Our sample also represents a diverse group of researchers targeting different disorders, including Parkinson's disease, dystonia, essential tremor, Tourette syndrome, depression, and obsessive-compulsive disorder (OCD). One participant was not specifically involved in aDBS but in conventional DBS and other next-generation DBS.

Participants were asked about their perspectives on pressing ethical issues in aDBS research and challenges they personally

TABLE 1 | Demographic information of respondents ($n = 23$) involved in aDBS research trials.

Gender ($n = 23$)	
Male	13 (57%)
Female	9 (39%)
Prefer not to answer	1 (4%)
Race/Ethnicity ($n = 23$)	
Asian	3 (13%)
White	18 (78%)
Prefer not to answer	2 (9%)
What degree(s) do you currently hold? ($n = 23$)	
M.D. or equivalent	8 (35%)
Ph.D. or equivalent (clinical)	3 (13%)
Ph.D. or equivalent (research)	4 (17%)
Both M.D. and Ph.D. or equivalent (clinical)	2 (9%)
Both M.D. and Ph.D. or equivalent (research)	1 (4%)
B.Eng. or M.Sc. Engineering	2 (9%)
B.A. or B.S.	3 (13%)

face in their research. We also asked researchers specifically about concerns pertaining to distinctive features of aDBS devices, including the device's ability to measure brain activity, automatically adjust stimulation, and store neural data. Our interview guide was developed based on a review of key issues raised in bioethics and neuroethics literature, during participant observation in a lab conducting aDBS research, and in discussions with experts in the aDBS field. Respondents were also asked questions about other topics, including several questions related to aDBS data sharing. We report those results elsewhere (Zuk et al., unpublished). The study was approved by the Institutional Review Board at Baylor College of Medicine.

Interviews were conducted via phone and Zoom, and were audio-recorded, transcribed verbatim, and analyzed using MAXQDA 2018 software (Kuckartz, 2014). Each interview transcript was coded independently by at least two members of the research team to identify researcher responses to six questions related to neuroethical concerns in aDBS research. Inconsistencies in coding were discussed to reach consensus among the research team. Utilizing thematic content analysis (Boyatzis, 1998; Schilling, 2006, p.28–37), information from coded segments was progressively abstracted to identify the content and frequency of emergent themes.

RESULTS

We identified eight overarching themes in researchers' responses to six questions about neuroethical concerns and challenges in aDBS research (**Table 2**). Starting with the most frequent, these include concerns related to (1) data privacy and security (noted by 91% of researchers); (2) risks and safety (83%); (3) informed consent and adequate patient understanding (74%); (4) automaticity and device programming (65%); (5) patient autonomy and control over stimulation (57%); (6) patient selection for aDBS candidacy (39%); (7) post-trial access to care and device maintenance (39%); (8) and potential effects on personality and identity (30%). While some of these ethical concerns may be broadly relevant to both conventional and adaptive DBS, most were identified by our respondents as being exacerbated by certain characteristics distinctive of aDBS, particularly its capacity to measure and store brain activity and to respond using automatic stimulation. The ways in which these concerns were specifically raised in response to our six questions is illustrated in **Table 2** and elaborated below.

Data Privacy and Security

Nearly all (91%) respondents expressed concerns about data privacy and security in relation to the capacity of aDBS systems to measure and store neural activity data (NAD). There was disagreement about the sensitivity of NAD. Some researchers felt that "brain recordings themselves [are] not identifiable" (R_013) because researchers currently do not know enough about what the recordings mean to be able to identify sensitive information, however, this could change in the future (See **Table 3**). Researchers also pointed out that stored data could be inappropriately used or shared: "The fact that we have the ability to report this data suggests that perhaps it can be used as evidence. Could this be forensic evidence that's used in lawsuits, in courts, or to settle discussions or arguments?" (R_022). We explored researchers' views on the sensitivity of NAD as they relate specifically to data sharing elsewhere (see also Zuk et al., unpublished; Naufel and Klein, 2020).

Researchers also discussed device "hacking," including the potential for stored data or algorithms to be manipulated to disrupt therapy or control patients. One researcher suggested, "We'd have to make sure that there are lots of safety measures in place [.] so that the algorithm can't be adjusted. Or if we have someone controlling stimulations remotely, like the clinicians. if someone were to steal that control and send the person into a manic state or something maliciously, that would be really bad" (R_017). Some respondents felt that data security risks are minimal because aDBS systems are HIPAA-compliant and researchers who study them are required to submit plans to protect patient information to the FDA. Others, however, emphasized that data security risks could grow as researchers learn more about recordings, and that further plans should be put in place to anticipate future challenges in protecting NAD.

Risks and Safety

Most (83%) respondents raised ethical challenges surrounding risks and safety, particularly in relation to unique features of aDBS devices (i.e., capacity to measure and store neural activity and automatically adjust stimulation) compared to conventional DBS. In some cases, researchers are inserting additional electrodes in different brain regions (cortical and subcortical) to identify biomarkers that allow for automatic or responsive stimulation. One researcher explained, "Whenever we are pushing the envelope of neuromodulation with new, additional implanted devices, [there is] increased risk of hemorrhage, seizure, stroke, any kind of additional manipulation or extension of the surgery. So, I always have to weigh what the risks and benefits [are] for this specific person" (R_021). A number of researchers discussed unknown risks and unintended effects of aDBS, particularly in relation to automatic delivery of stimulation in new environments outside of the controlled clinical setting (See **Table 3**). One researcher wondered, "Are there any spot gaps that need to be in place in certain contextual situations that it could fire and do something in a way that we haven't imagined yet? We haven't actually thought through and imagined all the potential situations that could play out" (R_015). Unanticipated effects were especially concerning because researchers do not constantly monitor devices, which also raises the "challenge of when to intervene as a clinician taking care of this patient [when] these systems are supposed to be autonomous" (R_020). As a way to potentially mitigate unforeseen risks, respondents emphasized the importance of working within safe stimulation parameters and maintaining researchers' ability to intervene when necessary.

Other researchers raised concerns that stimulation could inadvertently and unknowingly affect other neural circuits, potentially causing side effects. The risk of overlooking these side effects may be exacerbated in aDBS because researchers – and aDBS systems operating autonomously – could be overly focused on therapeutic outcomes. As one researcher described,

TABLE 2 | Percentage (%) of respondents (n = 23) who discussed main ethical concerns related to aDBS.

Questions explored	Data privacy and security	Risks and safety	Informed consent and patient understanding	Automaticity and device programming	Autonomy and control	Patient selection and candidacy considerations	Post-trial access to care and device maintenance	Personality and identity
Across Questions	91	83	74	65	57	39	39	30
(1) When you think about the current state of aDBS, what do you think are the most pressing ethical issues in adaptive DBS research?	17	30	43	0	26	26	26	26
(2) From a more personal perspective, what are the biggest ethical challenges that you have had to deal with in your own adaptive DBS research?	9	26	52	0	13	17	9	4
(3) Compared to conventional DBS, are there ethical issues unique to adaptive DBS?	30	65	17	43	26	13	9	0
(4) As you know, an important component of adaptive DBS is that it works by measuring the participant's brain activity. What, if any, ethical concerns does this raise?	61	17	4	17	0	0	0	4
(5) The adaptive DBS system automatically changes stimulation based on the participant's brain activity. What, if any, ethical concerns does this raise?	9	30	4	39	35	0	0	4
(6) The adaptive DBS system stores the data it collects about the participant's brain activity. What, if any ethical concerns does this raise?	78	17	0	4	9	0	4	4

Thematic percentages do not sum to overall totals due to overlapping concerns raised across multiple questions (i.e., a researcher who raised the same thematic concern in response to multiple questions was only counted once in overall total).

"We've always looked at therapeutic outcomes, but then became increasingly aware of the side effects. . . So the potential is to cause more side effects unknowingly, especially in an adaptive system that's not tuned to the right outcome" (R_023). Respondents also discussed risks specific to certain subpopulations of aDBS patients, such as overstimulation leading to hypomanic states in patients with OCD.

Informed Consent and Patient Understanding

A majority (74%) of researchers said that one of the most pressing ethical concerns in aDBS studies is ensuring that patients understand and are able to provide informed consent to aDBS. Over half of respondents reported having encountered related challenges in their own aDBS research. Some researchers raised the concern that patients may feel pressured to participate, particularly because "some of the patients who are looking at this kind of procedure don't really have other helpful interventions" (R_005). Patients may also feel pressured to participate in aDBS research due to an established therapeutic relationship with clinician-researchers leading aDBS research studies (See **Table 3**). Further potential compromises to informed consent can stem from therapeutic misconception and therapeutic misestimation. One respondent explained patients can potentially "lose track of the investigational nature of the study" (R_011), and another respondent suggested that it is challenging to ensure realistic patient expectations about aDBS during the consent process: "DBS. . .seems, to them – because it's so risky, but can have such promise – that it's like a silver bullet, so to speak" (R_005). Patients must understand that aDBS is a complex intervention and not "one size fits all" (R_015).

Researchers also reflected on how the automatic nature of aDBS raises unique ethical concerns about patient consent. One researcher wondered whether patients can robustly consent to automatic, moment-to-moment changes in stimulation, explaining that "it's almost as though the intervention is changing at each time point" (R_018). Researchers stressed the need to ensure that patients who explicitly consent to the adaptive component of aDBS at the beginning of their treatment are continuing to implicitly consent to ongoing stimulation changes, which evolve as device recognition of a patient's neural activity improves and likely occur outside of a patient's conscious awareness. To address this concern about patient consent, one researcher suggested that devices could be designed to notify patients when they detect symptom-related brain activity: "It would be interesting to have a device be able to [.] give the patient an alert somehow. '[If] I [the device] think you're dyskinetic, I'm going to turn myself down.' The patient could override it" (R_013). Researchers conveyed that improving patient understanding about when and how the device adjusts stimulation can help to ensure that patients are continuing to consent to the device's automatic changes. Consent challenges may be especially pronounced among certain subpopulations of patients, including those with severe psychiatric symptoms that potentially influence decisional capacity.

Automaticity and Device Programming

Researchers (65%) raised unique concerns related to automaticity and device programming for aDBS systems. They stressed

TABLE 3 | Researcher responses across main ethical concerns related to aDBS.

Ethical theme	Researcher responses
Data privacy and security	"I think the main concerns would be privacy of the data. We stream these data to external computers. Someone's brain data is now [...] it could be considered personal health information, in a way. Eventually, we may be able to decode specific things about that person's identity and personality from their brain data. So, we do have to consider it as personal health information, even if it's de-identified. At least if not now, then in the future, we'll have to consider that" (R_011).
Risks and safety	"There's the fact that we just don't know that much about DBS and how it works. That's the danger of doing any kind of experiment on humans directly, even though it's pretty well understood, what the random risks are" (R_006).
Informed consent and patient understanding	"In many cases, the person who has a therapeutic relationship with the patient is also an investigator, and so there might be possible duress or coercion to participate in these studies" (R_023).
Automaticity and device programming	"My concern is that it might stimulate when it's not supposed to, causing [an] unwanted side effect. Or the opposite, if it's not stimulating when it's supposed to causing the patient unnecessary suffering. Those are glitches that, as we develop these techniques, hopefully will not be an issue. But those are concerns that I have from an ethical perspective. And then, from a researcher point of view and a clinician, when is it going to be that moment [when] we're satisfied with that signal and that response to stimulation" (R_020).
Autonomy and control	"I think we need to be careful in affording control of the device to the patient. For any stimulation of the reward system, there's potential for self-abuse. There are restrictions [where] patients can turn the device off or on, but they can't modulate it. That strikes me as a wise precaution" (R_026).
Patient selection and candidacy considerations	"When you have a population that does not have a sufficient response to pretty much everything [other treatments], and you can have a 60% response rate in that group [to aDBS], good lord, that's incredible. I worry about the side effects of *not* doing something for those individuals" (R_018).
Post-trial access to care and device maintenance	"We basically thought, ethically, it would be best that they receive rechargeable non-sensing devices so that they can basically get this open-loop therapy for a long duration. I think those batteries last for like 9 years" (R_016).
Personality and identity	"In the study where we're manipulating mood potentially, the goal is to improve mood, which most people would say would be a good thing. But then at some point, do you give somebody a new mood that changes their personality? There are a lot of ethical issues behind potentially manipulating people's mood and personality [be]cause that could be a good thing or a bad thing" (R_010).

the importance of using validated, reliable biomarkers given that researchers are relying upon a device designed to make autonomous decisions to affect patients' mood, behavior, or movement. One researcher wondered, "How validated does a biomarker have to be before you start deploying a system like this and letting it deliver therapy in real time?" (R_023). Researchers explained that a biomarker lacking validity could cause devices to respond to false positives or negatives, leading to over- or under-stimulation. These "misreadings" of neural biomarkers could result in patients experiencing suboptimal symptom management or undesirable effects (See **Table 3**). One researcher shared,

"Let's say we come across. . . a good biomarker for hypomania, and it misreads the patient just having a really great weekend, because they're at a family member's wedding. Now all of a sudden, they're depressed again or they're feeling more of their OCD symptoms come on at that time. That's obviously a problematic situation we want to avoid" (R_007).

Respondents said that to avoid stimulation errors, devices would ideally be programmed so they could recognize when "the patient's behavior and mood is elevated beyond where it is beneficial to the patient" and subsequently "turn down the system" (R_019). Researchers were also concerned that patients may be unaware of inappropriate stimulation changes because the changes are occurring automatically, impacting patients' and clinicians' ability to actively intervene to mitigate negative consequences. As one researcher described, "There is still a decision being made on a second-by-second basis out in the field, in the wild, by an algorithm that may change that person's current mental status" (R_025). Another researcher stressed the ethical implications of this unique feature of aDBS, saying, "[Normally], we always have a physician intervening and assessing, [but aDBS] is an autonomous system making decisions about the delivery of therapy" (R_023).

Autonomy and Control

Related to the concerns about automaticity described above, over half (57%) of respondents raised concerns related to patient autonomy and control over stimulation. One researcher explained how "people's sense of autonomy may be altered by the use of a computer unit" if they believe their "motor state or their mental state. . . are being controlled by an external source or by a computer" (R_008). Researchers felt this concern could be particularly exacerbated for aDBS patients due to the fact that changes in stimulation occur automatically. Another researcher commented, imagining from a patient's perspective, "Even with open loop, there's the issue that now I have a device in my brain that's modulating and controlling some of my brain activity. I think as we develop closed-loop, that concern about allowing a device to take some command over your activity will be extenuated" (R_009). This researcher speculated that automatic device control may be even more concerning for psychiatric patients if they view the targets of aDBS adjustment – e.g., mood and anxiety – as central to their sense of self and identity. They said, imagining the perspective of a patient, "'A tremor doesn't represent me. It's a dysfunction.' [But] when you have a device that's modulating your mood or your anxiety level, your energy level, that's much more your core sense of being" (R_009) (See also Personality and Identity below).

Alternatively, one researcher noted, "[patients] seem to have an awareness of how the device is being set. They trust the researchers that are controlling it. They don't feel like there's any questionable agency to be concerned with" (R_008). According to another researcher, concerns about patients' sense of control, "are mitigated substantially by the design of these protocols, where patients do have a controller and at any point can flip themselves out of adaptive stimulation into conventional stimulation" (R_011). While some researchers highlighted this need to allow patients to override unwanted stimulation, others alluded to potential risks of giving patients substantive control over their stimulation. Some respondents noted that determining how much control patients should have over stimulation may depend on which areas of the brain are being stimulated. In cases like aDBS for OCD, in which part of the brain's reward circuit is stimulated, some researchers said they feel hesitant providing too much patient control due to the potential for stimulation abuse (See **Table 3**). Researchers said that other patients, such as those with essential tremor who receive stimulation elsewhere in the brain, could be given greater unilateral discretion to adjust stimulation. Overall, researchers stressed caution in deciding whether and how much patient control to allow.

Some researchers offered similar cautions against giving physicians too much control, advocating for limits to physician access to stimulation. As one respondent commented, "We still don't want the clinician to be kind of messing with it whenever they want to. How do you put in the safeguard so that only authorized people can access it, and even they can only do so with the patient's permission every time?" (R_022). Another respondent highlighted a tension between ensuring patient safety and respecting their autonomy, saying, "In the future, it would be important to have a button that the doctor could press remotely if they hear something is going on, like turn everything off or turn it down. . .But then that's like a doctor controlling remotely" (R_017). One researcher suggested that a potential solution to finding an ethical balance is to integrate all stakeholder groups – including patients and caregivers – in the development of control and safety policies.

Patient Selection and Candidacy Considerations

Over a third of researchers (39%) raised ethical concerns related to patient selection and candidacy for aDBS treatment. Because DBS treatment is an invasive therapy typically offered to patients who are treatment-resistant, some researchers said they want to be sure that patients have "tried enough different treatments, even some of the ones that are a bit more experimental" (R_009) in order to warrant taking on the challenges and risks of aDBS. Other researchers noted that the treatment-resistant nature of a patient's disorder supports not only their fit as an aDBS candidate but also the ethical imperative to make aDBS treatment available to them (See **Table 3**). Respondents pointed out that deciding whether and when a patient may benefit from aDBS requires that multiple clinical and demographic factors be taken into

consideration. For example, researchers discussed the difficulty of defining "normal" versus "abnormal" thoughts, moods, and behaviors in the context of aDBS. Ideally, aDBS treatment will be able to appropriately decipher between "normal" and "abnormal," however, some researchers said it may be problematic to expect a human, let alone a machine to make these fine distinctions. One researcher said,

"I think the most interesting, challenging question to me is, what are we defining as our set point or as our 'normal?' I think for a movement disorder [like] tremors, for example, 'normal' is not having tremors. When you're talking about mood and anxiety, like with OCD, how much time you spend thinking about whatever is your concern – contamination or orderliness or symmetry. . . Is that normal? Is that abnormal?" (R_022).

Post-Trial Access to Care and Device Maintenance

Nearly a third (30%) considered post-trial access to care and device maintenance to be an additional pressing ethical issue. Researchers said that some patients who want to continue aDBS are unable to access aDBS care and device maintenance after a research study ends: "I think, honestly, the biggest issue right now is the amount of money that it costs patients to maintain the device, or obtain a replacement after the study is over" (R_004). Reasons for this include the fact that conventional DBS and aDBS have not yet been approved by the FDA for some of the conditions targeted in trials, which may result in insurance providers not covering costs associated with battery or hardware replacements, thereby limiting post-trial access. Post-trial access to care may be particularly problematic for certain patients, such as those whose batteries need replacing early. For example, one researcher said, "For Tourette's therapy, amplitudes are really high, and [batteries] get depleted really quickly. And then it's not FDA approved, so they don't get it covered by insurance companies. We can't promise to provide them again with the study devices, even if they convert to standard DBS batteries" (R_016). Some researchers recommended giving patients conventional DBS with rechargeable batteries at the end of studies to extend these patients' access to DBS (See **Table 3**).

Personality and Identity

Researchers (30%) also discussed the important ethical challenge of mitigating potential unwanted effects of aDBS on personality and identity, including mania or hypomania caused by aDBS stimulation in patients with OCD. One researcher commented, "One [concern] is, changing someone's personality, and their behavior and how that can be manipulated through deep brain stimulation, either inadvertently or maliciously. That's one of my concerns" (R_021). Another researcher felt that the brain was a unique organ and different from, for example, the heart. They explained that altering brain activity and "directly stimulating reward tracks in the brain, generat[e] both hedonic responses" and other responses "that are really part of the fabric of personality." On the other hand, "for someone with heart irregularities, a cardiac pacemaker may be beneficial, expanding their range of motion and activity, but only very indirectly, if at all, affecting them as an individual" (R_026). While manipulating and improving mood could be the goal for some uses of aDBS, researchers expressed concern over lasting changes on personality (See **Table 3**). Furthermore, navigating these situations could be particularly challenging for researchers in cases where patients do not understand or acknowledge that their mental state is negatively affecting their functioning.

DISCUSSION

Minimizing Vulnerabilities in Cybersecurity

In this paper, we identified potential ethical issues and challenges that are heightened in or unique to aDBS research relative to conventional DBS, drawn from the perspectives of aDBS researchers working at the forefront of their field. Our findings suggest that the technical features that give aDBS distinct advantages over conventional DBS systems also raise distinct issues that should be addressed in order to ensure that patients receive the full benefits of these neurotechnologies while minimizing potential medical and non-medical harms. Among the most pressing concerns raised by researchers was the potential for aDBS systems to compromise patient privacy and data security. Researchers pointed out that while NAD that is recorded and stored by aDBS systems may not itself contain identifiers or other sensitive information presently, this could change in the future, which is a concern frequently raised in the theoretical neuroethics literature (Klein, 2016, p.1310; Zuk et al., 2018, p.45–46; Aggarwal and Chugh, 2020, p.160). Theoretical work further predicts that privacy concerns will increase as larger amounts of data are collected, advances in technologies make it easier to integrate data, and DBS devices interface with other devices in the future (Hendriks et al., 2019, p.1508; Klein, 2020, p.335). Researchers should therefore maintain awareness of advances in neuroscience and technology that could change the degree of NAD sensitivity and implement additional data protections if and when necessary. Researchers also have a responsibility to inform participants of what information could and could not be extrapolated from their neural recordings (Pugh et al., 2018, p.221). Moreover, researchers and clinicians will need to determine participants' desired boundaries around neural privacy and preferences around how their NAD is used in the future, which could require researchers to not collect or to filter certain kinds of neural recordings (Klein, 2020, p.335).

To avoid the possibility of device hacking, data manipulation, and therapy interruption, researchers and clinicians can incorporate additional security patches and upgrade software systems to reinforce the cybersecurity of both hospital-wide networks as well as patient devices linked to networks (Jaret, 2018; Pugh et al., 2018, p.221). The FDA should also hold device manufacturers accountable for identifying and addressing vulnerabilities in medical devices and ensure that the responsibility to safeguard devices is shared amongst providers and manufacturers. Currently, the FDA is exploring the development of a CyberMed Safety (Expert) Analysis Board, which is "a public-private partnership that would

complement existing device vulnerability coordination and response mechanisms and serve as a resource for device makers and FDA" (U.S. Food & Drug Administration, 2018). This board would function to assess vulnerabilities, patient safety concerns, and mitigation plans, which could play a large role in supporting aDBS researchers and addressing device security concerns.

Mitigating Risks and Advancing Biomarker Validity

A second highly salient concern raised by researchers is the need to mitigate risks and ensure safety for patients being treated with aDBS. Identifying valid neurophysiological biomarkers is an enduring challenge for researchers that involves a variety of strategies, depending on the disorder. For example, with essential tremor, researchers record NAD while patients perform a motor task (e.g., clasping a cup and brining it toward their mouth) (Opri et al., 2019). With Parkinson's Disease, researchers record NAD when patients are on and off medication and on and off therapeutic DBS (Swann et al., 2016).

Identifying biomarkers for psychiatric disorders, however, is especially challenging because there are often no external, visible symptoms as in motor disorders, and psychiatric symptoms involve highly complex and dynamic cognitive states and behaviors. Currently, researchers developing aDBS for OCD can utilize video recording of facial expressions and physiological measurements (e.g., heart rate) collected while patients perform psychophysical tasks (e.g., unscripted social interactions with strangers) (Girard et al., 2015; Provenza et al., 2019). However, the validity of biomarkers identified during these tasks depends on the extent to which they elicit the same brain processes associated with OCD symptomology as it manifests in everyday life. To help improve biomarker validity, particularly for psychiatric disorders, further research is needed into the translatability of clinic-derived biomarkers to neural processing and patient functioning in less controlled and more naturalistic settings (Provenza et al., 2019). This research could help address researchers' concerns and fill contextual blind spots that could cause aDBS devices to "misread" brain activity and either over- or under-stimulate. Improving biomarkers may also help to mitigate potential unwanted effects of aDBS on personality and identity, another significant concern raised by respondents, by avoiding device settings associated with any such effects.

Promoting Autonomy and Balancing Device Control

Researchers from our sample recognized that determining when clinicians should intervene to ensure patient safety is challenging for a number of reasons, including that researchers and patients may not be aware of when the device begins stimulating inappropriately, and researchers may feel uneasy about potentially violating patient privacy or undermining patient autonomy. Researchers' reflections on autonomy and patient control illuminate the challenging and complex nature of these issues and suggest possible tension between patient safety and patient autonomy. On one hand, some researchers suggested that patient autonomy requires that *clinicians* do not have too much control and that *patients* have adequate control over aDBS functionality, such as having the ability to reject an upcoming change in stimulation (Fins, 2009; Goering et al., 2017, p.65). One way to manage this and respect patient autonomy would be to engage patients and clinicians early in the consent process to discuss preferences and conditions for patient versus physician intervention within the larger context of a patient's treatment goals. Patients could also identify a close caregiver to provide assistance in adjusting stimulation parameters or finding appropriate medical care when clinicians or caregivers identify a concern during treatment, thus supporting patient autonomy in a *relational* way (Baylis, 2013, p.516–519; De Haan et al., 2015, p.22; Goddard, 2017, p.332–334; Goering et al., 2017, p.67; Gallagher, 2018).

On the other hand, some researchers suggested patients may trust or prefer clinicians to have a substantial amount of control, and for certain patients, providing them with too much control could lead to autonomy being undermined. Despite concerns about autonomy and control being raised frequently in theoretical neuroethics and sometimes in empirical work, some researchers believed that, at least in general, autonomy concerns are not highly problematic in the context of aDBS research context because patients trust clinicians to manage treatment modifications (Lipsman and Glannon, 2013, p.468; De Haan et al., 2015, p.6–16; Klein, 2016, p.1311; Gilbert et al., 2017, p.96; Gilbert et al., 2018). A study by Klein in 2016 found that the majority of patients receiving open-loop DBS expressed a preference for primarily clinician-controlled rather than patient-controlled stimulation settings, were such control to become available (Klein, 2016, p.3). Additionally, empirical work indicates that the brain region targeted is also an important consideration when examining potential effects that DBS could have on patient autonomy and control (Gilbert et al., 2017, p.101). Researchers in our sample similarly stated that it would be wise to limit the degree of control of patients with OCD given that they receive stimulation in the reward system (i.e., ventral striatum), which could lead to stimulation abuse. Over-stimulation of this brain region could result in mania and increased risk-taking behaviors, which could alter judgment or diminish the degree of control patients have over their actions, thus undermining autonomy (De Haan et al., 2017, p.23; Gilbert et al., 2017, p.98–99).

One can foresee a potential conflict between the above considerations if, for example, a patient receiving aDBS for OCD in the ventral striatum is limited in their ability to adjust stimulation and feels on that basis that they lack adequate control. These considerations are further complicated by the positive impact of symptom relief, which could outweigh potential diminishments in autonomy resulting from a lack of control over device functionality (Lázaro-Muñoz et al., 2017, p.74). Ideally, a balance between patient and clinician control over stimulation will be achieved through the assessment of individual patient preferences, targeted brain region, and different means of device control. All relevant stakeholders will need to be involved in these discussions, including patients, caregivers, clinicians, programmers, and engineers. This process may be assisted by development of multi-faceted empirical measures

incorporating different conceptions of autonomy, which will be particularly useful given patients have been found to use the idea of "becoming a new person" inconsistently and not all researchers in our sample made a clear distinction between autonomy and sense of autonomy (Roskies, 2015, p.6; Sullivan, 2015, p25; De Haan et al., 2017, p.17–18; Zuk and Lázaro-Muñoz, 2019).

Enhancing Patient Knowledge and Ongoing Informed Consent

Researchers pointed out that issues related to safety and autonomy highlight the need for patients to adequately understand and provide informed consent to aDBS treatment, which is a concern that is frequently raised in empirical and theoretical neuroethics literature (Cabrera et al., 2014, p.37–42; De Haan et al., 2015, p.25; Chiong et al., 2018, p.32–33; Klein, 2020, p.330). Pre- and post-operative counseling and psychosocial support could provide opportunities for patients to learn about aDBS, including how aDBS works, the role and rationale behind automaticity, and what the unique features of aDBS imply for ongoing consent. These forums would provide patients with multiple opportunities to voice any concerns or uncertainties about their treatment so that problems may be mitigated or avoided early on and at different time points throughout a patient's treatment trajectory (De Haan et al., 2015, p.20).

Severe, refractory symptoms combined with a lack of treatment alternative suggests that patients considering aDBS are in a more vulnerable position than most and may perceive research participation as their only option, a situation that could be further influenced by the presence of a therapeutic relationship between the patient and a study investigator (Cabrera et al., 2014, p.39–42; Chiong et al., 2018, p.32, p.34; Zuk et al., 2018, p.48; Morain et al., 2019, p.11; Klein, 2020, p.333). Researchers shared these same concerns around patient consent and acknowledged that they have a responsibility to ensure that consent is not inadvertently biased by a patients' perceptions or expectations. More specifically, researchers felt that patients should be adequately informed of aDBS devices' unique ability to automatically adjust stimulation, which could potentially prevent some autonomy related concerns (Aggarwal and Chugh, 2020, p.156). More research is needed to clarify patient understandings about what they believe they are consenting to when they agree to participate in an aDBS trial, how consent may change over the span of the trial, and how understandings affecting consent may differ among certain patient subpopulations (Chiong et al., 2018, p.33–34).

Adequate patient understanding of aDBS research participation will also require that patients are informed about potential post-study uncertainties and issues (Lázaro-Muñoz et al., 2018, p.317–318; Hendriks et al., 2019, p.1511; Sierra-Mercado et al., 2019, p.760). Researchers expressed the need to help ensure post-trial access to care and device maintenance. They were concerned that patients who wanted to continue DBS may not be able to due to a lack of FDA approval for certain indications, causing insurance providers to not cover costs associated with battery or hardware replacements and clinical visits in some cases. Ensuring that patients understand these potential limitations to post-trial access to aDBS or conventional DBS was viewed by respondents as a critical aspect of informed consent procedures for these trials (Klein, 2016, p.1308). In addition to informing patients of the current realities of post-trial access, ongoing discussions are needed to determine different stakeholders' obligations and potential responses, such as funders making supplementary funds available and device manufacturers covering costs to help improve post-trial access to care and device maintenance (Zuk et al., 2018, p.46; Hendriks et al., 2019, p.1511).

Our results should be considered within the limitations of our study. The lack of representation of all clinical applications of developing aDBS systems limits the generalizability of our findings. Our sample includes researchers working on aDBS systems for six different disorders, however, a more robust sample size could enhance insights into different uses of aDBS systems and closed-loop devices more generally. Furthermore, the researchers interviewed are experts working on the development of these technologies in a translational research context, thus, their perspectives may not capture the range of ethical considerations that could arise if aDBS systems are adopted more widely in clinical care. Researchers are just one of the key stakeholder groups involved in the development of aDBS systems. Other groups such as patients and caregivers may have different perspectives which are critical to understand to promote the responsible use and development of these technologies. Although we ensured recruitment of researchers who have various professional roles in aDBS trials, 78% of the sample identified as white, reflecting a lack of racial and ethnic representation in our sample, which could be addressed through more purposeful sampling. Other limitations of qualitative research include potential ambiguity in interview responses, which could lead to misinterpretation of data. Thematic content analysis was performed by at least two independent team members and inconsistencies in abstracted coded segments were discussed to reach a consensus among the research team to mitigate the potential impact of this limitation.

CONCLUSION

Drawing on the perspectives of expert stakeholders working at the forefront of aDBS research, we identified potential ethical issues and challenges that are heightened in or unique to aDBS research relative to conventional DBS. Due to the need to measure and store neural data, aDBS researchers raised concerns about protecting the privacy of neural data and preventing unwanted third-party access to data. The automatic nature of stimulation sparked risk and safety concerns associated with the experimental nature of identifying biomarkers to automatically adjust stimulation outside the clinic. Additionally, researchers discussed challenges of determining the degree of control researchers and patients should have over adaptive stimulation and challenges of ensuring that patients provide appropriate consent to continuous alterations in stimulation. Our findings therefore suggest that the technical features that give aDBS

advantages over conventional DBS systems also raise distinct issues. We identified four areas where researcher concerns can begin to be addressed, including minimizing cybersecurity vulnerabilities, advancing biomarker validity, promoting the balance of device control between patients and clinicians, and enhancing ongoing informed consent. Further research and ethical analysis of these pressing issues are needed to better ensure that patients receive the full benefits of these neurotechnologies while minimizing potential medical and non-medical harms.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because full datasets must remain unavailable in order to ensure de-identification of interview participants.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Baylor College of Medicine Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Verbal consent was obtained from each research participant before beginning interviews.

AUTHOR CONTRIBUTIONS

All authors contributed to project design. SO, LT, DSM, and RH conducted interviews and contributed to data collection. KAM, KK, CS, and LK completed data analysis. RH provided assistance in identifying global themes that emerged during data analysis. KAM, KK, PZ, and GLM conceptualized the manuscript. KAM drafted the manuscript. KK, PZ, and GLM made substantial revisions to the manuscript. SP, JOR, and AM also provided feedback and suggested edits on the manuscript. DSM provided insight on the technical points raised in the paper. SP, AM, GLM, JOR, and BAK provided senior-level leadership for the project.

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The Use of Tractography-Based Targeting in Deep Brain Stimulation for Psychiatric Indications

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Deep Brain Stimulation (DBS) has been investigated as a treatment option for patients with refractory psychiatric illness. Over the past two decades, neuroimaging developments have helped to advance the field, particularly the use of diffusion tensor imaging (DTI) and tractographic reconstruction of white-matter pathways. In this article, we review translational considerations and how DTI and tractography have been used to improve targeting during DBS surgery for depression, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD).

Keywords: deep brain stimulation, depression, obsessive compulsive disorder, post-traumatic stress disorder, diffusion tensor imaging, tractography

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INTRODUCTION

Psychiatric illness remains among the leading causes of disability worldwide (World Health Organization, 2017). Common conditions such as major depressive disorder (MDD) and obsessive compulsive disorder (OCD) are resistant to guideline-concordant pharmacotherapy and psychotherapy in up to one third of cases (Trivedi et al., 2006; Hirschtritt et al., 2017). Patients with treatment resistant psychiatric illness have a significantly increased usage of healthcare resources and risk of suicide (Kessler, 2012; World Health Organization, 2017). The high prevalence and often fatal prognosis of refractory psychiatric illnesses emphasizes the need to develop novel treatment options for this patient population.

Psychiatric surgery, namely deep brain stimulation (DBS) or ablative neurosurgery, is an important treatment option for patients with refractory psychiatric illness. DBS involves the surgical placement of electrodes in the brain, which deliver continuous low-level stimulation to a precisely targeted node (Awan et al., 2009; Hamani and Nobrega, 2010, 2012; Hamani et al., 2010). Ablative neurosurgery, involves the creation of a focal lesion in the brain—performed either with surgery (Christmas et al., 2011), stereotactic radiosurgery (Rasmussen et al., 2018), or magnetic resonance guided focused ultrasound (MRgFUS) (Kim et al., 2018; Davidson et al., 2020b).

Over the past two decades, the field of neuroimaging has evolved considerably. Advanced magnetic resonance imaging (MRI) sequences such as echo-planar imaging, used for functional MRI (fMRI), and diffusion tensor imaging (DTI), used for the tractographic reconstruction of white-matter pathways, has added a dizzying array of possibility, but also complexity, to performing

psychiatric neurosurgery. In 2013, Schlaepfer et al. reported the use of DTI to target a structure termed the "superolateral branch of the medial forebrain bundle" (slMFB) (Schlaepfer et al., 2013), which has since been renamed the ventral tegmental area projection pathway (VTApp) (Coenen et al., 2020). Since then, there has been extensive translational work, resulting in improved outcomes (Riva-Posse et al., 2018) and the emergence of a new era of circuit-based neurosurgery (Boutet et al., 2019; Horn, 2019).

In this article, we review the use of advanced neuroimaging techniques in psychiatric DBS, particularly highlighting the methods which have been translated into clinical practice. This review will be divided based on the major targets currently used for psychiatric surgery: subcallosal cingulum (SCC), VTApp, ventral capsule/ventral striatum (VC/VS).

VENTRAL TEGMENTAL AREA PROJECTION PATHWAY

The first translation of advanced neuroimaging techniques to psychiatric surgery in humans was in the stimulation of the VTApp in the treatment of MDD (Schlaepfer et al., 2013). The VTApp was originally selected as a potential target following the observation of hypomania developing in a patient with Parkinson's disease who received subthalamic nucleus (STN) DBS, where the active contact was located too medially (Coenen et al., 2009). Though originally referred to as the slMFB, several groups have suggested that this tract may in fact be a hyper-direct connection from the prefrontal cortex to the anteromedial STN. For the purposes of this article, we will refer to this tract as the ventral tegmental projection pathway.

The VTApp is consistently found within a region recently coined as the "therapeutic triangle," located immediately lateral to the ventral tegmental area (Coenen et al., 2018). The therapeutic triangle is defined anteriorly by the mamillary body, posteromedially by the red nucleus, and posterolaterally by the substantia nigra/STN. Since the VTApp cannot be appreciated on standard structural MRI sequences, deterministic DTI is used to optimize the electrode depth and trajectory, so as to maximize contact with the VTApp. Due to the close proximity of the oculomotor nerve, the acute stimulation effect of diplopia and dizziness serves as a confirmation of accurate electrode placement, but also limits the amplitude of stimulation. **Figures 1A,B** depicts an electrode placed in the region of the VTApp (Coenen et al., 2018).

In the first open-label trial of VTApp DBS (FORSEE I; FORebrain Simulation dEprEssion), clinical response and remission were achieved in 6/7 and 4/7 patients, respectively (Schlaepfer et al., 2013). Particularly impressive was the fact that all 7 patients experienced acute intraoperative appetitive responses, and 5/7 patients achieved responder status by 1 week post-operatively. Such a rapid rate of improvement was unprecedented in the psychiatric DBS field, even amongst open-label studies. At long-term follow-up, these improvements were maintained for at least 4 years (Bewernick et al., 2017). In a second open-label series of VTApp DBS from the same group (FORSEE II), there was a nearly 50% reduction in the mean depression ratings as early as 1 week, and a 100% response rate at 12 months (Coenen et al., 2019).

The approach to targeting the VTApp reported in the FORESEE trials, has been implemented by at least two other centers, with one reporting promising results (Fenoy et al., 2018). The other center reported a lack of robust intraoperative findings or postoperative response among two anhedonic MDD patients despite following a similar DTI-based targeting approach (Davidson et al., 2020a). Although the VTApp remains an appealing target for DBS in the treatment of refractory MDD, especially given its reported rapid clinical response rates, more nuanced patient or target selection may be required; different targets may offer better clinical effect depending on depression subtypes, neuroimaging biomarkers, or the results of intraoperative stimulation (Widge et al., 2018). For example, given the high rate of intraoperative appetitive responses among those patients who obtain clinical benefit with VTApp DBS, it could be hypothesized that in patients where appetitive responses are not observed, an alternative target should be stimulated. It is also important to acknowledge that all VTApp data to date has come from open-label studies, and although promising, a large randomized trial is still needed (Coenen et al., 2019).

SUBCALLOSAL CINGULUM

The SCC target was first selected based on its critical role in the network involved in the modulation of negative affect (Seminowicz et al., 2004; Mayberg et al., 2005). Despite promising open-label data, an industry-sponsored randomized controlled trial (RCT) failed to show a difference between active and sham stimulation at 6 months (Holtzheimer et al., 2017). Connectivity-based studies have suggested that DTI-based targeting, may be one of many critical factors needed to demonstrate efficacy (Mayberg et al., 2016; Widge et al., 2016).

In the first published series, DBS electrodes were implanted at the transition between gray and white matter beneath the genu of the corpus callosum (Hamani et al., 2011). Based upon anatomic positioning of the active contacts, there was no appreciable difference in location between responders and non-responders (Hamani et al., 2011). On subsequent analyses, it soon became apparent that the therapeutic benefit was associated with the pattern of axonal white-matter tracts stimulated, rather than the location within the gray matter (Riva-Posse et al., 2014).

In a proof of concept analysis, the white matter tracts stimulated by SCC DBS electrodes were mapped using probabilistic DTI in a single subject who responded to treatment (Lujan et al., 2013). On both the left and right side, the therapeutic contact was positioned at the intersection of the cingulum, forceps minor, and frontostriatal projections. Importantly, the most ventral contacts, located at the gray–white junction, did not intersect with this white matter blueprint, and only contacted frontostriatal fibers. Based on these results, a larger retrospective analysis in patients who had received open-label SCC-DBS demonstrated a shared connectome blueprint amongst responders than was not seen in non-responders

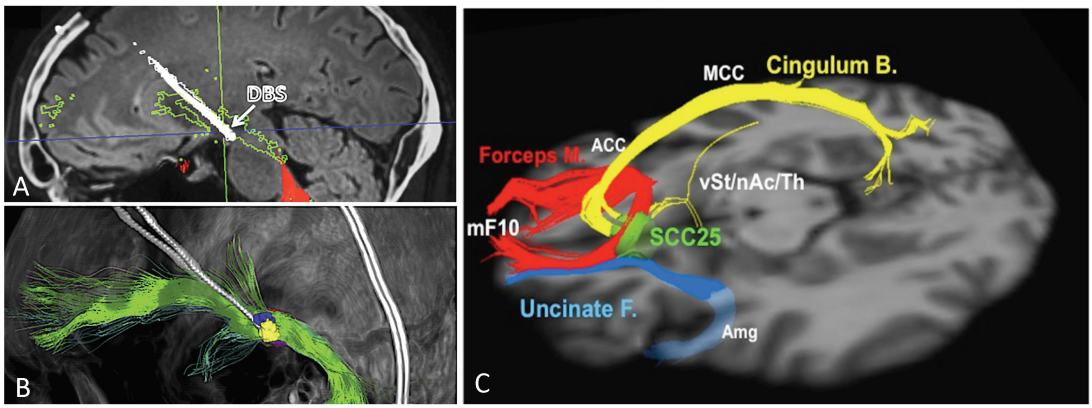

FIGURE 1 | Ventral tegmental area projection pathway (VTApp) DBS. **(A)** Outline shows how DBS electrode traverses the VTApp, formerly suggested to be the superolateral branch of the medial forebrain bundle (green). **(B)** Three-dimensional view from lateral and left. **(C)** Optimal SCC DBS Fiber Bundle Target Template. Red: Forceps Minor, Blue: Uncinate Fasciculus, Yellow: Cingulate Bundle. Abbreviations: mF10, medial frontal (Brodmann Area 10); Forceps M., forceps minor; Uncinate F., uncinate fasciculus; Cingulum B., cingulum bundle; vSt, ventral Striatum; nAc, nucleus accumbens; Th, thalamus; SCC25, subcallosal cingulate cortex (BA25); Amg, amygdala; ACC, anterior cingulate cortex; MCC, middle cingulate cortex. Adapted and reprinted from Coenen et al. (2018), with permission from Elsevier. Reprinted from Riva-Posse et al. (2014), with permission from Elsevier.

(Riva-Posse et al., 2014). In this study, the strongest response was observed in patients where the volume of tissue activated (VTA) was situated at the intersection of the forceps minor, cingulum bundle, frontostriatal projections, as well as the uncinate fasciculus (UF) (**Figure 1C**). When this white-matter blueprint targeting strategy was used prospectively in an open-label study, the 6-month response rate improved from 41 to 73% (Riva-Posse et al., 2018). The acute autonomic effects of SCC DBS observed intraoperatively appear to be directly correlated to the degree of structural connectivity between the VTA and the mid-cingulate cortex (via the cingulum bundle) (Riva-Posse et al., 2019).

The white-matter blueprint SCC targeting scheme is now being used by other groups in trials of SCC-DBS (Hamani et al., 2020; Ramasubbu et al., 2020), demonstrating the translational impact of this work. One group has attempted to disentangle the contribution of each of the four tracts in this blueprint toward an eventual clinical response (Clark et al., 2020). Using data from an open-label study, they reported that excessive stimulation of the forceps minor (especially its dorsal component) is associated with non-response, while stimulation of the UF is associated with clinical improvement (Clark et al., 2020). These results are not necessarily contradictory to the findings of Riva-Posse and colleagues, who have yet to report each individual tract's association with clinical response. It should also be noted that these two groups use different methods for predicting the size of the VTA (Butson et al., 2007; Chaturvedi et al., 2013), leading to dramatic differences in activated volume. The use of open-source VTA-modeling software, such as that provided by the Lead-DBS software might help with the generalizability of these studies (Horn et al., 2019).

Recently, our group extended this DTI-based SCC targeting approach to the treatment of refractory post-traumatic stress disorder (PTSD) (Hamani et al., 2020). PTSD, which develops as a maladaptive response to previous traumatic events, is characterized by hypervigilance, frequent "re-experiencing" of traumatic events, and dissociation/depersonalization. There is a high rate of comorbid depression and anxiety (Kessler et al., 2005). Preclinical and human studies of PTSD have demonstrated hyperactivity in the amygdala, which is likely due to inadequate top-down inhibition from an underactive ventromedial prefrontal cortex (Milad et al., 2009; Reznikov et al., 2015). In a rodent model, DBS delivered to the infralimbic cortex (considered to be homologous to the rodent homolog of the SCC) (Hamani et al., 2014a; Reznikov et al., 2016) improved fear-extinction and reduced anxiety-type behavior while decreasing cell-firing of principal cells in the basolateral amygdala (Reznikov et al., 2018).

Based on these results, we hypothesized that the DTI-informed white matter SCC target could be beneficial in the treatment of PTSD, partly through stimulation of UF fibers passing from the prefrontal cortex to the amygdala, and partly through the modulation of the affective network through the cingulum and forceps minor. In order to maximize stimulation of the UF and the cingulum bundle, we used directional DBS, with current directed toward the uncinate fasciulus as well as to the fiber blueprint proposed by Riva-Posse et al. (2014) (**Figure 2**). In a open-label proof-of-concept index case, this directional stimulation approach led to a dramatic and robust reduction in PTSD symptoms (Hamani et al., 2020). As additional centers begin to apply this DTI-informed targeting of the SCC, it will likely be possible to further optimize this approach, potentially associating improvement in specific symptom subtypes with individual tracts of the blueprint.

Recently two articles have suggested potential imaging-based biomarkers of response to SCC-DBS. In the first study, a voxel-based morphometry analysis of 27 patients with SCC DBS suggested that a larger preoperative SCC volume is associated with eventual clinical response (Sankar et al., 2020). Another center reported that preoperative SCC hypermetabolism may predict responder status (Brown et al., 2020). Although there

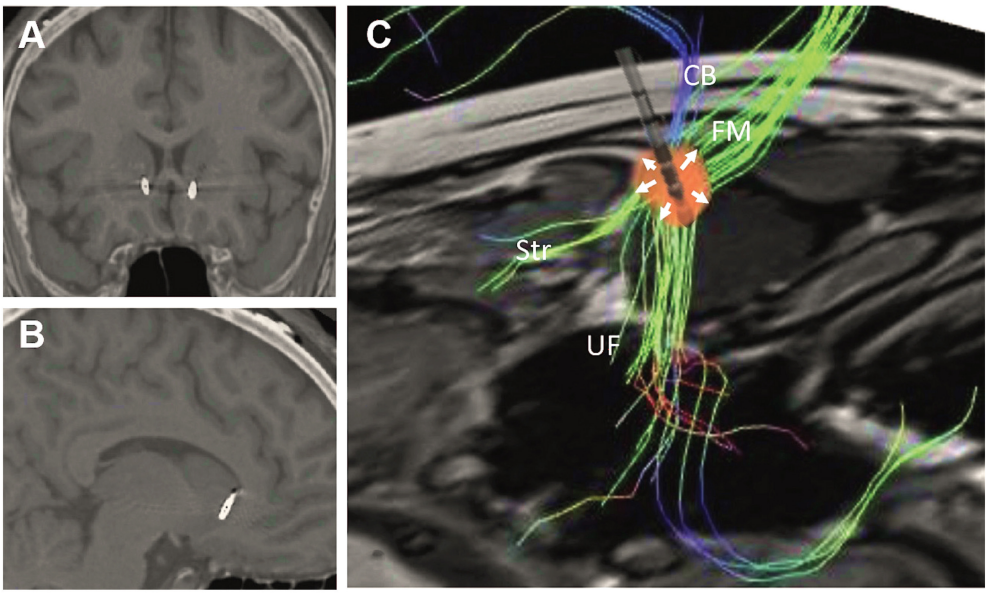

FIGURE 2 | Postoperative computed tomography fused with preoperative magnetic resonance images showing the location of the electrodes in the **(A)** coronal and **(B)** sagittal planes. **(C)** Reconstruction of preoperative tractography and schematic representation of an implanted electrode. The presented spread of current (red spherical shape) was adapted to reflect the fact that 67% of the current was delivered medially through contacts in third ring (arrows pointing upward), while 33% spread laterally though a lateral contact in the second ring (arrows pointing downward). Under these circumstances, stimulation through the second ring would largely affect the uncinate fasciculus (UF), whereas stimulation of the third ring would largely modulate the cingulate bundle (CB), forceps minor (FM), and frontostriatal (Str) projections. Reprinted from Hamani et al. (2020), with permission from Elsevier.

is not yet sufficient evidence to use these biomarkers to select patients, the field seems to be moving toward imaging-based patient and target selection.

VENTRAL STRIATUM/VENTRAL CAPSULE

The ventral striatum/ventral capsule (VC/VS), used here to refer to the highly similar ventral anterior limb of the internal capsule (vALIC) and the nucleus accumbens (NAc) targets, is the most common DBS target in the treatment of OCD (Hamani et al., 2014b; Denys et al., 2020), but also frequently used in the treatment of MDD (Dougherty et al., 2015). Although open-label trials of VC/VS DBS have yielded long-term response rates ranging from 40 to 66% for OCD and MDD (Greenberg et al., 2010; Bewernick et al., 2012; van der Wal et al., 2019; Winter et al., 2020), an industry-sponsored RCT of VC/VS DBS for MDD failed to show a difference between true and placebo stimulation for MDD (Dougherty et al., 2015). An analogous RCT has not been published with VC/VS DBS for OCD, though class I evidence has been obtained from an RCT showing that STN DBS was better than sham stimulation (Mallet et al., 2008). VC/VS DBS studies in which patients underwent a blinded active vs. sham stimulation phase following long-term optimization have shown a positive outcome for both OCD (Denys et al., 2010) and depression (Bergfeld et al., 2016). The use of DBS for OCD is approved in many countries, some under humanitarian-device exemption.

VC/VS DBS was originally implemented as means of mimicking the effect of stereotactic lesioning (Nuttin et al., 1999), a procedure known as anterior capsulotomy, which has been performed since 1949 (Talairach et al., 1949). Over the years, the VC/VS target has migrated posteriorly, almost to the level of the anterior commissure, based solely on clinical experience of better outcomes associated with more posterior stimulation (Greenberg et al., 2010; Luyten et al., 2016; Raymaekers et al., 2017). To our knowledge, there has not yet been prospective use of advanced imaging techniques, such as DTI or fMRI, for targeting within the VC/VS, although this is likely to change given the multitude of recent studies delineating the anatomical nuances of this region (Hartmann et al., 2015; Avecillas-Chasin et al., 2019; Coenen et al., 2020).

Currently, VC/VS DBS or vALIC ablation is targeted based on standardized measurements relative to the anterior commissure and the midline, despite there being numerous distinct projection bundles found in the vicinity. These white matter projections are organized along a ventral-dorsal and medial-lateral gradient. Within the ALIC, fibers located ventromedially are more likely to project to ventromedial cortical targets, such as the ventromedial prefrontal cortex, whereas fibers found dorsolaterally project to targets such as the dorsolateral prefrontal cortex (Lehman et al., 2011; Avecillas-Chasin et al., 2019). Despite this consistent topographic organization, there is substantial inter-individual variability, as well as "interweaving" of fibers within the ALIC (Makris et al., 2016; Nanda et al., 2017).

Three recent studies have suggested that the VTApp within ALIC (which may represents the hyperdirect cortical-STN

connection), may be a critical fiber tract leading to clinical response in DBS for OCD (Baldermann et al., 2019; Liebrand et al., 2019; Li et al., 2020). ALIC fibers associated with a good outcome have been postulated to run dorsal to the NAc, near the bed nucleus of the stria terminalis, entering the ventral part of the thalamus at the border of the anterior and inferior thalamic peduncle (Baldermann et al., 2019). These ultimately connect the prefrontal cortex with the medial dorsal nucleus of the thalamus and the STN (Baldermann et al., 2019). Furthermore, connectivity to the medial frontal gyrus may mediate antidepressant effects (Baldermann et al., 2019).

Another approach is to categorize the tracts on the ALIC based on their involvement in specific circuits, with reward and affect circuits being found more ventrally, and cognitive control/decision making circuits being located more dorsally (Coenen et al., 2020). As DBS and ablative procedures are both theorized to function by interrupting pathological circuit-based oscillations, targeting could be adjusted in the ventral-dorsal or medial lateral direction based on a patient's symptom profile. For example—in OCD patients with especially prominent symptoms of cognitive inflexibility, a more dorsally activated contact (or lesion) may be optimal, whereas patients with more prominent mood symptoms might benefit from ventral targeting (Coenen et al., 2020).

INDIVIDUALIZED VS. NORMATIVE IMAGING

As neuroimaging techniques evolve to the point of translation into clinical care, a dilemma has arisen as to the comparative value of individualized DTI and fMRI data, vs. large normative "averaged" datasets. The advantages of large normative datasets include an improved signal-to-noise ratio (SNR), potential use of state-of-the art equipment (i.e., Human Connectome Project) (Van Essen et al., 2013), and allowing for a more universal scientific language and comparison between centers (Horn and Blankenburg, 2016). However, given the considerable inter-individual variability in brain structure and connectivity, applying normative imaging at the patient level might prevent the ability to "personalize" neuromodulation treatments (Fox et al., 2013; Cash et al., 2020). For instance, some authors have suggested that the inter-individual variability of tract positioning within the ALIC will require subject-specific high-resolution DTI in order to personalize targets (Makris et al., 2016; Nanda et al., 2017). On the other hand, single-subject DTI can introduce substantial variance, and according some authors, may not be ready for mainstream use in targeting (Jakab et al., 2016; Petersen et al., 2017).

In a small double-blinded sham-stimulation controlled series of VC/VS implanted OCD patients, it was demonstrated that individualized fMRI/DTI could be used to determine optimal electrode contacts (Barcia et al., 2019). Patients underwent a symptom provocation task during fMRI scanning, revealing distinct areas of cortical activation based on their predominant compulsion symptoms (i.e., contamination obsessions activate a different cortical region than checking obsessions). Among responders, the most effective contacts could be distinguished by their connectivity to the cortical region displaying activation on the symptom-provocation fMRI. In some patients, this involved a more dorsal contact, while in others more ventral contacts proved most effective. This suggests that prospectively, patients could be programed based on their individual fMRI pattern of prefrontal activation during symptom provocation. Although these findings are preliminary, they emphasize the need to continue developing patient-specific advanced neuroimaging methods, despite the challenges of low SNR and high variability.

In contrast, emphasizing the advantage of large normative datasets, a recent study used DTI data derived from the HCP, to identify a common tract distinguishing responders from non-responders following VC/VS DBS for OCD (Li et al., 2020). The tract is part of a hyperdirect circuit, projecting from the anterior cingulate and lateral prefrontal cortex to the anteromedial STN. Their analysis included patients from four different centers, with DBS implanted at the VC/VS or STN. In patients with VC/VS DBS, non-responders tended to have a VTA placed too ventrally, with the critical tract passing above. In patients with STN DBS, a VTA located too dorsally resulted in the tract passing below, and a reduced likelihood of clinical response. Through the use of several cohorts, they were able to demonstrate significant out-of-sample predictive capabilities of this tract, suggesting a unified mechanism underlying clinical response to both STN and ALIC DBS in refractory OCD. It should be noted that this multi-centered data-sharing effort used a mixture of open-label and blinded clinical data.

Currently, the only prospective implementation of DTI for psychiatric surgery involves patient-level data, for SCC and VTApp stimulation. It has yet to be assessed if and how these targets would be affected by using normative data. Normative datasets have to be non-linearly warped into patient-space, which can introduce an additional source of error, and may erode some of the advantages of higher-resolution imaging.

CORRELATING IMAGING FINDINGS WITH OUTCOMES

Many of the neuroimaging advances seen in psychiatric surgery are translated from the field of movement disorders (Horn et al., 2017). Application in psychiatric surgery, however, is complicated by two central factors. Firstly, outcome measurement is much more challenging in psychiatric disorders than movement disorders, where clinical improvements are often immediate and easily quantified (i.e., the Unified Parkinson's Disease Rating Scale). Following psychiatric surgery, clinical results often take months to manifest, and even then, there is considerable debate over the optimal way to measure outcomes (Rabin et al., 2020). Although the outcome of most psychiatric surgery trials is distilled down to a single clinical score, psychiatric illness may not be accurately characterized in such a manner. To some degree, the success of neuroimaging analyses in psychiatric surgery is related to the validity of outcome scores. As neuroimaging analyses become increasingly sophisticated, it will be crucial for measurement of psychiatric outcomes to

similarly become more nuanced. Secondly, the amount of data available for analysis is often limited, due to factors including limited funding, lack of access, and a reluctance to refer patients for psychiatric surgery (Mendelsohn et al., 2013; Cormier et al., 2019). Multi-centered data-sharing efforts, such as the recent study by Li et al. (2020), are increasingly becoming a necessity.

CONCLUSION

Advanced neuroimaging techniques have now begun to influence the clinical practice of psychiatric neurosurgery. DTI targeting methods are being used routinely in SCC and VTApp DBS for MDD. Although VC/VS targeting is still performed with conventional targeting based on structural MRI, the findings of several recent DTI and fMRI studies have suggested methods for improved targeting. There continues to be a role for the use of both patient-specific imaging and large normative datasets, with both offering distinct advantages. As an added wrinkle of complexity, the clinical scores upon which imaging analyses are based, are often not well represented by a single number, and future imaging studies will need to develop more advances ways of accommodating clinical heterogeneity. With advanced neuroimaging having already been translated into human clinical trials, the future of neuroimaging in psychiatric surgery is very promising.

AUTHOR CONTRIBUTIONS

BD, YM, and CH wrote the manuscript. NL, JR, and PG provided insightful comments and reviewed content. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Deep Brain Stimulation of the Subthalamic Nucleus Modulates Reward-Related Behavior: A Systematic Review

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Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective treatment for the motor symptoms of movement disorders including Parkinson's Disease (PD). Despite its therapeutic benefits, STN-DBS has been associated with adverse effects on mood and cognition. Specifically, apathy, which is defined as a loss of motivation, has been reported to emerge or to worsen following STN-DBS. However, it is often challenging to disentangle the effects of STN-DBS *per se* from concurrent reduction of dopamine replacement therapy, from underlying PD pathology or from disease progression. To this end, pre-clinical models allow for the dissociation of each of these factors, and to establish neural substrates underlying the emergence of motivational symptoms following STN-DBS. Here, we performed a systematic analysis of rodent studies assessing the effects of STN-DBS on reward seeking, reward motivation and reward consumption across a variety of behavioral paradigms. We find that STN-DBS decreases reward seeking in the majority of experiments, and we outline how design of the behavioral task and DBS parameters can influence experimental outcomes. While an early hypothesis posited that DBS acts as a "functional lesion," an analysis of lesions and inhibition of the STN revealed no consistent pattern on reward-related behavior. Thus, we discuss alternative mechanisms that could contribute to the amotivational effects of STN-DBS. We also argue that optogenetic-assisted circuit dissection could yield important insight into the effects of the STN on motivated behavior in health and disease. Understanding the mechanisms underlying the effects of STN-DBS on motivated behavior-will be critical for optimizing the clinical application of STN-DBS.

Keywords: deep brain stimulation (DBS), subthalamic nucleus (STN), reward, motivation, rodent, operant

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INTRODUCTION

Deep brain stimulation (DBS) is a surgical therapy whereby electric current is passed through electrodes implanted into specific brain nuclei. DBS applied to the subthalamic nucleus (STN-DBS) has been extensively used to treat motor symptoms of Parkinson Disease (PD) for more than 30 years (Benabid et al., 2009). This neurosurgical treatment is typically applied in patients after years of first-line dopamine replacement therapy (i.e., L-DOPA), which eventually loses its efficacy

and starts to induce dyskinesias which further reduce its therapeutic utility (Poewe, 1994; Ahlskog and Muenter, 2001; Obeso et al., 2004). STN-DBS significantly improves PD motor symptoms of tremor, rigidity and akinesia (Limousin et al., 1995; Krack et al., 2003; Fasano et al., 2010) and thus reduces the required dose of dopaminergic agonist or replacement therapy (Moro et al., 1999). Because of its reliable therapeutic efficacy, it has been proposed to apply STN-DBS earlier in the course of PD, before dopaminergic therapy loses efficacy or the emergence of L-Dopa induced dyskinesias (Deuschl et al., 2013; Schuepbach et al., 2013). Moreover, case reports have suggested that STN-DBS may reduce compulsive (Mallet et al., 2002; Fontaine et al., 2004) or addiction-like behaviors (Witjas et al., 2005), which has led to the suggestion that STN-DBS could be applied in patients suffering from obsessive compulsive disorder (Mallet et al., 2008) or to reduce symptoms of substance use disorders (Krack et al., 2010; Rouaud et al., 2010; Pelloux and Baunez, 2013). As a result of earlier intervention with STN-DBS for PD, as well as the increasing indications, the population of patients treated with STN-DBS will expand to more heterogeneous populations.

Along with its therapeutic benefits, neuropsychiatric side effects of STN-DBS have been reported since its first applications. Reported effects range from new onset or worsening of impulsivity, apathy or anhedonia to improvement of pre-existing behavioral symptoms (Chaudhuri and Schapira, 2009; Castrioto et al., 2014). Dissociating the effects of STN-DBS itself from underlying neuropathology and co-occurring pharmacological treatment is critical to understand the etiology of these side effects. One of the most frequently reported side effects of STN-DBS in the clinic is apathy, defined as a loss of motivation or reduction in goal-directed behavior accompanied by flattened affect (Marin, 1996; Levy and Dubois, 2006). Apathy is a core neuropsychiatric symptom of PD, that can be present before STN-DBS and alleviated by dopaminergic agonists (Leentjens et al., 2009). Apathy can be exacerbated following STN-DBS (Drapier et al., 2006; Le Jeune et al., 2009; Wang et al., 2018), which then compromises the quality of life benefits of STN-DBS (Maier et al., 2013, 2016; Martinez-Fernandez et al., 2016). The prevailing explanation for the emergence or worsening of apathy following STN-DBS is a withdrawal-like syndrome due to the reduction of dopaminergic treatment (Thobois et al., 2010; Chagraoui et al., 2018), although there is also evidence supporting a role for STN-DBS itself in this pathogenesis (Le Jeune et al., 2009; Zoon et al., 2019). However, because of the interaction between STN-DBS, pharmacological co-treatments and the progression of PD pathology, it is difficult to determine the underlying causes of motivational symptoms arising after STN-DBS in the clinic.

In this respect, pre-clinical models have the advantage of being able to isolate the contribution of STN-DBS alone to motivation-related behaviors, and to elucidate the neural mechanisms underlying these behaviors. To date, several studies have sought to determine the involvement of STN modulation on motivational processes (for reviews see Temel et al., 2009; Baunez and Gubellini, 2010; Hamani et al., 2017). However, several methodological differences exist between these studies, including the behavioral paradigm used to assess motivation, the parameters of stimulation or the reward used, which has precluded any clear consensus regarding the effects of STN-DBS on motivation and reward processing. To address this controversy, we performed a systematic review of the pre-clinical literature, extracting features of studies focused specifically on reward motivation and consumption behaviors. We identify a consistent pattern of decreased reward seeking, motivation and consumption induced by STN-DBS, which was not evident in studies of STN lesion or inactivation. We also identify several stimulation and experimental parameters that are associated with STN-DBS-induced motivational deficits. Our analysis provides a rationale for using pre-clinical models to dissect the neural mechanisms underlying specific behavioral effects of STN-DBS. This mechanistic understanding will be critical for optimizing STN-DBS as it is applied to expanding patient populations and for increasing clinical indications.

METHODS

We systematically analyzed all pre-clinical studies investigating the effect of STN-DBS, STN Lesion, or pharmacological inhibition of the STN on motivation for reward.

Identification of Pertinent Literature

A systematic analysis of the international literature was carried out by selecting articles published in peer-review journals, using PubMed, and BioRxiv databases. The last search was conducted on September 11, 2020. Restrictions were made, limiting the study to academic publications in which the full text was published in English. Search terms were as follows: "subthalamic nucleus" AND "stimulation" AND ("reward" OR "motivation" OR "self-administration" OR "addiction" OR "cocaine" OR "FOOD"); and "subthalamic nucleus" AND ("inactivation" OR "lesion").

Screening and Eligibility

From the list of potential articles produced by systematic research, we selected studies relevant to the topic on the basis of their title and abstract. In brief, we excluded clinical, *in vitro* and *ex vivo* investigations, along with experimental studies on rodents not assessing motivation or reward-related behaviors. We then excluded studies applying neuromodulation techniques other than electrical stimulation, lesion or pharmacological inactivation, or studies not providing metrics relevant to the criteria outlined below (**Figure 1**).

Studies Included

Following this approach, we included 46 relevant experiments across 25 published studies between 1997 and 2020. We summarize the composition of these studies in **Figures 2–4**.

In rodents, assessment of motivation often relies on reward seeking tasks, during which the animal has to perform an operant behavior to receive a reward (Koob and Weiss, 1990). The majority (33/46) of the experiments in our analysis used a standard operant reinforcement task consisting of lever pressing or nose poke to induce reward delivery. Twenty two of the 33 studies used a fixed ratio (FR) paradigm, in which a fixed number

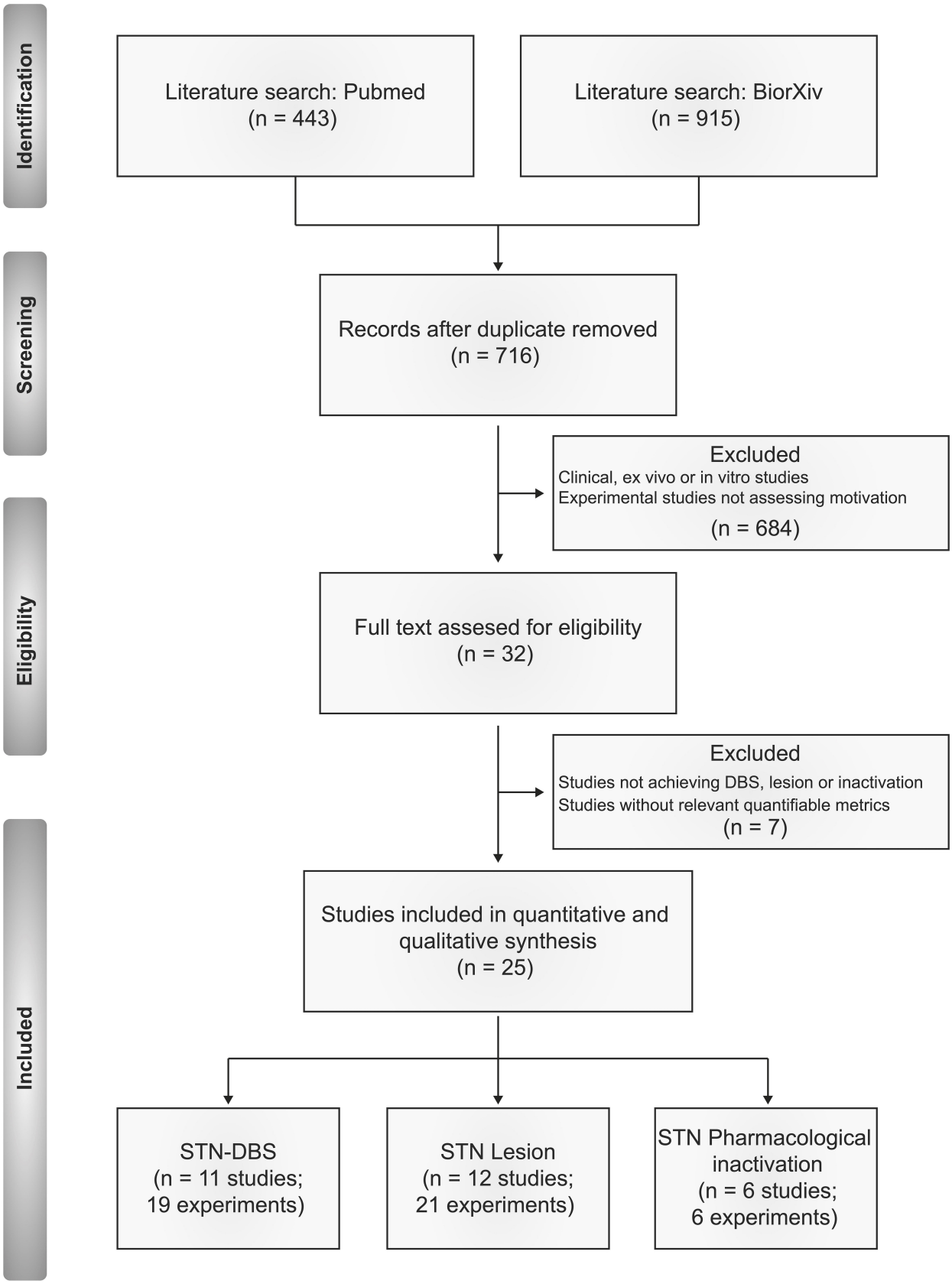


FIGURE 1 | PRISMA flow diagram of the inclusion criteria of studies eligible for systematic review.

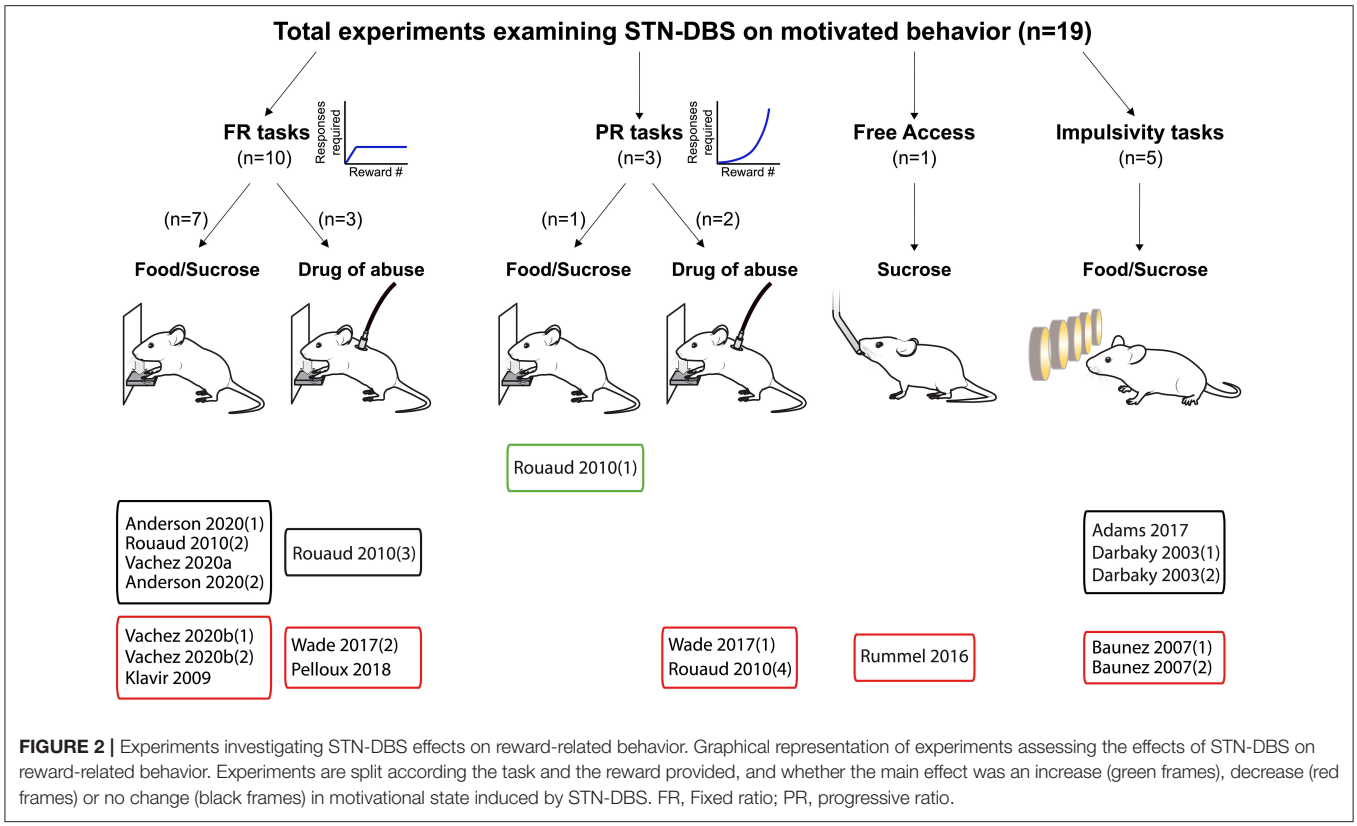


FIGURE 2 | Experiments investigating STN-DBS effects on reward-related behavior. Graphical representation of experiments assessing the effects of STN-DBS on reward-related behavior. Experiments are split according the task and the reward provided, and whether the main effect was an increase (green frames), decrease (red frames) or no change (black frames) in motivational state induced by STN-DBS. FR, Fixed ratio; PR, progressive ratio.

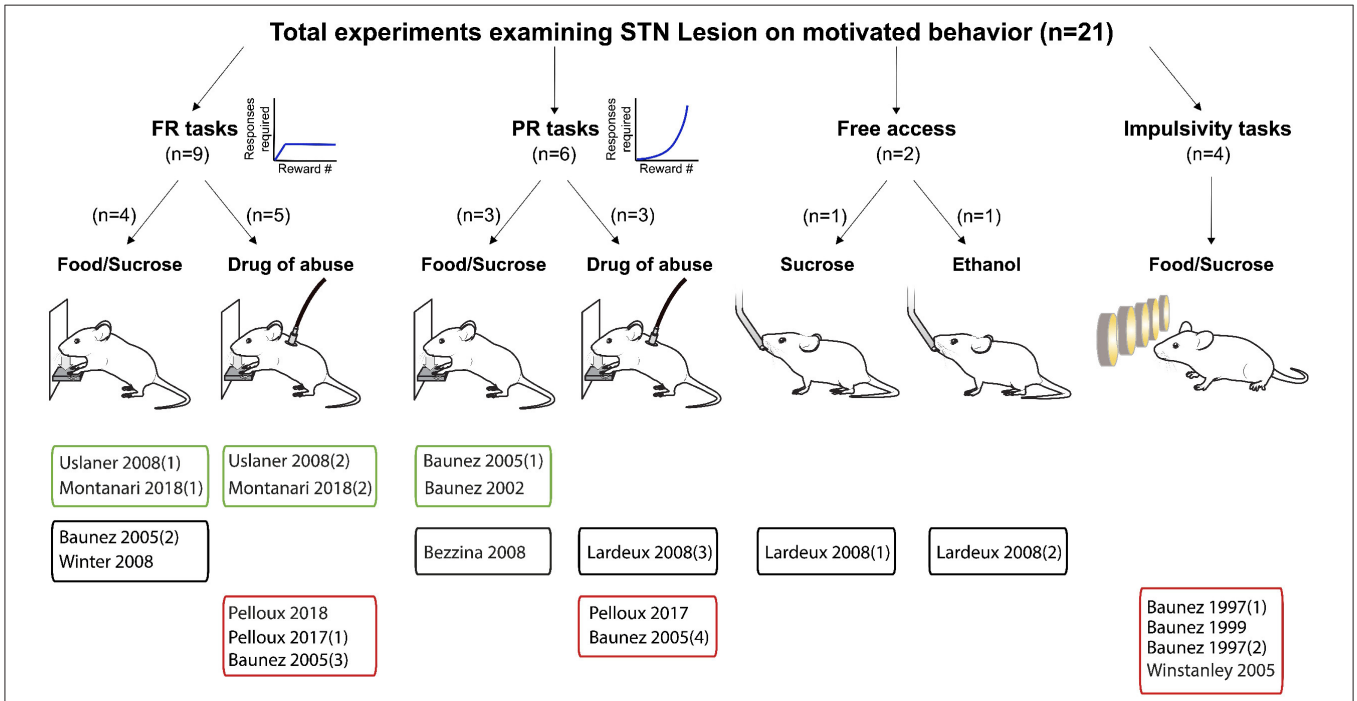


FIGURE 3 | Experiments investigating STN lesion effects on reward related behavior. Graphical representation of experiments assessing the effects of STN lesion on reward-related behavior. Experiments are split according the task, the reward provided and whether the main effect was an increase (green frames), decrease (red frames) or no change (black frames) in motivational state following lesion of the STN. FR, Fixed ratio; PR, progressive ratio.

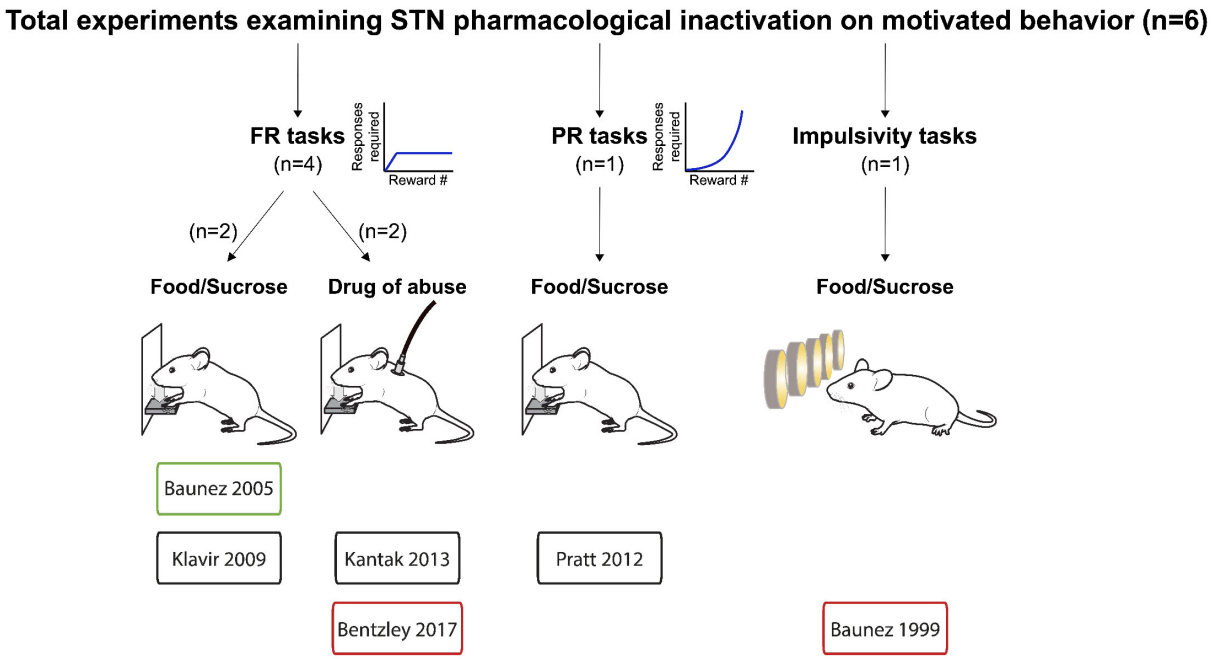


FIGURE 4 | Experiments investigating STN pharmacological inhibition effects on reward related behavior. Graphical representation of experiments assessing the effects of pharmacological inactivation of the STN on reward-related behavior. Experiments are split according the task, the reward provided and whether the main effect was an increase (green frames), decrease (red frames) or no change (black frames) in motivational state following pharmacological inactivation of the STN. FR, Fixed ratio; PR, progressive ratio.

of operant responses (lever press or nose poke) is necessary to earn a reward. Most studies (19) used a FR1 paradigm; here, we extracted the number of operant responses and earned rewards to evaluate motivational changes. The remaining 11 operant experiments used the progressive ratio (PR) task, in which the number of required operant responses increases incrementally with each reward earned during the task (Arnold and Roberts, 1997; Bradshaw and Killeen, 2012). The PR task is used to assess motivation by establishing "break-point," or the number of operant responses the animal is willing to execute in order to obtain the reward (Griffiths et al., 1975). We extracted the break-point, or, if not available, the number of rewards earned. Few additional experiments ($n = 3$) provided the reward in a free access task, which require no explicit amount of work to obtain a reward. We thus use the consumed reward quantity as an outcome measure.

Finally, we included ten experiments that use tasks designed to assess impulsive behavior in the context of reward seeking. The majority of these studies ($n = 8$) used variations of the five-choice serial-reaction time task (5-CSRTT) (Robbins, 2002), while single studies using a delay discounting task (Evenden and Ryan, 1996) and rat Iowa Gambling Task (rIGT; van den Bos et al., 2014). In each of these paradigms, the start of the trial is cued, and the animal is required make the choice to complete a trial or not, and to consume the reward if the trial was successful.

The primary outcome of these tasks is to assess impulsivity by using metrics such as pre-mature responses. However, several additional parameters such as the number of non-completed trials (omissions), failures to retrieve the reward, degree of perseverative responding or the latency to execute the operant behavior or reward retrieval can be gleaned from these tasks. Changes in these parameters can reflect altered cognitive processing, motor impairments, attentional deficits or motivational changes. Motivational changes can be inferred with caution by the evolution of the numbers of omissions, especially when coupled with an increase in response latency (Robbins, 2002; Higgins and Silenieks, 2017). In few occasions, perseverative responses have been interpreted as reflecting changes in motivation (Baunez and Robbins, 1997; Baunez et al., 2007), although they are more frequently interpreted as evidence for compulsive behaviors rather than motivation *per se* (Robbins, 2002; Higgins and Silenieks, 2017). Thus, in order to extract the motivational components of the task of these different studies in a comparable and consistent way, we limited our analysis to the quantification of reward omissions.

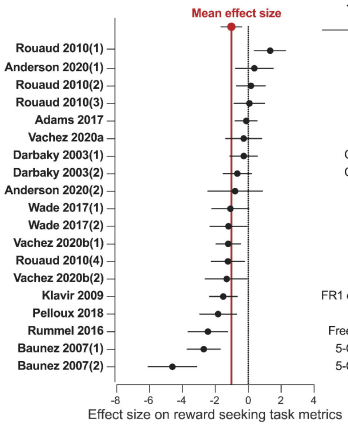
The studies in our analysis also varied in terms of type of reward. In 29 of 45 experiments, the delivered reward was palatable food, generally sucrose pellets or solution. While in the remaining 16 experiments, a drug reward (cocaine, heroin or ethanol) was used.

When precise metrics were not provided in the results description, means and SEM were extracted from graphical results section using Engauge Digitizer 12.1 software. For each experiment we calculated the Cohen's d standardized mean difference (mean difference divided by the pooled standard deviation) as an estimate of the effect size (Lee, 2016). Thus, we

excluded studies if data were not shown or if the precise number of animals for each experimental group was not provided. We represented each effect size ± 95% confidence intervals on forest plots (**Figures 5**–**7**).

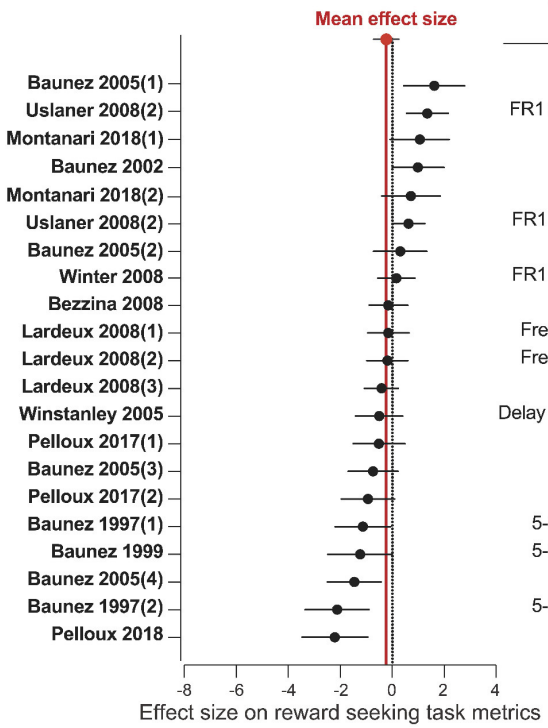
RESULTS

Our results reveal a consistent effect of STN-DBS decreasing reward motivation and consumption (**Figures 2**, **5**). These results



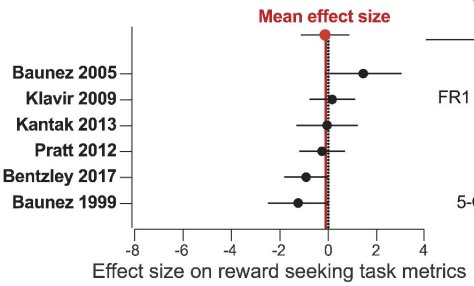
Task	Reward	Metric	Pathophysiology	Food	Bilateralism	Polarity	Chronicity	Frequency (Hz)	Pulse width (µS)	Intensity (µA)
PR	Sucrose	Pellets	Naive	Restricted	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Sucrose	Lever presses	Naive	Restricted	Unilateral	Bipolar	Acute	100	100	100-500
FR1	Sucrose	Pellets	Naive	Restricted	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Cocaine	Infusions	Cocaine	*Ad libitum*	Bilateral	Bipolar	Acute	130	60	50-130
rIGT	Sucrose	Omissions	Naive	Restricted	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Sucrose	Rewards earned	Naive	*Ad libitum*	Unilateral	Monopolar	Chronic	130	60	100-225 (176 +/- 11)
CRTT	Food	Trials initiated	Naive	Restricted	Unilateral	Bipolar	Acute	130	60	50
CRTT	Food	Trials initiated	PD	Restricted	Unilateral	Bipolar	Acute	130	60	50
FR1	Sucrose	Lever presses	PD	Restricted	Unilateral	Bipolar	Acute	100	100	100-500
PR	Heroin	Break-point	Heroin	*Ad libitum*	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Heroin	Presses	Heroin	*Ad libitum*	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Sucrose	Rewards earned	Naive	*Ad libitum*	Bilateral	Monopolar	Chronic	130	60	100-225 (183 +/- 13)
PR	Cocaine	Infusions	Cocaine	*Ad libitum*	Bilateral	Bipolar	Acute	130	60	50-130
FR1	Sucrose	Rewards earned	PD	*Ad libitum*	Bilateral	Monopolar	Chronic	130	60	100-225 (183 +/- 13)
FR1 extinction	Food	Lever presses	Naive	*Ad libitum*	Bilateral	Bipolar	Acute	130	100	100
FR1	Cocaine	Infusions	Cocaine	*Ad libitum*	Bilateral	Bipolar	Acute	130	80	80
Free access	Sucrose	Quantity	Naive	Restricted	Bilateral	Monopolar	Acute	130	100	100
5-CSRTT	Food	Omissions	PD	Restricted	Bilateral	Bipolar	Acute	100	60	50
5-CSRTT	Food	Omissions	Naive	Restricted	Bilateral	Bipolar	Acute	100	60	50

FIGURE 5 | STN-DBS decreases reward related behavior. Forest plot of the Cohen's d standardized mean difference for reward seeking effect of STN-DBS. Mean effect size is depicted by the dashed red line. Key details of the experimental design, and DBS stimulation parameters are summarized in the associated table. All the studies provided water *ad libitum*. 5-CSRTT, Five choice serial reaction time; CRTT, choice reaction time task; PD, Parkinson's disease; FR, Fixed ratio; PR, progressive ratio; rIGT, rat Iowa Gambling Task.



Task	Reward	Metric	Pathophysiology	Food	Water
PR	Sucrose	Pellets	Naive	Restriction	*Ad libitum*
FR1 extinction	Sucrose	Cue interactions	Naive	Restriction	*Ad libitum*
FR5	Sucrose	Pellets	Naive	*Ad libitum*	*Ad libitum*
PR	Food	Break-point	Naive	Restriction	*Ad libitum*
FR5	Cocaine	Infusions	Cocaine	*Ad libitum*	*Ad libitum*
FR1 extinction	Cocaine	Cue interactions	Cocaine	*Ad libitum*	*Ad libitum*
FR1	Sucrose	Pellets	Naive	Restriction	*Ad libitum*
FR1 extinction	Food	Lever presses	Naive	Restriction	*Ad libitum*
PR	Food	Ratio	Naive	Restriction	*Ad libitum*
Free access	Sucrose	Quantity	Naive	*Ad libitum*	deprived
Free access	Ethanol	Quantity	Ethanol	*Ad libitum*	deprived
PR	Ethanol	Ratio	Ethanol	*Ad libitum*	deprived
Delay discounting	Sucrose	Omissions	Naive	Restriction	*Ad libitum*
FR1	Ethanol	Rewards earned	Ethanol	*Ad libitum*	*Ad libitum*
FR1	Cocaine	Infusions	Cocaine	Restriction	*Ad libitum*
PR	Ethanol	Rewards earned	Ethanol	*Ad libitum*	*Ad libitum*
5-CSRTT	Food	Omissions	Naive	Restriction	*Ad libitum*
5-CSRTT	Food	Omissions	Naive	Restriction	*Ad libitum*
PR	Cocaine	Infusions	Cocaine	Restriction	*Ad libitum*
5-CSRTT	Food	Omissions	Naive	*Ad libitum*	*Ad libitum*
FR1	Cocaine	Infusions	Cocaine	*Ad libitum*	*Ad libitum*

FIGURE 6 | STN lesion does not consistently affect reward related behavior. Forest plot of the Cohen's d standardized mean difference for reward seeking effect of STN lesion, ranked in order of positive to negative effect. Mean effect size is depicted by the dashed red line. 5-CSRTT, five choice serial reaction time; FR, Fixed ratio; PR, progressive ratio.



Task	Reward	Metrics	Pathophysiology	Food	Drug	Dose (ng)
PR	Sucrose	Pellets	Naive	Restriction	Muscimol	3
FR1 extinction	Food	Lever presses	Naive	Restriction	Muscimol	$1.25\ 10^{-6}$
FR5	Cocaine	Infusions	Cocaine	Restriction	Lidocaine	0.1
PR	Sucrose	Breakpoint	Naive	*Ad libitum*	Muscimol	3
FR1	Cocaine	Infusions	Cocaine	*Ad libitum*	muscimol	6.8
5-CSRTT	Food	Omissions	Naive	Restriction	Muscimol	3

FIGURE 7 | Pharmacological inactivation of the STN does not consistently affect reward related behavior. Forest plot of the Cohen's d standardized mean difference for reward seeking effect of STN pharmacological inactivation, ranked in order of positive to negative effect. Mean effect size is depicted by the dashed red line. 5-CSRTT, five choice serial reaction time test; FR, fixed ratio; PR, progressive ratio.

also highlight specific experimental factors related to task design or stimulation parameters that may influence the magnitude of STN-DBS effect on reward-related behavior. Finally, while early hypotheses posited that STN-DBS induces a "functional lesion" of the STN through inactivation via depolarization block (Beurrier et al., 2001; Magarinos-Ascone et al., 2002; Jakobs et al., 2019), our analysis indicates that this decrease in reward seeking is not recapitulated by lesioning or pharmacologically inhibiting the STN (**Figures 3**, **4**, **6**, **7**).

STN-DBS Decreases Reward Seeking

The systematic analysis of studies using STN-DBS revealed a consistent pattern of decreased reward-seeking, which is summarized in **Figures 2**, **5**. In fact, only a single study reported an increase (30%) in motivation for reward measured by the number of sucrose pellets earned during a PR task (Rouaud et al., 2010). The majority of investigations reported a significant decrease in reward motivation (10/19), while a smaller number found no effect (8/19) (Darbaky et al., 2003; Rouaud et al., 2010; Anderson et al., 2020). In FR or PR operant tasks, STN-DBS consistently decreased intravenous self-administration of addictive drugs (Rouaud et al., 2010; Wade et al., 2017). And while the effects of STN-DBS on motivation for natural rewards is more heterogeneous, the predominant effect of STN-DBS is also a decrease in rewards earned and consumed (Rummel et al., 2016) (Vachez et al., 2020b), but see (Rouaud et al., 2010; Vachez et al., 2020a). A decrease in reward seeking was also evident in extinction tasks, i.e., where STN-DBS operant responses were decreased in the absence of a previously available food pellet (Klavir et al., 2009). Finally, STN-DBS increased the rate of trial omissions in impulsivity tasks (Baunez et al., 2007; Adams et al., 2017), which is one index of decreased reward motivation (Robbins, 2002). In summary, the predominant effect of STN-DBS across these tasks is a reduction in reward seeking and motivation, measured by decreased operant responses, rewards earned, rewards consumed or increased trial omissions. In the following section, we discuss factors that contribute to the variance in results found between studies, which are important to consider when assessing the translational impact of these findings.

Acute vs. Chronic DBS

When interpreting the clinical relevance of STN-DBS in experimental models, one has to keep in mind that patients are stimulated chronically, continuously and that prolonged STN-DBS can drive long term plasticity within the STN or its target nuclei (Shen et al., 2003; Lavian et al., 2013; Chassain et al., 2016). In patients, some therapeutic motor effects of STN-DBS, such as tremor cessation, appear immediately, while it can take several weeks for other symptoms, such as postural instability, to improve (Herrington et al., 2016). The same acute vs. chronic distinction can be made regarding neuropsychiatric symptoms. Some symptoms occur immediately upon STN-DBS onset, such as hypomania, laughing or crying (Krack et al., 2001; Mallet et al., 2007; Wojtecki et al., 2007; Abulseoud et al., 2016), while other symptoms, typically apathy, progressively emerge with chronic stimulation (Drapier et al., 2006; Le Jeune et al., 2009).

In our analysis, only three experiments applied STN-DBS chronically, and two of these experiments showed a significant decrease of sucrose or food self-administration over time (Vachez et al., 2020b). This is in contrast with the absence of motivational deficits during acute STN-DBS during a similar FR1 task or even the increased motivation during a PR task (Rouaud et al., 2010). These differential effects could suggest potential long-term adaptations in the mesolimbic system underlying motivational deficit following chronic STN-DBS. Further investigations specifically using chronic STN-DBS (Melon et al., 2015; Chassain et al., 2016) are needed to understand the long-term effect of STN-DBS on reward-related behavior, and potential plasticity mechanisms underlying these behavioral adaptations.

Unilateral vs. Bilateral DBS

Another important factor to consider when interpreting the effects of STN-DBS on reward seeking is whether the stimulation is applied unilaterally (to a single hemisphere) or bilaterally. One set of studies performed under matched conditions from the same group reported that chronic unilateral STN-DBS during a FR1 task (Vachez et al., 2020a) did not recapitulate the sustained reward seeking deficit that occurred with chronic, bilateral stimulation (Vachez et al., 2020b). With the unilateral STN-DBS, the effect was only transient and lasted no more than

5 days. Overall, the few studies using unilateral STN-DBS do not report robust reward seeking deficits, or report deficits that are only transient (Darbaky et al., 2003; Anderson et al., 2020; Vachez et al., 2020a). In the clinic, bilateral STN-DBS is generally associated with superior reduction in motor symptoms relative to unilateral stimulation (Bastian et al., 2003; Lizarraga et al., 2016), but may also induce more non-motor side-effects (Lee et al., 2011; Sjoberg et al., 2012). Notably, a study within the same clinical center observed apathy following bilateral (Le Jeune et al., 2009) but not unilateral STN-DBS (Vachez et al., 2020a). These observations suggest that preserving function of one STN by applying DBS unilaterally protects against a reward seeking deficits in patients or in animal models. It is also possible that DBS may drive compensatory metabolic or neural circuit changes in the un-stimulated hemisphere that may mitigate reward-seeking deficits induced by STN-DBS. Thus, whether STN-DBS is applied uni- or bilaterally is an important factor to consider when interpreting STN-DBS effects in animal models and its relevance to clinical populations.

Stimulation Polarity

In patients, monopolar electrodes are preferentially used, with the pulse generator within the chest being the ground pole of stimulation (Benabid et al., 2009; Amon and Alesch, 2017). In contrast, most rodent studies use bipolar electrodes. Bipolar stimulation generates a more focal electric field than monopolar electrodes and consequently activates a smaller volume of tissue (Temel et al., 2004; Chaturvedi et al., 2013; Hancu et al., 2019). While there are very few published direct comparisons of bipolar and monopolar stimulation within patients, monopolar stimulation is associated with greater improvement of rigidity, tremor and bradykinesia, but also with a higher incidence of side-effects such as confusion or mania (Deli et al., 2011; Chopra et al., 2012). We found a single study that directly compared monopolar and bipolar STN-DBS (Badstuebner et al., 2017). Consistent with clinical observations, monopolar STN-DBS was also associated with a greater reduction in akinesia, sensorimotor neglect and amphetamine-induced rotation than bipolar DBS in 6-OHDA lesioned rats (Badstuebner et al., 2017). However, monopolar STN-DBS is rarely used in rodent studies, so it is difficult to draw firm conclusions regarding the difference between monopolar and bipolar stimulation on reward-related behavior. Interestingly, the only studies that reported STN-DBS-induced reward seeking deficits in low effort tasks (FR1 or free access consumption) used monopolar electrodes (Rummel et al., 2016; Vachez et al., 2020b). This potential greater decrease in reward motivation with monopolar STN-DBS could be explained by differences in current spread. As we will discuss in subsequent section, although the motor territory of the STN is targeted with DBS, electric current can feasibly spread to associative or limbic territories, or even to adjacent neural structures (Mandat et al., 2006; Tan et al., 2013). Because the electric field induced by monopolar stimulation is more diffuse than with bipolar stimulation, this current spread could be an important driver of decreased reward seeking and motivation.

Pathophysiological and Metabolic State

Finally, the underlying pathophysiology and metabolic state of animals must be carefully considered when interpreting effects of STN-DBS on reward-related behavior. Although STN-DBS has primarily been studied in the context of PD, few studies have directly examined the effects of STN-DBS on reward seeking and motivation in experimental models of PD. In rodents, PD is typically modeled by the selective ablation of dopaminergic neurons with intracranial injections of 6-hydrodopamine (6-OHDA) to mimic the degeneration of dopaminergic neurons observed in PD (Deumens et al., 2002). Dopamine is critical for encoding reward value, action selection and vigor as well as updating behaviors based on past history of prior rewards and punishments [for review, see Berke (2018)]. Therefore, according to the specificity and extent of the dopaminergic lesion, decreased motivation and operant responding for sucrose frequently occurs in 6-OHDA-lesioned animal models independent of STN-DBS (Drui et al., 2014; Favier et al., 2014, 2017; Magnard et al., 2016). Yet, the characteristic striatal dopaminergic denervation in these PD models does not appear to influence the outcome of STN-DBS reward-related behavior. In intact and in 6-OHDA-lesioned rats, STN-DBS induces a similar rate of omission in choice reaction time task (Darbaky et al., 2003; Baunez et al., 2007) and an equivalent decrease of the number of sucrose rewards earned during a FR1 task (Vachez et al., 2020b).

A related factor that definitely affects motivation and thus outcomes of reward seeking tasks is the baseline satiety state of the animal (Berridge, 2004). Some level of food restriction is commonly used to invigorate seeking behaviors and learning in complex tasks such as the 5-CSRTT, and it does so by increasing the motivational value of the reward (Cabeza de Vaca and Carr, 1998; Mosberger et al., 2016). Thus, it is likely that basal food restriction can account for some of the lack of effect of STN-DBS observed in sucrose self-administration studies under low demand conditions [i.e., FR1, Rouaud et al. (2010) and Anderson et al. (2020)], while experiments with this same FR1 task conducted without food restriction have found decreases in reward seeking (Vachez et al., 2020b). The interpretation is that under conditions of basal food restriction, homeostatic drive for calories in sucrose overrides more subtle effects of STN-DBS; when there is no underlying metabolic demand for sucrose, the effects of STN-DBS on incentive motivation are more readily apparent.

Food or Drug Reward

A final and related consideration is whether food or drug reward is used to probe the effects of STN-DNS on reward seeking. Whereas 5/14 experiments reported decreased motivation for sucrose or food reward, 4/5 studies using drug reward found that STN-DBS decreases motivation for the drug. Briefly, bilateral STN-DBS decreases on-going self-administration and escalation of drug taking for both cocaine and heroin (Rouaud et al., 2010; Wade et al., 2017; Pelloux et al., 2018) and decreases relapse to heroin seeking following protracted abstinence (Wade et al., 2017). Importantly, STN-DBS has opposite effects in the same investigation according to the reward; decreasing cocaine self-administration but increasing sucrose taking (Rouaud et al.,

2010). Some evidences suggest that the STN encodes reward value (Lardeux et al., 2009); and that sucrose and cocaine elicit activity of different subthalamic neuronal populations (Lardeux et al., 2013). Thus, it is hypothesized that different microcircuits within the STN separately drive motivation for "natural" reward or for addictive drugs. It is therefore possible that these microcircuits could be differentially impacted by STN-DBS, which may explain the more consistent effects of STN-DBS on decreasing motivation for drugs of abuse. Additional work is needed to understand how motivation for drugs abuse is encoded within the STN during different phases of the addiction cycle, which will have important implications for optimizing STN-DBS as a potential therapy for substance use disorders.

Summary

Overall, when applied chronically, bilaterally and with monopolar electrodes to model clinically-relevant conditions, STN-DBS consistently decreases reward seeking behavior. This STN-DBS-induced decrease in reward seeking is consistent across operant tasks but is most evident in satiated rats. Some attempts have been made to harness this feature, by proposing STN-DBS as a potential therapy for addiction (Rouaud et al., 2010; Pelloux and Baunez, 2013; Creed M. C., 2018).

However, this review highlights that STN-DBS has the capacity to decrease seeking for natural rewards as well as for drugs of abuse. A related consideration is that chronic application of STN-DBS leads to the emergence of learned-helplessness behaviors in shuttle-box or forced swim tasks (Temel et al., 2007; Tan et al., 2011; Creed et al., 2013). These results suggest that a general amotivational state may be induced by chronic STN-DBS in rodents, and emphasize the need for a mechanistic understanding of how STN-DBS induces its effects on reward-seeking in order to optimize the therapy for movement or substance-use disorders.

DETERMINING THE NEURAL MECHANISMS UNDERLYING THE EFFECTS OF STN-DBS

STN-DBS Is Not Equivalent to Functional Inactivation

One early hypothesis regarding the mechanism of action of DBS is that stimulation silences local cell bodies (Grill et al., 2004; McIntyre and Anderson, 2016), producing a functional lesion. In PD models and patients, lesioning the STN abolishes pathological hyperactivity and burst firing within the nucleus (Bergman et al., 1994; Hassani et al., 1996; Kreiss et al., 1997; Vila et al., 2000) that is correlated with motor symptoms (Bergman et al., 1990; Guridi et al., 1994, 1996; Wichmann et al., 1994; Henderson et al., 1999; Baron et al., 2002; Kühn et al., 2009; Baunez and Gubellini, 2010). Consistent with this silencing mechanism, STN-DBS inhibits firing of local STN neurons both *ex vivo* and *in vivo* (Benazzouz et al., 2000b; Tai et al., 2003; Filali et al., 2004; Welter et al., 2004; Meissner et al., 2005; Shi et al., 2006; Wade et al., 2017). Multiple mechanisms have been proposed to account for this inhibition, including voltage-dependent activation of potassium conductance resulting shunt inhibition (Shin et al., 2007; Florence et al., 2016), inactivation of sodium channels (Beurrier et al., 2001; Magarinos-Ascone et al., 2002) neuronal energy depletion (Lozano et al., 2002) or excitation of pallidal GABAergic terminals to the STN (Filali et al., 2004). While a functional lesion effect has been proposed to account for many of the motor effects of DBS, whether this functional silencing also accounts for adverse psychiatric effects of STN-DBS is less clear. To address this question, we analyzed pre-clinical studies that examined the effect of either electrolytic lesion or pharmacological inactivation of the STN on reward seeking. This inactivation was achieved with muscimol (an agonist of the GABAA receptor which fluxes chloride ions into the cell, thereby hyperpolarizing the membrane) or lidocaine (an antagonist of voltage-gated sodium channels, which are required for action potential firing).

Results of STN lesion studies were more heterogeneous than with DBS, with increases ($n = 6$), decreases ($n = 9$), or no change in reward seeking ($n = 6$) being reported (**Figures 3**, **6**). This heterogeneity cannot be completely explained by the type of reward used; STN-lesions had heterogeneous effects on responding for sucrose and food (Baunez and Robbins, 1997, 1999a; Baunez et al., 2002, 2005; Winstanley et al., 2005; Bezzina et al., 2008; Lardeux and Baunez, 2008; Uslaner et al., 2008; Winter et al., 2008), as well as for addictive drugs (Baunez et al., 2005; Lardeux and Baunez, 2008; Uslaner et al., 2008; Pelloux and Baunez, 2017; Montanari et al., 2018; Pelloux et al., 2018).

The heterogeneity could partially be explained by the behavioral paradigm used. STN lesion did not affect reward intake in free access (Lardeux and Baunez, 2008) or extinction paradigms (Winter et al., 2008) where the cost of responding is low. In impulsivity tasks, STN lesion consistently increased the rate of trial omissions and response latency (Baunez and Robbins, 1997, 1999a; Winstanley et al., 2005), which can be interpreted as decreased motivation (Robbins, 2002; Higgins and Silenieks, 2017) (**Figures 3**, **6**). However, when assayed using classical FR or PR operant tasks, STN lesion either increased (Baunez et al., 2002, 2005; Uslaner et al., 2008; Montanari et al., 2018) or did not change (Baunez et al., 2005; Bezzina et al., 2008; Winter et al., 2008) self-administration of food or sucrose. Decreased cocaine or ethanol taking is the predominantly reported effect of STN lesion (Baunez et al., 2005; Pelloux and Baunez, 2017; Pelloux et al., 2018). However, absence of effect (Bezzina et al., 2008) and even slightly increased drug seeking (Uslaner et al., 2008; Montanari et al., 2018) has also been reported following STN lesion.

Fewer studies have investigated pharmacological inactivation of the STN (**Figures 4**, **7**). Of the six total studies, one experiment reported an increase of food pellets earned during an operant task (Baunez et al., 2005), while three studies reported no effect on food or sucrose pellets (Klavir et al., 2009; Pratt et al., 2012) or cocaine administration (Kantak et al., 2013). Finally, two experiments showed decreased reward seeking with STN inactivation, measured as increased omissions in a food-rewarded 5-CSRTT (Baunez and Robbins, 1999b; Bentzley and Aston-Jones, 2017) or reduced cocaine self-administration (Bentzley and Aston-Jones, 2017). Overall, the mean effect size of STN lesion or inhibition is null, owing to the high variability

in experimental outcomes reflecting the heterogeneity of the experimental conditions in terms of task, reward, physiological and metabolic state. These results are in stark contrast to the consistent effects of STN-DBS across studies, and suggest that STN-DBS effects cannot be emulated with lesion or pharmacological inactivation.

STN-DBS Modulates Activity Throughout the Basal Ganglia

The difference in behavioral outcomes between STN-DBS and STN-lesion and inactivation is not entirely surprising. While the predominant effect of DBS on local tissue is depolarization block (Benazzouz et al., 1995; Beurrier et al., 2001; Tai et al., 2003), DBS can modulate distal brain regions through antidromic and orthodromic activation (Fedele and Raiteri, 1999; Li et al., 2007; Kang and Lowery, 2014). These effects are dissociable from effects on stimulated cell bodies, due to lower threshold of activation in fibers relative to cell bodies (Nowak and Bullier, 1998; Dostrovsky et al., 2000; McIntyre et al., 2004). Consequently, STN-DBS and STN-inactivation have distinct effects on activity throughout the basal ganglia (Creed et al., 2012), which is crucial, since coordinated activity in the basal ganglia network is necessary for driving reward seeking behavior (Sesack and Grace, 2010). Another consequence of network modulation by STN-DBS is that it induces striatal dopamine release (Benazzouz et al., 2000a; Bruet et al., 2001; Zhao et al., 2009; Shon et al., 2010; He et al., 2014), which is also not observed with STN lesion (Winter et al., 2008; Walker et al., 2009). Striatal dopamine release signals the difference between expected and experienced reward to drive reward learning, and invigorates action selection including reward seeking (For reviews, see Howe et al., 2013; Berke, 2018). By inappropriately elevating dopamine levels, STN-DBS could increase the noise in the dopamine-mediated reward-prediction error signal, or could induce long-term plasticity in the striatum which could also contribute to impairments in reward seeking behavior (Benazzouz et al., 2000a; Bruet et al., 2001; Gubellini et al., 2006; Carcenac et al., 2015).

STN-DBS Potentially Induces Ectopic Stimulation

An alternative hypothesis to explain the effects of STN-DBS on reward seeking is current spread outside the motor territory of the STN and potentially outside the STN itself. The STN can be divided into three functional territories (**Figure 8**): motor, associative and limbic, based on its afferent and efferent connections (Lambert et al., 2012; Hamani et al., 2017; Emmi et al., 2020). The caudal and dorsolateral part form the motor STN; it receives inputs from the primary motor cortex and GPe and projects to the GPi and the striatum (Benarroch, 2008). The associative STN lies in the ventral lateral aspect of the rostral nucleus, it receives input from the dorsolateral prefrontal cortex and innervates the SNr (Benarroch, 2008). Activity in the associative territory supports cognitive aspects of motor behavior, including impulsivity and attentional control (Frank, 2006; Alegre et al., 2013; Obeso et al., 2013). Finally, the rostromedial tip of the STN constitutes the limbic territory.

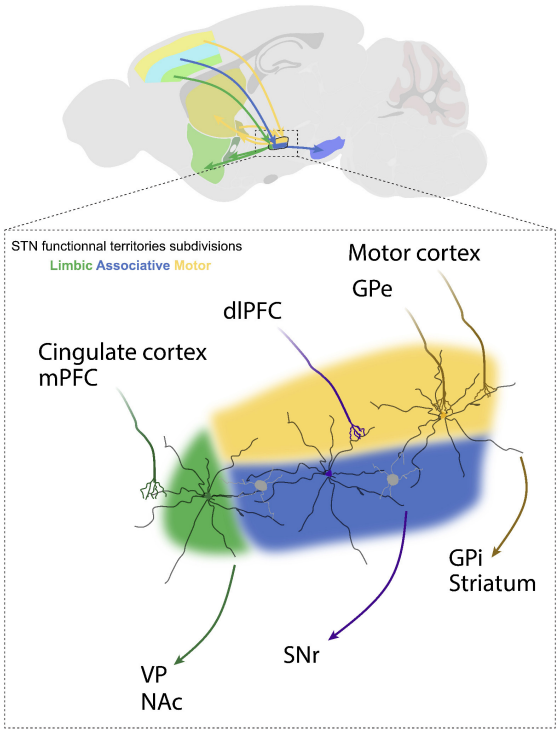


FIGURE 8 | Afferent and efferent connections of STN functional subdivisions. The subthalamic nucleus (STN) is subdivided into a dorsolateral motor territory, a ventromedial associative territory, and a medial limbic territory. Each functional territory receives input from different cortical regions or the external segment of the globus pallidus (GPe), and in turn projects to different downstream structures, including the internal segment of the globus pallidus (GPi), substantia nigra pars reticulata (SNr), nucleus accumbens (NAc) and ventral pallidum (VP). These input-output interactions provide for parallel control of motor, cognitive, and emotional functions. The STN is composed of interneurons and glutamatergic projection neurons whose dendrites may arborize over a distance of up to 500 μm. This is important, because individual STN neurons may physically span into adjacent territories and be effected by DBS applied to these adjacent subdivisions.

This division receives inputs from the medial prefrontal and anterior cingulate cortices and projects to the ventral pallidum and the nucleus accumbens (Cavdar et al., 2018; Emmi et al., 2020). Limbic functions of the STN involve reward encoding and sensory integration to drive appropriate emotional states (Drapier et al., 2008; Lardeux et al., 2009; Eitan et al., 2013; Zenon et al., 2016). Therefore, stimulation of the limbic and/or associative territories is one possible explanation for the effects of STN-DBS on reward-related behavior (Mallet et al., 2007; Zoon et al., 2019). While these subdivisions are established in human and non-human primate, the well-defined topographic segregation is less clear in rodents (Alkemade et al., 2015). In rats, STN neurons with cell bodies localized in a given territory can extend dendrites across the length of the nucleus (Afsharpour, 1985). Thus, the current spread from STN-DBS electrodes, even if well-placed within the motor territory of the STN could also modulate STN neurons in non-motor territories (**Figure 8**). Beyond this, the STN is embedded within the zona incerta, and sits adjacent to the internal capsule and pallidofugal system

(Hamani et al., 2004; Parent and Parent, 2004). These areas would be modulated by current spread outside the STN, and could be relevant for non-motor effects of STN-DBS. As mentioned above, in rodent studies, monopolar stimulation (which induces a larger current spread relative to bipolar stimulating electrodes) is associated with greater deficits in reward seeking (**Figure 5**). While the effects of monopolar vs. bipolar stimulation on induction of apathy or reward seeking behavior have not been directly compared in the clinic, there is evidence to suggest that high current amplitude and the use of monopolar electrodes are associated with worse psychiatric outcomes (Deli et al., 2011; Chopra et al., 2012). This is consistent with the hypothesis that reward-seeking deficits could be accounted for by current spread to limbic or associative territories of the STN, or to STN-adjacent nuclei and fiber tracts (Tan et al., 2013).

Even if it is current spread to STN subterritories and adjacent structures, and not modulation of the motor STN *per se* that drives reward-seeking deficits, this still does not explain the precise mechanisms underlying these deficits. For example, the reward-related effects could also be due to antidromic activation of afferent structures such as the prefrontal cortex (Irmen et al., 2020), or to modulation of downstream structures such as ventral pallidum or nucleus accumbens (Hahn et al., 2008; Cavdar et al., 2018). Likewise, STN-DBS modulates dopamine tone through polysynaptic outputs of the STN proper leading to stimulation of midbrain dopamine neurons, or through direct activation of dopamine fibers arising from current spread beyond the STN borders (Benazzouz et al., 2000a; Bruet et al., 2001; Tan et al., 2011, 2012; Carcenac et al., 2015). To disentangle these different possibilities, sophisticated approaches to circuit dissection, such as optogenetics, will be required.

DETERMINING THE NEURAL MECHANISMS UNDERLYING THE EFFECTS OF STN-DBS: FUTURE PROSPECTS WITH OPTOGENETICS

Optogenetics refers to a suite of engineered ion channels that are activated by light in a specific wavelength, and flux ions in response to activation. Channelrhodopsin (ChR2) is non-selective cation channel, that when exposed to blue light (∼473 nm), allows sodium and calcium to flow into the cell along their concentration gradients, thereby inducing depolarization and action potentials (Nagel et al., 2003). Conversely, the inhibitory halorhodopsin is a chloride pump that is activated upon stimulation with amber light (∼590 nm), increases the intracellular chloride concentration, thereby hyperpolarizing the cell and inhibiting the firing action potentials (Zhang et al., 2007). The location of the injected virus expressing the opsin and placement of the optic fiber for light delivery allows for spatial control of neural activation, while cell-type or projection-specific control of neural populations can be achieved by expressing viruses using intersectional genetic strategies. Finally, the pattern of light stimulation allows for tight temporal control of neural activity (Liewald et al., 2008). Optogenetics has yielded highly valuable insight to functional connectivity and activity within intact or pathological circuits, and could be leveraged to resolve outstanding questions regarding STN-DBS mechanisms.

Optogenetics was first leveraged to elucidate the role of STN in motor processes over 10 years ago, when a seminal study by Gradinaru et al. (2009) targeted the STN with excitatory and inhibitory optogenetic approaches. This investigation first tested the hypothesis that the motor effects of STN-DBS were due to local inhibition. However, optogenetically silencing cell bodies of the STN by activation of halorhodopsin was unable to rescue motor deficits in a 6-OHDA model of PD. Instead, using ChR2 to selectively activate terminal fields of cortical afferents into the STN rescued unilateral motor deficits in the PD model, suggesting a critical role of antidromic activation of "hyperdirect" cortico-STN pathway in the motor effects of DBS (Li et al., 2007; Fraix et al., 2008). Optogenetic activation of STN cell bodies also did not rescue motor deficits, arguing that STN-DBS does not exert its effects through driving action potentials in efferent STN fibers. However, these experiments stimulated at 130 Hz, while kinetics of the variants of ChR2 available at the time were not able to follow such high stimulation frequencies (Gunaydin et al., 2010). More recent studies with mutated opsins [i.e., Chronos, which is capable of following frequencies over 100 Hz (Saran et al., 2018)] have suggested that activation of cell bodies at frequencies relevant to DBS may indeed rescue motor deficits in a PD model (Yu et al., 2020). As with DBS, these investigations demonstrate a frequency-dependence of optogenetic effects, and have elucidated multiple neural mechanisms driving the therapeutic motor effects of STN-DBS in animal models.

The neural mechanisms underlying the potential adverse psychiatric effects of STN-DBS have received considerably less attention (Pan et al., 2014; Yoon et al., 2014, 2016; Tian et al., 2018). In the future, stimulating the STN with fast opsins such as Chronos or ChETA (Gunaydin et al., 2010) in the context of motivation and reward-learning paradigms will provide unique insights about the causality of the STN itself for the effects of STN-DBS on reward-related behavior. A single report has suggested that optogenetic stimulation of STN cell bodies at frequencies >100 Hz can reduce the breakpoint for sucrose, and that this effect is critically dependent on stimulation frequency and pulse width (Tiran-Cappello et al., 2018). However, this report did not distinguish between STN subdivisions, and as discussed above, current spread to the limbic and/or associative STN territories is one prevailing hypothesis for decreased reward seeking following STN-DBS. This hypothesis could be tested by selectively manipulating those functional subterritories. Because of the small size of the STN in rodents such a spatial resolution could be achieved by targeting pathway-specific output structures. For example, a recent study investigated PD-related pain, by injecting ChR2 within the STN and placing optic fibers in different STN output structures, such as substantia nigra reticulata or ventral pallidum to target the motor and limbic STN subterritories, respectively (Luan et al., 2020). Or, akin to the work by Gradinaru et al. (2009), antidromic activation of afferents can be modeled by expressing excitatory opsin in STN-projecting structures and placing fibers above the STN (Sanders and Jaeger, 2016; Sanders, 2017). The medial prefrontal and anterior cingulate cortices constitute major limbic inputs

to the STN; thus, manipulations of these pathways could yield important insight into the role of STN-DBS in the context of reward seeking.

The application of optogenetics has also shown promise for the development of novel deep brain stimulation protocols. In the clinic, and in all pre-clinical literature cited here, stimulation is applied at high frequencies (above 50 Hz, **Figure 5**). However, with optogenetics, specific cell types can be stimulated at precise physiological frequencies, and these physiological activity patterns can be used to drive plasticity within activated circuits. Proof of concept of this approach have been demonstrated for the motor symptoms of PD (Mastro et al., 2017) and for addiction (Pascoli et al., 2011, 2014; Creed et al., 2015; Creed M., 2018). In both of these applications, targeted stimulation of genetically-defined neural circuits was able to reverse behavioral impairments by selectively normalizing circuit function. While this strategy has not yet been demonstrated with STN stimulation, it is possible that selective activation of STN subdivisions at frequencies capable of driving long-term adaptations may induce persistent motor benefits without requiring continuous stimulation that carries with it the potential for adverse motivational effects.

In sum, sophisticated circuit dissection with optogenetics could be used to understand the role of the STN and its functional subterritories in coordinating adaptive motor and reward-related behaviors. With this insight, it may be possible to rationally stimulate the STN in order to achieve sustained motor benefits with lower risk of adverse effects on reward-related behavior. Conversely, it is possible that targeted manipulation of the associative or limbic territories of the STN could be leveraged to optimize or develop novel DBS paradigms to treat symptoms of addiction or obsessive compulsive disorder.

CONCLUSION

STN-DBS has become a mainstay therapy for movement disorders, and has been proposed to be applied earlier in course of PD, and potentially expanded to other indications, such as obsessive and compulsive disorders or addiction. Clinically, side effects such as depression, impulsivity and apathy have been reported with STN-DBS, which presents a major therapeutic limitation. To prevent side-effects, we must understand their neural underpinnings. In this respect, pre-clinical models have the advantage of being able to dissociate the effects of STN-DBS *per se* from underlying disease pathology or confounding effects of dopaminergic medications. Here, we focus our review on the specific dimensions of reward motivation, seeking and consumption, which can be clearly defined in operant tasks. When limiting our review to this specific scope, we find that STN-DBS consistently decreases reward motivation, seeking and consumption across a variety of behavioral models. Interestingly, studies that lesioned or inactivated the STN showed no consistent effect on reward-related behavior. Moreover, monopolar stimulation and bilateral stimulation, which both increase the volume of tissue activated, tend to be associated with more severe reward seeking deficits. Together, these observations suggest that reward seeking deficits may not be mediated by local effects within the STN *per se*, but by modulation of afferent or efferent structures of the limbic territory of the STN, or by current spread to adjacent fiber tracts. To definitively address these questions, optogenetic tools could be used to dissect the STN circuitry and establish links of causality between DBS effects on STN microcircuitry and reward seeking deficits, as has been done for the motor domain of STN-DBS.

A final consideration is that, we focused our review on only the dimension of reward motivation, seeking and consumption in tasks without conflict. Impulsivity, which is another commonly reported effect of STN-DBS is beyond the scope of the current review. However, extensive evidence has implicated the STN in arresting behavior, particularly under conditions of conflict to allow more time to accrue for an optimal decision to be made in rodents (Baunez and Robbins, 1997, 1999b) and patients (Bastin et al., 2014; Benis et al., 2016). This was recently elegantly demonstrated using optogenetic modulation of the STN; STN activation was able to abruptly interrupt reward consumption, while STN-inhibition prevented the ability of novel, salient stimuli to abort reward consumption (Fife et al., 2017). In real-world contexts, reward-related behavior often occurs under conditions of conflict, or with costs associated to reward seeking or consumption. This is particularly relevant in the context of impulse control disorders or addictions, in which reward seeking becomes maladaptive because of its association with adverse consequences. Therefore, future directions for understanding the effect of STN-DBS on reward-related behavior in a translational context will require the application of decision-making tasks that capture dimensions of risk-reward balance, as well as cognitive and motor impulsivity. Understanding the mechanisms underlying the potential adverse psychiatric effects of STN-DBS, and disentangling these from the substrates underlying its beneficial motor effects will be necessary for optimizing its therapeutic potential.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YV performed the literature review. YV and MC wrote the manuscript. Both authors contributed to the article and approved the submitted version.

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Cognitive Outcomes for Essential Tremor Patients Selected for Thalamic Deep Brain Stimulation Surgery Through Interdisciplinary Evaluations

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Objective: Deep brain stimulation (DBS) targeted to the ventral intermediate (VIM) nucleus of the thalamus is effective for motor symptoms in essential tremor (ET), but there is limited data on cognitive outcomes. We examined cognitive outcomes in a large cohort of ET DBS patients (pre-DBS and 1+ year after DBS).

Methods: In a retrospective analysis, we used repeated-measures ANOVA testing to examine whether the age of tremor onset, age at DBS surgery, hemisphere side implanted with lead, unilateral vs. bilateral implantations, and presence of surgical complications influenced the cognitive outcomes. Neuropsychological outcomes of interest were verbal memory, executive functioning, working memory, language functioning, visuospatial functioning, and general cognitive function.

Results: We identified 50 ET DBS patients; 29 (58%) males; the mean age of tremor onset was 35.84 (±21.50) years with a median age of 38 years. The mean age at DBS was 68.18 (±10.07) years. There were 37 unilateral 30 left, seven right, and 13 bilateral brain implantations. In the subgroup analysis, there was a significant interaction between assessment (pre vs. post) and age of tremor onset (<38 vs. >38 years); $F_{(1,30)} = 4.47$; $p = 0.043$ for working memory. The *post hoc* testing found improvements for younger onset ET. Similarly, there was a significant interaction between assessment (pre vs. post) and complications vs. no complications subgroups; $F_{(1,45)} = 4.34$; $p = 0.043$ for verbal memory with worsening scores seen for ET patients with complications. The remaining tests were not significant.

Conclusion: In this large cohort of ET patients with (>30% improvements), DBS was not accompanied by a significant decline in many cognitive domains. These outcomes were possibly related to the selection of patients with normal cognitive functioning before surgery, unilateral DBS implantations for the majority, and selection of patients with optimal response to DBS.

Keywords: neuropsychology, DBS (deep brain stimulation), essential tremor, working memory, cognitive

INTRODUCTION

Deep brain stimulation (DBS) directed to the ventral intermediate (VIM) nucleus region of the thalamus is an efficacious intervention for the motor symptoms in essential tremor (ET; Wilkes et al., 2020). ET is associated with cognitive impairments evident on tests of attention, verbal fluency, and response inhibition (Bermejo-Pareja and Puertas-Martin, 2012). DBS has been increasingly applied to treat many movement disorders, including Parkinson's disease, dystonia, and Tourette's syndrome. DBS settings used for the treatment of motor symptoms can be accompanied by a further decline in cognition, and a small decrement in cognitive function after DBS can have demonstrable effects on the quality of life (Tröster and Massano, 2015). While DBS in Parkinson's disease has shown a consistent decline in verbal fluency (Okun et al., 2009; Demeter et al., 2017; Mehanna et al., 2017), the data for ET is sparse and in some cases conflicting. In one study, VIM DBS impaired the word output dynamics during verbal fluency tasks (Ehlen et al., 2017), whereas Fields et al. (2003) observed that there was a significant improvement in general cognitive assessment, verbal memory and visuoperceptual functions following DBS. However, these studies did not evaluate the baseline factors that influenced cognitive performance following surgery. We retrospectively examined the neuropsychology outcomes in a relatively large cohort of ET patients presenting to our center for VIM DBS surgery. We sought to examine whether factors including the age of onset for ET, the hemisphere side implanted with the DBS lead, unilateral vs. bilateral implantation procedures, and the presence of surgical complications influenced cognitive performance following DBS surgery. We further examined whether disease duration, age at DBS surgery, tremor severity, and the electrical energy used for DBS programming predicted cognitive outcomes.

MATERIALS AND METHODS

The Institutional Review Board of the University of Florida that follows the ethical standards according to the Declaration of Helsinki approved our plans for retrospective analysis of data. We extracted outcomes for neuropsychology assessment performed at about 1 year after DBS electrode implantation to compare against the baseline. Participants in this study followed standard procedures followed at the University of Florida for DBS surgery. First, medication-refractory ET patients were evaluated by an interdisciplinary team of Neurology, Neurosurgery, Psychiatry, Neuropsychology, Physical, Occupational, and Speech therapy. Patients were deemed eligible for DBS if the tremor impacted the activities of daily living, and significant surgical or psychiatric comorbidity (moderate to severe depression), balance disorder, speech dysfunction, and dementia were not present. When patients had substantial bilateral tremors impacting the manual dexterity, staged bilateral DBS procedure was offered if safe from a cognitive and gait/balance perspective. These staged procedures included unilateral implantation followed 6 months later by the second sided implant. If patients opted for only one DBS lead, we targeted either their dominant hand or worse hand tremor.

For patients who underwent staged bilateral DBS, we extracted cognitive data that was recorded 1 year after the second electrode was implanted. DBS electrodes (model 3387, Medtronic, Minneapolis, MN, USA) were implanted upon identification of the target with imaging techniques involving CT and stereotactic magnetic resonance imaging (MRI) using a fusion process. Target identification was further refined with intraoperative microelectrode recording. Once the lead was implanted, intraoperative stimulation was performed to ensure there was adequate tremor control at lower voltages and side effects such as muscle contraction and speech deficits arising from internal capsule stimulation were only present at higher voltages. The fusion of postoperative helical CT scans with preoperative MRI scans was used to localize the entry zones of the DBS electrode in the cortex as well as the active contact in the brain. Following the lead implantation procedure, about 30 days later under general anesthesia, a pulse generator connected to an electrode lead was placed subcutaneously in the subclavicular region. DBS programming was initiated about 2–4 weeks after the pulse generator surgery. Lead contact and optimal stimulation parameters were determined based on empirical monthly programming sessions performed on an outpatient basis.

The following methods that are specifically relevant to our study were applied. We included ET DBS subjects who underwent neuropsychology assessments before DBS (pre-DBS) and 1–2 years after surgery (post-DBS). These assessments were performed while the patients continued tremor medications, and DBS was kept "on" for the post-surgery neuropsychology assessments. The exclusion criteria were: neurological disorder besides ET suboptimally placed DBS lead, defined by <30% improvement in tremor at 6 months after implantation of the lead, neuropsychology assessment before the surgery was performed at other institutions, and patients who reported a history of prior thalamotomy.

All participants consented to have their data stored in an IRB approved database at the Norman Fixel Institute for Neurological Diseases. In addition to neuropsychology measures, we extracted demographics, handedness, education status, disease-related measures, side of surgery for DBS implantation, and the stimulation parameters used for DBS programming in this cohort. Tremor severity was assessed with the Fahn-Tolosa-Marin Tremor Rating Scales (TRS; Fahn and Marin, 1993). Beck Depression Inventory-II and State-Trait Anxiety Inventory scale scores were also collected as measures of depression and long-standing anxiety (Beck and Brown, 1996; Spielberge, 2010). We also recorded the total electrical energy delivered (TEED) to the optimal lead contact as calculated with the standard formula at the time of follow-up neuropsychology assessment (post-DBS; Fakhar et al., 2013).

Cognitive measures consistent with our past experience involving neuropsychological assessments were grouped into six cognitive domains: verbal memory, executive functioning, working memory, language, visuospatial functioning, and global cognitive function (Sheline et al., 2006). The verbal memory

domain consisted of the delayed free recall scores of the Logical Memory Stories from the Wechsler Memory Scale-III and the delayed free recall of the Hopkins Verbal Learning Test-Revised. Tests of executive functioning included the Trails Making Test, part B, the color-word trial of the Stroop Color-Word Test (Golden version), and a letter fluency task (Controlled Oral Word Association Test; COWA). Working memory tests included the Forward Span and Backward Span trials of the Digit Span subtest from the Wechsler Adult Intelligence Scale-III. Language tests consisted of the Boston Naming Test (total items correctly named) and a semantic fluency test. The Judgment of Line Test and the Benton Facial Recognition Test were used as tests of visuospatial functioning. Finally, general cognitive functioning was assessed with the Dementia Rating Scale-II (DRS-II). Raw scores were normed on age and gender-based on test-specific manuals or previously published norms and converted to a Z-metric (Heaton, 2004). The individual test *z*-scores were averaged to form the domain composites (Jiménez-López et al., 2017).

Statistical Analyses

We used IBM SPSS Statistics version 26 to analyze the data. We examined whether cognitive outcomes after surgery in each domain of assessment differed according to the baseline characteristics including the age of tremor onset, age at DBS surgery, disease duration, baseline TRS score, unilateral vs. bilateral DBS, right DBS vs. left DBS (amongst the unilateral DBS patients); the amount of TEED and complications during and immediately after surgery. We used univariate regression to determine the effects of age at DBS surgery, disease duration, baseline tremor severity, and TEED and we employed repeated measures ANOVA to determine the main and interaction effects of assessment time (pre- vs. post-DBS) and assignment to subgroup (younger vs. older onset ET; unilateral vs. bilateral; right hemisphere vs. left hemisphere; complications vs. no complications). We set the significance to $p < 0.05$, and significant effects were further probed using Bonferroni-corrected pairwise comparisons. We employed a *t*-test for comparing motor and mood changes with DBS.

RESULTS

The baseline demographic and clinical characteristics of the ET patients included in the study are presented in **Table 1**. We included 50 ET patients (29 males, 21 females) who underwent DBS surgery at UF, had baseline neuropsychological assessments and presented for a follow-up 1 year after surgery. The mean ± SD for age at first DBS surgery was 68.18 (±10.1) years with a range of 34–83 years; the mean disease duration was 33.1 (±20.4) years with 10–60 years as the range; the mean duration of education was 14.2 (±3.5) years, and the mean tremor severity was 54.3 (± 14.7) before the surgery. There were 44 right-handed and six left-handed patients. There were 30 patients with left-brain implantation and seven patients with right-brain implantation and the goal was to control the arm tremor that was most bothersome to the patients. There were 13 patients with bilaterally staged surgeries used to target bilaterally significant symptoms. For these patients, the cognitive assessment performed 1 year after the second side implantation surgery was compared against the baseline assessment obtained before their first side was implanted. The anatomical coordinates for the active contacts relative to the mid-commissural points (MCP) were: 14.3 ± 1.6 (mm), lateral to midline; −4.3 ± 1.5 (mm) posterior to MCP; 2.1 ± 2.3 (mm) dorsal to intercommissural plane. The stimulation settings (mean ± SD and range) at 1-year follow-up after implantation were as follows: voltage (2.7 ± 0.7, 1.0–4.7), pulse width (102.3 ± 34.7, 60–210), and frequency (154.6 ± 23.7, 130–210). The values for two brain sides were averaged for individuals who had bilateral DBS surgeries. The TEED calculation was 123 μJ (±20.4) with the values for two brain sides averaged for bilateral DBS surgeries. There were no significant effects of age at surgery, duration of ET, baseline tremor severity, and TEED value calculations seen across all domains of cognitive outcomes. At baseline, on average the ET patients were intact on all cognitive domains with a relative weakness in language abilities (baseline mean = −0.43; SD = 0.9; **Figure 1**). We determined the cognitive functioning to be intact as the average performance of the cohort was generally closer to the mean normative values. Two patients could not complete the entire neuropsychology testing battery for the follow-up assessment because of time constraints and scheduling conflicts. Neuropsychologists performing the follow-up testing were blind to surgical complications, tremor ratings, and stimulation parameters.

Cognitive Changes Following DBS

The analyses of pre-post changes among the entire sample revealed that there were no significant longitudinal changes for all cognitive domains included in the study (*p*-values range from 0.133 to 0.891).

Cognitive Changes by Age at Tremor Onset

In our cohort, while the range for age of tremor onset was from five to 76 years of age, we found there was a bimodal distribution pattern with a median at 38 years. We, therefore, had two groups of patients; younger onset ET (<38 years) and older onset ET (>38 years).

For working memory, while the main effects were not significant, there was a significant interaction between time of assessment (pre vs. post) and age at onset ($F_{(1,47)} = 4.47$, $p = 0.043$). *Post hoc* testing revealed no significant change for the older onset ET, but the working memory improved for younger onset ET after DBS surgery. Except for working memory, there were no significant group differences in verbal memory, executive function, visuospatial function, language function, and general cognitive function.

Cognitive Changes by DBS Type (Unilateral vs. Bilateral Lead Implantation)

There were 30 patients with left-brain implantation, seven patients with right-brain implantation, and 13 patients with bilateral surgeries. We combined the left and right brain to compare unilateral against bilateral DBS

TABLE 1 | Clinical characteristics of essential tremor (ET) patients before deep brain stimulation (DBS) by DBS laterality.

	Left *n* = 30	**Right *n* = 7**	**Bilateral *n* = 13**		
	Mean (SD)	Mean (SD)	Mean (SD)	*F*, χ^2	*P*-value
Age (years)	68.9 (9.0)	72.3 (8.4)	64.2 (12.5)	1.72	0.19
Education (years)	13.8 (3.6)	15.0 (2.9)	14.5 (3.6)	0.43	0.66
Duration of tremor (years)	32.7 (22.4)	41.3 (24.6)	30.2 (12.5)	0.62	0.54
Tremor Rating Scale total (years)	58.4 (15.5)	45.9 (9.7)	47.7 (9.9)	3.77	0.03
Dementia Rating Scale Total (*z* score)	−0.40 (0.89)	0.33 (0.94)	0.08 (0.84)	2.62	0.08
Working Memory Composite (*z* score)	−0.26 (0.68)	0.22 (0.80)	−0.22 (1.16)	0.93	0.40
Executive Composite (*z* score)	0.69 (1.14)	0.55 (0.84)	0.37 (0.95)	0.41	0.67
Verbal Memory Composite (*z* score)	−0.28 (1.24)	0.10 (1.47)	−0.30 (1.57)	0.24	0.79
Language Composite (*z* score)	−0.40 (0.99)	−0.77 (0.99)	−0.36 (0.70)	0.50	0.61
Visuospatial Composite (*z* score)	−0.04 (0.71)	0.08 (0.95)	0.45 (0.77)	1.88	0.17

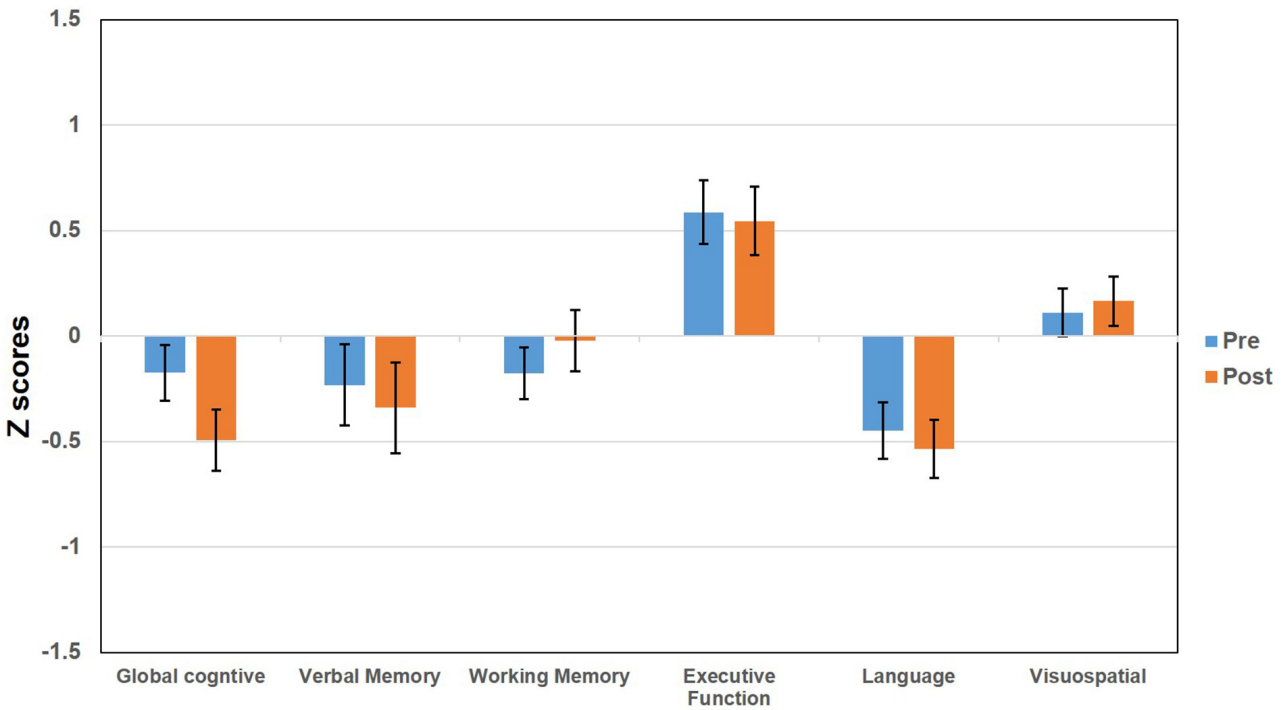

FIGURE 1 | Bar graphs represent the pre and post deep brain stimulation (DBS) score (*z* scores) for essential tremor (ET) patients tested across multiple domains including global cognitive function, verbal memory, working memory, executive functioning, language, and visuospatial functioning. The error bars represent the standard error of the mean.

surgeries. We found, there were significant main effects of unilateral vs. bilateral DBS for general cognitive function ($F_{(1,50)}$ = 2.71, p = 0.036) and visuospatial domain ($F_{(1,48)}$ = 2.36, p = 0.01) but the main effects of time of assessment were not significant and there was no interaction between the time of assessment and assignment to unilateral vs. bilateral DBS. *Post hoc* pairwise comparisons revealed that the bilateral group scored higher in general cognitive function and visuospatial function than did the unilateral group.

There were no significant effects for the language, working memory, and executive function; however for verbal memory, while the main effects were not significant, there was a significant interaction effect between assessment time (pre vs. post) and unilateral vs. bilateral group ($F_{(1,45)}$ = 5.20, p = 0.027). In the *post hoc* comparisons, bilateral DBS had higher verbal memory scores at post DBS evaluation compared to the unilateral; however, these comparisons only approached significance (p = 0.055).

Cognitive Changes by Left vs. Right DBS (Laterality)

Within the subset of patients who underwent unilateral DBS, there were 30 left DBS patients and seven right DBS patients. Except for DRS, there were no significant effects observed for verbal and working memory, executive function, language, and visuospatial function. For the DRS, there was a significant main effect for the time of assessment ($F_{(1,37)}$ = 4.61, p = 0.04) with a significant (p = 0.02) decline in score after surgery. However, there was no evidence for the effect of laterality or interaction.

Cognitive Changes by Complications vs. No Complications

Five patients presented to our center with complications during and immediately after surgery comprising of stroke (n = 2, MCA territory hemisphere involved was nondominant and contralateral to the side of implantation), intracerebral hemorrhage (n = 1, small hemorrhage at the site of VIM target, resolved within 4 weeks), infection (n = 1, resolved with antibiotics), and subdural hemorrhage (n = 1, same side as implantation, resolved within 2 weeks). These patients had a complete clinical/radiological recovery within weeks of the onset of complications. When the cognitive outcomes were assessed, there was a significant interaction effect between assessment time and complications vs. non-complications group ($F_{(1,45)} = 4.34$, $p = 0.043$) for the verbal memory. In the *post hoc* comparisons that were Bonferroni-corrected, we found the verbal memory score decreased significantly (1.2 ± 0.9; $p = 0.03$) after surgery for those patients who developed complications after surgery. The remaining cognitive domains did not change significantly.

Mood and Motor Changes After DBS Among ET Patients

Pre- and post-DBS changes in tremor severity (TRS), depression (BDI), and trait anxiety (STAI-T) were examined among ET patients. Results from repeated measure T-tests revealed a significant improvement in tremor severity following VIM DBS (the mean difference in TRS score = 26.4; $p < 0.001$). There were no significant changes in depression or trait anxiety after VIM DBS surgery even when subgroups analysis was performed (all $p > 0.1$).

DISCUSSION

Our ET DBS cohort that had intact neuropsychology assessment before the surgery and responded optimally to VIM stimulation at 6 months follow-up after surgery revealed no further cognitive decline at a 1-year follow-up. The neuropsychology assessment battery encompassed multiple cognitive domains, including global cognitive functions, executive functions, visuospatial functions, and language functions. Interestingly, working memory in patients who had tremor onset at a younger age improved after the surgery, but the verbal memory worsened in patients who developed complications during or immediately after the surgery albeit this was a small cohort.

Essential tremor is one of the most common movement disorders and is associated with cognitive impairments (even without DBS) that may be present in several domains (Bermejo-Pareja and Puertas-Martin, 2012). Tröster et al. (2002) found in a cohort of 101 ET patients, 25% scored below the standard cut-off for dementia in the Mattis Dementia Rating Scale. These patients revealed lower than average scores on measures of complex auditory and visual attention, response inhibition, executive functions, verbal fluency, and immediate recall of a word list. In another study, Duane and Vermilion (2002) found executive functioning and visual attention was impaired in 28% of patients. Deficits in attention and visuoperception were also confirmed in two further studies when extended psychometric batteries were applied (Higginson et al., 2008; Kim et al., 2009). These cognitive symptoms likely represent the disruption of the cerebellar-thalamocortical pathways projecting to the frontal lobe (Bermejo-Pareja and Puertas-Martin, 2012).

In patients with ET who receive DBS therapy, it would not be surprising to see the worsening of cognition given that trajectory of the lead when targeted to the VIM nucleus in the thalamus traverses the frontal lobe and in some patients may traverse the caudate nucleus (Heber et al., 2013), and thalamus has a definite role in cognitive functioning. However, there is limited data on the cognitive impact of VIM DBS in ET with many studies that do not support this theory (**Table 2**). In one of the earlier studies, Tröster et al. (1999) found statistically significant but clinically modest gains on tasks of visuoperceptual and constructional ability, visual attention, delayed word list recognition, and prose recall at 3 months follow-up after surgery. There was a slight worsening of lexical verbal fluency. The same group presented their findings of a longer follow-up of 12 months that showed improvements in on a cognitive screening measure and in aspects of verbal memory, fine visuomotor, and visuoperceptual functions (Fields et al., 2003). Heber et al. (2013) found the cognitive domains of memory, executive and intellectual functions and verbal fluency did not worsen even 6 years after DBS surgery. In another study of 17 ET DBS patients, verbal fluency, both semantic and phonemic was worse when VIM was stimulated at high-frequency (120–150 Hz) compared to low-frequency (10 Hz). However, there were no differences observed between high-frequency stimulation and when DBS was turned off (Pedrosa et al., 2014).

The overall nature of stable cognitive outcomes observed in our study and many other studies may be a selection bias since there was an inclusion of patients who did not have significant deficits before DBS surgery. The effects may therefore be possibly dependent on the baseline cognitive reserves. Fields et al. (2003) found the verbal fluency to decline significantly in 4/40 patients however these patients had diminished verbal fluency before they received the DBS, suggesting that a baseline deficit may have predisposed them to experience a further decline. The decline in ET DBS verbal fluency in the Fields study was similar to that seen in patients with Parkinson's disease. Finally, the word output was found to decrease after bilateral DBS implantation surgeries (Ehlen et al., 2016) whereas, in another study that mainly comprised of unilateral DBS surgeries, language processing was impaired at the level of syntax however the speed, rates of errors, word classes, and lexical diversity were largely unaffected (Ehlen et al., 2017).

Recently, DBS studies in ET have focused on stimulation of caudal zona incerta (ventral to the VIM region) stimulation beyond the VIM as the two structures are common to the tremor circuitry involved in ET. Fytagoridis et al. (2013) found while DBS adversely influenced the verbal fluency immediately after surgery when compared against a baseline, this effect dissipated at 1 year both on and off stimulation suggesting the deterioration likely reflected a micro-lesion effect. In a study involving caudal zona incerta stimulation, although the

TABLE 2 | Summary of ET DBS studies.

Reference	*N*	Target	Surgical details	Length of Follow-up	Outcomes and comments
Tröster et al. (1999)	40	VIM	Unilateral	3 months	Stable cognition
Woods et al. (2003)	49	VIM	Unilateral	3 months	Tremor onset >37 years and high pulse width settings associated with worsening cognition
Fields et al. (2003)	40	VIM	Unilateral	1 year	Stable cognition; verbal fluency declined in 10% patients, these patients had baseline deficits
Heber et al. (2013)	9	VIM	Unilateral	6 years	Stable cognition
Pedrosa et al. (2014)	17	VIM	Bilateral	4.6 years	Stable cognition; High frequency compared to low frequency stimulation worsened verbal fluency but no difference seen when compared to off stimulation
Ehlen et al. (2016)	13	VIM	12 unilateral, 1 bilateral	3.5 years	language change; more use of para tactical compared to syntactic structure
Ehlen et al. (2017)	13	VIM	Bilateral	2.8 years	Decrease in word output
Klein et al. (2017)	26	VIM	Bilateral	2 years	Stable cognition
Fytagoridis et al. (2013)	17	CZI	Unilateral	1 year	slight decline in semantic verbal fluency
Philipson et al. (2019)	26	CZI	20 Unilateral, 6 bilateral	2 year	decline in verbal fluency

VIM, ventral intermedius nucleus; CZI, caudal zona incerta.

overall cognitive functioning was stable, there was a slight but statistically significant decline in semantic fluency at a 1-year follow-up (Philipson et al., 2019).

A few studies have also shown improvement of cognitive functioning for ET with DBS besides the earlier work by Tröster et al. (1999). In one study, there was an improvement of simple reaction time when the DBS was turned on (Heber et al., 2013). In another study, there were improvements in attention and general cognitive functions (Klein et al., 2017). Our study found while the age at surgery had no significant influence, the working memory improved after DBS in ET patients who developed tremors at a younger age. The working memory performance was likely not influenced by other factors such as mood and anxiety levels that remained stable through the length of follow-up.

Although we did not find a group level change in verbal memory with DBS, we found persistently impaired verbal memory scores on the Hopkins Verbal learning test and Wechsler Memory Scale III scale in patients who developed surgical complications. The complication rate seen in our group was similar to that published by other large DBS studies (Rezai et al., 2006; Voges et al., 2006), and in our study, persistent cognitive impairment was observed despite a complete clinical recovery. Verbal memory was also observed to remain unaffected after DBS by other investigators at long-term follow-up (Heber et al., 2013). Fields et al. (2003) reported improvements in verbal memory assessed with the California Verbal Learning scale and the Wechsler Memory revised scale in addition to those seen in general cognitive functions, visuomotor, and visuoperceptual functions at 1-year follow-up. However, these studies did not examine the influence of surgical complications. It has long been known that the thalamus plays an important role in explicit memory (Thomas and Gash, 1985). Specifically, the ventral anterior (VA) nuclei of the thalamus have been involved in the encoding of information, and the medial dorsal (MD) nuclei of the thalamus play a role in the retrieval of information (Van der Werf et al., 2003). Future studies should examine the contribution of these nuclei to memory performance following VIM DBS.

We acknowledge our study did not include a DBS naïve ET control group; most patients in the cohort had unilateral DBS implantation, and the length of follow-up was limited. Additionally, the current study was unable to address the exact influence of medication dosages and the extent that cognitive changes could be a persistent lesion effect or a stimulation effect (i.e., examining memory performance among post-DBS patients who do not have the stimulator "turned on"). However, our study does report the cognitive outcomes from one of the largest cohorts to date and includes a comprehensive neuropsychological test battery encompassing all aspects of cognitive assessment. Our study included several relevant DBS related factors including the electrical energy delivered with stimulation.

In summary, the cognitive outcomes with VIM DBS in our cohort were stable likely related to the selection of patients with well-preserved cognitive reserves at baseline. There were isolated gains in working memory for younger onset ET and circumscribed decline in verbal memory for patients who developed surgical complications, but the underlying basis for these effects will be better understood if the future studies include imaging-based tractography to shed insights into the specific fiber pathways that are affected by stimulation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB University of Florida. The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JJ, TO, WH, ZJ, DB, SC, AR-Z, KF, MO, and AW fulfilled the authorship criteria by substantial contributions to the conception of the work, providing data for the work, revisiting it critically for important intellectual content, approving the final version, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Researcher Perspectives on Data Sharing in Deep Brain Stimulation

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The expansion of research on deep brain stimulation (DBS) and adaptive DBS (aDBS) raises important neuroethics and policy questions related to data sharing. However, there has been little empirical research on the perspectives of experts developing these technologies. We conducted semi-structured, open-ended interviews with aDBS researchers regarding their data sharing practices and their perspectives on ethical and policy issues related to sharing. Researchers expressed support for and a commitment to sharing, with most saying that they were either sharing their data or would share in the future and that doing so was important for advancing the field. However, those who are sharing reported a variety of sharing partners, suggesting heterogeneity in sharing practices and lack of the broad sharing that would reflect principles of open science. Researchers described several concerns and barriers related to sharing, including privacy and confidentiality, the usability of shared data by others, ownership and control of data (including potential commercialization), and limited resources for sharing. They also suggested potential solutions to these challenges, including additional safeguards to address privacy issues, standardization and transparency in analysis to address issues of data usability, professional norms and heightened cooperation to address issues of ownership and control, and streamlining of data transmission to address resource limitations. Researchers also offered a range of views on the sensitivity of neural activity data (NAD) and data related to mental health in the context of sharing. These findings are an important input to deliberations by researchers, policymakers, neuroethicists, and other stakeholders as they navigate ethics and policy questions related to aDBS research.

Keywords: neuroethics, data sharing, neuromodulation, deep brain stimulation, closed-loop, neural activity data, mental health data, commercialization

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INTRODUCTION

Deep brain stimulation (DBS) and adaptive DBS (aDBS) research are ongoing for a variety of movement disorders and psychiatric disorders. There is wide recognition of the importance of data sharing for the advancement of this research (Deeb et al., 2016; Rossi et al., 2016). While some disease-specific DBS registries exist, no central registry has yet emerged housing information on

therapeutic outcomes and technical specifications across different conditions for which DBS is used (Lozano et al., 2019). Addressing this disconnect requires understanding the potential benefits and risks of data sharing, barriers to sharing, and potential solutions to these barriers from the perspective of key stakeholders. Further, a sustainable approach to data sharing must take into consideration DBS researchers' conceptual understandings and ethical views about data sharing that are informed by their interactions with patient-participants and by knowledge of the evolving scientific details of DBS systems (Lázaro-Muñoz et al., 2019).

MATERIALS AND METHODS

We conducted semi-structured, open-ended interviews in which researcher-participants (n = 23) were asked about their perspectives on data sharing practices, ethics, and policy in aDBS research. Queried topics included whether, how, and where the researchers we interviewed are sharing their research data, their attitudes toward data sharing from aDBS research, whether they would be uncomfortable sharing any data related to their research, their potential concerns about other researchers having access to their data and how sharing could affect patents or trade secrets, and their attitudes about sharing particular data types [neural activity data (NAD) and data related to mental health]. We developed the interview guide based on a review of key issues and concerns identified in the bioethics and neuroethics literature on data sharing, during participant observation in a lab conducting aDBS research, and in discussions with other experts. While the interview guide included additional questions related to other important neuroethics issues (including what researchers view as the most pressing ethical issues in aDBS research, what issues they have personally encountered in their research, and questions about specific features of aDBS), we report researchers' views on those topics elsewhere (Muñoz et al., 2020) and report here specifically on results about researchers' attitudes and perspectives towards data sharing. We have used identification numbers in this piece that are different than those in Muñoz et al. (2020) to help ensure de-identification of researcher-participants.

We conducted 23 interviews, recruiting researcher-participants based on their involvement in aDBS trials. We employed purposeful sampling with a snowball strategy (Patton, 2002; Cresswell and Plano Clark, 2011; Palinkas et al., 2015), including the use of NIH RePORTER. We aimed for the representation of distinct researcher roles (e.g., trial coordinators, neurologists, neurosurgeons, mental health clinicians, and engineers) and target conditions [e.g., Parkinson's disease, dystonia, essential tremor, Tourette syndrome, obsessive-compulsive disorder (OCD), and depression]. One researcher was involved in conventional DBS and next-generation DBS research but not currently working on aDBS directly. We conducted interviews until reaching theme saturation, defined as the point at which new interviews no longer raised novel themes relative to previous interviews (Saunders et al., 2018). Baylor College of Medicine's Institutional Review Board approved our research.

Researchers were invited to participate by email. Interviews were conducted *via* phone and Zoom. These interviews were recorded and their transcripts were analyzed with the aid of MAXQDA 2018 qualitative data analysis software (Kuckartz, 2014). Four members of the research team (PZ, KK, LT, and RH) inductively developed a codebook to identify thematic patterns in researchers' responses to the questions outlined above, as well as in other parts of the interview where researchers discussed their concerns or attitudes about data sharing. Two members of the research team (PZ and CS) applied thematic content analysis (Boyatzis, 1998) to these interview segments to identify a list of more fine-grained themes. These fine-grained themes structure the analysis and frequencies presented below.

RESULTS

Participant characteristics are summarized in **Table 1**. The majority of participants were male, white, and had an advanced degree.

Data Sharing Practices and Importance

When asked whether they were sharing data outside their project team, 10 researchers (44%) said that they were sharing at least some data. Another nine (39%) said that they were not currently sharing but planned to in the future. However, among those currently sharing, there was variation in the type of sharing partner, with comparatively few making data available to registries or other research teams (**Table 2**).

Researchers viewed sharing data as important and provided several reasons why data from aDBS trials in particular should

TABLE 1 | Researcher demographics.

Gender (n = 23)	
Male	13 (57%)
Female	9 (39%)
Prefer not to answer	1 (4%)
Race/Ethnicity (n = 23)	
Asian	3 (13%)
White	18 (78%)
Prefer not to answer	2 (9%)
What degree(s) do you currently hold? (n = 23)	
M.D. or equivalent	8 (35%)
Ph.D. or equivalent (clinical)	3 (13%)
Ph.D. or equivalent (research)	4 (17%)
Both M.D. and Ph.D. or equivalent (clinical)	2 (9%)
Both M.D. and Ph.D. or equivalent (research)	1 (4%)
B.Eng. or M.Sc. Engineering	2 (9%)
B.A. or B.S.	3 (13%)
Project roles (n = 23)	
Clinical trial coordinator	4 (17%)
Engineer	5 (22%)
Mental health clinician	4 (17%)
Neurologist	5 (22%)
Neurosurgeon	5 (22%)
Research focus (n = 23)	
Movement disorders	6 (26%)
Psychiatric disorders	8 (35%)
Both	9 (39%)
Mean years of research experience (n = 23)	
Years of experience related to conventional DBS	8.7
Years of experience related to a DBS	4.5

TABLE 2 | Data sharing practices.

Is data currently being shared outside of the project team? (*n* = 23)	
Yes	10 (44%)
No, but planning to do so in the future	9 (39%)
Unsure of project's data-sharing practices	3 (13%)
Did not express a clear answer	1 (4%)
If data are being shared, with whom? (*n* = 10)	
Device manufacturers	4 (40%)
Registries	3 (30%)
Other research groups	1 (10%)
Government agency	1 (10%)
Did not specify	1 (10%)

be shared (**Table 3**). The most common justification for sharing data was to advance aDBS research. Data sharing was seen as particularly important in aDBS research because of the small number of participants in any given trial, making it difficult for individual studies and labs to draw definitive conclusions. As one researcher put it:

> *"[T]here aren't enough people that are implanting these devices for us to move forward because even expert centers are only going to implant a few devices per year every other year. How can you ever get enough data to pull it together? [...] So how are we going to collect enough cases to even move the field forward and learn from each other as to what targets, what approaches?" (R_12).*

Data sharing can also facilitate secondary analysis of one group's dataset by others. This was seen as important because groups conducting secondary analyses could take up and answer research questions not asked by the original data generators, both in the context of the same disorder and for other disorders. Thus, researchers felt that a collaborative approach to aDBS research is needed. A few researchers also said that data sharing would promote scientific honesty and transparency, which were seen as important commitments in biomedical research.

Concerns and Barriers Related to Data Sharing

Privacy and Confidentiality

Despite recognizing the importance of data sharing to advance research, researchers raised various concerns about sharing data. Nearly all (21, or 91%) researchers mentioned at least one concern, with the most commonly cited concern being participant privacy (mentioned by 15 researchers, or 65%). While most researchers felt that careful de-identification is sufficient to safeguard participant privacy, some suggested that aDBS research has features warranting additional caution (**Table 4**). The small number of participants in aDBS trials potentially complicates de-identification, and some types of data are more identifying by their very nature (e.g., videos of participants and highly individualized symptoms, such as specific obsessions or compulsions in OCD): "Currently, the number of patients who are enrolled, it's a small number. With a little bit of identifying information, it might not be that hard to figure who people are. So, I think we need to be thoughtful about making data available" (R_23). Also, a few researchers worried that despite the implementation of privacy protections, there was a potential threat of hacking or data breaches. These researchers were unsure what exactly malicious actors would attempt to do or stand to gain from aDBS data, but counseled caution nonetheless. One researcher explained, "I don't know what they would do with it, but who knows. The point is we don't want to find out" (R_19).

Data Usability

A majority of researchers (12, or 52%) also raised concerns about the usability of shared data due to difficulties in interpretation (**Table 5**). Researchers repeatedly stressed the necessity of including appropriate context and annotation in shared data due to the diversity of measures, collection procedures, and behavioral tasks performed by patients. Without this information, data may be difficult or even impossible to accurately interpret, especially neural data, limiting the usefulness of the data for other researchers. The difficulty of data interpretation could also potentially allow researchers to formally fulfill sharing obligations without the data being genuinely meaningful to others. As one researcher put it, "I've had some researchers [. . .] tell me if you want people to not be able to use your data, put it in a registry" (R_12).

Ownership and Control of Data

A majority of researchers also raised concerns about data sharing related to ownership or control of the data [mentioned by 12 researchers (52%)]. Some researchers felt that because their research is NIH-funded, the data ultimately belongs to society at large and thus ought to be shared. One researcher said, "The data is not really ours. It was paid for by the American taxpayer, so the idea that we can hoard it and not have other people be able to do ethical research on it doesn't make sense. It belongs to the public, fundamentally" (R_08). All 12 of these researchers were also concerned about control of the data from the perspective of

TABLE 3 | Importance of data sharing for adaptive deep brain stimulation (aDBS) research.

"**I think the world of aDBS is still small**, so the numbers that are being evaluated at individual sites are small, and **there's power in the data sharing** to be able to have a broader sense or a broader scope of the disease process to be able to understand it better and to understand the signals better" (R_21).

"I think it's going to take **large numbers of patients with large numbers of recordings** that are acquired in different settings to really try to get a handle on this [research] and to do it responsibly" (R_10).

"I think teams, as they're realizing that science is much more **collaborative and team-based**, I think that's [data sharing] become kind of the norm" (R_15).

"[T]here's **a lot of other ways that the data could be looked at**. There's **a lot of other questions** that we're not even looking at that perhaps could be answered for the same disorder or many others" (R_19).

"[T]he more open and accessible it is, **the more honest the science** is, too, and the more honest everybody is about it. There shouldn't be anybody feeling like they're having to hide anything. **It keeps everybody working in honest, compliant ways**, I think" (R_04).

TABLE 4 | Concerns about participant privacy.

"**We have to be a little careful as to what is identifying and not identifying information** but there aren't a large number of aDBS studies, For example, [. . .] we have video data of the person, let's say that's not made available or some extraction of that is that's not identifiable. There are so few people in these types of studies that with the data, if someone had all the data we collected in our study, they could probably figure out which person it was, or they might be able to" (R_22).
"[I would feel uncomfortable sharing] data that can be easily tagged to a patient's identity. That in particular, or certainly anything that has any **financial implication** or whatever. Anything that if lost, could lead to **identity theft**" (R_19).
"**I don't think videos of the face should ever be shared**. We have to, if we're sharing the face, a video of someone, I think **their face has to be blurred unless we have their specific consent** to not blur the face" (R_14).

TABLE 5 | Concerns about usability of shared data.

"[T]he data collected haven't all been collected the same way, **so they're not comparable**" (R_06).
"I think generally, **especially with neural data, it's really hard to interpret it if you weren't the one collecting it** and you don't know all the details. So I personally wouldn't want to use people's data that I don't know" (R_14).
"**[I]f data is not annotated very well, it is useless**. If you don't know exactly when it was collected, how it was collected, what are the various conditions? If those things are not carefully documented, the data's of limited utility" (R_08).
"I think that often the biggest challenge is that we can each capture whatever data we want to capture at our own sites for the work that we want to do, **but that may not be the same data or may not be captured the same way as other people or other sites**, so then it becomes hard to evaluate those in the same way" (R_21).
"I'm even worried about my students leaving things the way that's **interpretable** for future students" (R_13).

TABLE 6 | Concerns about commercialization of shared data

"**[A]nything that we can scientifically extract from the brain data, I don't ethically find that anything out of that should be patented** [. . .] Again, we're trying to make a scientific contribution. I don't think a discovery should be patented. A system that's invented could be, **but I really don't think scientific discovery should be patented**" (R_13).
"[T]here are other companies in this space who are making their business models off of a **cross-site or cross-disease, cross-study data mining** [. . .] using large, large, large datasets across lots of studies and sites to make insights and it's interesting that—it seems like **whatever NIH suggests should not be something that is related to a commercial interest**. But I don't think that's been made clear from the NIH. I don't know where they want us to put stuff, if they have a place" (R_22).
"**[A] lot of times we're the ones developing it, giving them the information they need to take it to the next step, we have the ideas** but we can't manufacture these devices to put in humans so then they end up doing it and claiming all the IP. **And they end up with the big payday**. So I think we do get screwed at some point on this" (R_12).
"[W]e're sort of put in a spot where if we want to do this research, we have to use these devices that are coming only from say these companies and so we're sort of in a bind where we have very little leverage to make any more beneficial arrangement with the company. **We have no leverage in the relationship essentially**" (R_22).

academic or professional fairness. Several worried about sharing data before publishing on it because they did not want to be "scooped" by researchers who did not themselves collect the data. This would be unfair, researchers thought, because of the time and intellectual effort expended designing studies and generating data. They also worried that this could limit career opportunities that depend on receiving appropriate credit for one's effort. As one researcher summed it up, "Fundamentally, the issue is about recognition for the work that was done to set up this trial and get the data" (R_22).

Researchers (7, or 30%) also raised related concerns about the commercialization of data, expressing concern about how for-profit interests in this data can impact data sharing and progress in the field (**Table 6**). As one researcher said:

> *"[C]ommercialization, in many ways, is the enemy of science. You know, because as soon as you start thinking about commercializing your findings, okay, you want to be careful what you share. And you may also want to be careful about who you include as a collaborator. And you may also want to be careful about the kinds of questions that you ask or measures that you make. I think all of these extra-scientific concerns come in, and they have the potential to really restrict advancement. This has been my experience, and I don't claim it's representative, but that these are things that I've seen" (R_23).*

Two questioned the fairness of device manufacturers' practices related to intellectual property resulting from aDBS research, maintaining that researchers often do not receive benefits commensurate with their vital role in generating these companies' profits. One of these also offered broader worries about the commercial use of aDBS data, remarking that some companies are engaging in "cross-study data mining" and suggested that NIH should avoid sharing requirements that promote commercial activities of this kind. Other researchers raised concerns about unintended commercial uses of shared data, including for predictive diagnostics, neuromarketing, and neuroenhancement.

Limited Resources for Data Sharing

Three researchers (13%) mentioned that resources needed for sharing can be a barrier, particularly time, effort, and funding. One suggested that effective data sharing would require a dedicated research assistant. Another described

the difficulty of securely transferring data on a large scale and explained that, in some of their work, physical storage devices were transported between study sites instead: "[R]ight now it can be quite cumbersome to encrypt and transmit large quantities of data. I think for some of the work that we're doing, actually physical drives have to be sent back and forth because it's too time-consuming to send electronically" (R_16).

Potential Solutions to Sharing Challenges

Researchers discussed various solutions to several of these issues (**Table 7**). Regarding concerns about privacy, researchers suggested safeguards such as facilitation of data encryption and additional protections or tiered access for sensitive data types such as data related to mental health. Researchers felt that data standardization (e.g., implementing a common set of measures and using a common interface or format for sharing data), as well as transparency in analysis techniques, could help manage concerns related to interpretation. In response to concerns about data ownership, control, and professional fairness, researchers suggested professional norms such as a holding period during which researchers would have a reasonable amount of time to publish on their data before sharing, as well as the clear linkage of datasets with the generating researchers and identification of ways to credit these researchers to provide professional incentives. Regarding intellectual property, one researcher suggested that investigators who contribute to improving aDBS devices could potentially share patents with device manufacturers. To address issues related to insufficient resources, it was suggested that streamlining secure transmission of data would ease the burden of sharing. Finally, some described general governance solutions related to the question of sharing practices and policy, mainly looking to NIH for guidance.

Sensitivity of Neural Activity Data (NAD)

Several researchers (9, or 39%) commented that NAD is **less sensitive** than other data that are typically shared, such as genetic data. Among the reasons given were: (1) NAD is not inherently identifying (at least at present); (2) NAD does not support inferences about current or future disease state; (3) there is a general lack of knowledge about what information can be gleaned from NAD; (4) it presents a lower risk of stigma and discrimination; and (5) NAD is less informative and definitive than genetic data due to more noise and weaker correlations with phenotypes.

Other researchers (5, or 22%) felt that NAD and genetic data are **equally sensitive** in the context of sharing. These researchers believe that NAD might one day be identifying and could potentially be used in harmful ways, for example, "in a legal case" or "by a health insurance company" (R_04), or for "fingerprinting or identifying somebody" (R_19). One researcher said that NAD could someday affect a person's life prospects in various areas in a way similar to "HIV status or gene mutation data" (R_08).

Three researchers (13%) felt that NAD is, in fact, **more sensitive** than genetic data because the moment-to-moment mental states it potentially allows to be inferred change over time in a way that one's genetic makeup does not, and that the gap between genotype and phenotype present in the genetics context is absent in the NAD context. One researcher put it this way: "Your neurological data, it is happening. That is the full expression of what's going in some part of your body. It may necessarily be more personal because of that" (R_05).

The remaining researchers took more ambivalent positions, with one saying that NAD is **equally or more sensitive** or at least will be once it is better understood, one saying that NAD **might be more sensitive** but ultimately being unsure, three saying it was **unclear** whether one is more sensitive than the other, and one not expressing a clear view on the topic.

Several researchers provided specific comparisons and analogies to illustrate their views on the sensitivity of NAD in the context of sharing (**Table 8**).

Sensitivity of Mental Health Data

Researchers also offered various views on whether data related to mental health is more sensitive and should be treated differently than other data types in the context of data sharing (**Table 9**). Several (9, or 39%) maintained that it should be treated differently because data sharing can exacerbate mental health stigma and the risk of discrimination and mental health symptom states are potentially more personal, or least may be *perceived* as revealing more about a person, than

TABLE 7 | Potential solutions to various types of concerns.

Privacy

"I think the major consideration is how to be able to do that in a way that maintains privacy, yeah, just maintaining the privacy and **keeping it within an approved set of investigators, perhaps somehow some approval process or some application process** [in order to access data]" (R_21).

Interpretation

"I think as repositories get set up, knowing the conditions of the collections and things, and **standardizing that so you know what you're getting** so that you don't get an overinterpretation of data is going to be super important" (R_12).

Ownership

"I'd like to see a little bit of **a holding period, just for the people who collected it to be able to look at it**. Those are the people who know it best. But beyond some reasonable holding period for those investigators, then it should be shared" (R_08).

Commercialization

"If we maybe see an improvement on something, we could **discuss that with [the device manufacturer], and it could be patented, co-patented**, or something like that" (R_13).

Lack of Resources

"I think **developing or facilitating the secure transfer of information**" (R_16).

TABLE 8 | Comparisons and analogies regarding sensitivity of neural activity data (NAD).

In favor of special sensitivity
"**15 years from now it could be identical to having patients' intimate medical records revealed** [. . .] but today we don't have the understanding to know what these fingerprints mean" (R_16).
"So, I mean, it could be another way of kind of **fingerprinting or identifying somebody** like genetic data, so I think we need to be careful with that" (R_19).
"I think the brain signals should be treated somewhat differently, because they will, if not now then the future, they will be in **this sensitive category like HIV status or gene mutation data** that can affect, in principle, things like someone's insurability, their job hiring, their compatibility for a partner in life. It potentially will have that same level of sensitivity" (R_08).
"I guess if somebody were to get ahold of that data and use it in some way to discriminate against that patient or exclude them for any reason based on that data, **much like HIV information on patients is protected** because it used to be used against patients by their employers. We certainly wouldn't want that to happen" (R_04).
Against special sensitivity
"**It's not like DNA. It's not like an iris scan**. I think if we find a useful biomarker, it's gonna be relatively universal. That's what you hope for, right? You're not looking for something, a neural recording that just identifies that individual. You're gonna want **something that is common across individuals** for it to be useful" (R_06).
"Again, from a neurophysiology standpoint, **I'm not aware of any fingerprint type situation that could identify a patient**, so I think the concerns are maybe a little less. I think it's when it gets to other features of that data in terms of either outcomes or symptoms or things of that nature where some of those concerns would come in" (R_21).
"Again, this information in my opinion and I'm not a neurophysiologist, but **I think is very different than for example, DNA, which is much more personal, and potentially identifiable** for a specific individual. Brain recordings are not" (R_17).

other types of data. However, a majority of researchers (12, or 52%) maintained that mental health data should not be treated differently than other data types because data sharing procedures that ensure successful de-identification are not likely to put patient privacy in jeopardy, and because sharing information about mental health conditions is not fundamentally different than sharing information about neurological or other physical illness. These researchers referred to distinctions between mental health and other kinds of conditions as "artificial" (R_19) or "arbitrary" (R_02, R_19) and argued against making such distinctions on scientific and conceptual grounds. One mentioned that drawing a distinction could perpetuate mental health stigma, saying, "I think that we've got to get rid of the stigma, and as long as we keep treating it differently, we're not going to get rid of the stigma that exists [. . .] You don't do it with other illnesses because it's not beneficial, and I also think it creates more stigma in our community, you know?" (R_11). Two researchers did not express a clear view on whether mental health data should be treated differently.

There was some, but not complete, overlap between those who said mental health data is especially sensitive and those who said that NAD is especially sensitive. Of those who said that at least one of the two data-types is sensitive ($n = 13$), five said this about both data-types, four said this about mental health data but not about NAD, and four said this about NAD but not about mental health data.

DISCUSSION

We conducted interviews with aDBS researchers to learn about their data sharing practices and views on barriers and concerns related to sharing aDBS research data. Most researchers were committed to sharing but were not currently sharing as widely as their expressed commitment might suggest. Researchers expressed several concerns related to data sharing, including concerns about the privacy and confidentiality of participants, usability of shared data by others, ownership and control of data, and limited resources for data sharing, as well as potential solutions to these challenges. We also found that researchers were relatively split on the issues of whether NAD is especially sensitive in the context of sharing and whether data related to mental health should be treated differently from other data types.

These results overlap with themes also identified in work on the attitudes of brain-computer interface (BCI) researchers (Naufel and Klein, 2020). While their work focused on ownership and other rights over neural data, especially on the part of patients, they identified researcher concerns about the following issues: interpretability or meaningfulness of neural data, permitting patients to donate or sell neural data to corporations or other entities, being "scooped," intellectual property, and resources required to share neural data with patients. They also asked BCI researchers whether raw neural data counts as *medical* data, such that it "contains within it potentially sensitive health information," with a majority saying that it does (Naufel and Klein, 2020, p. 6). Whereas Naufel and Klein (2020) focus on the sharing of data with patients and patients' rights over such data, we asked researchers about data sharing more generally and received responses primarily concerning sharing among expert stakeholders (such as other investigators and device manufacturers). They also focus on the sharing of neural data in particular, while our project both asked about aDBS-related data in general and posed specific questions about NAD and mental health data.

Researchers expressed a commitment to sharing, saying that they either already were sharing some data or planned to in the future. However, there was diversity in the extent of sharing, both in terms of data types shared and how widely data was shared. This suggests that more detailed policy guidance may be needed as the field matures. Researchers are likely to support the overarching aims of such policy guidance because they believed that sharing is beneficial and even necessary to advancing

TABLE 9 | Whether mental health data should be treated differently than other types of shared data.

Mental health data should be treated differently
"I think patients' psychiatric illness and mental health data, **it's a topic very similar to things like HIV** or other illnesses where patients' ability to have fulfilling and productive lives would be affected by the release of that information" (R_16).
"[S]omething like EKG data is not as consequential to the patient if it is discovered, whereas mental health, there is **a lot of assumptions that are made** about how a person thinks, and how they act, and what they do. There are a lot more consequences with that data getting released" (R_04).
"A medical diagnosis, such as a depression, or anxiety, or a bipolar disorder, things like that. I think there is some extra sensitivity needed there just because of the **social stigma** of having some of those conditions" (R_01).
"Yes, because of the stigma involved and—yeah, mostly because of stigma, and you worry about how it will **impact relationships and work opportunities**" (R_06).
"I struggle with this. On the one hand, it's like, 'Well, no. It's all health. Let's stop dividing it.' But nonetheless, **there is still stigma out there**. There is patient provider. So, I think because of that, we want to consider them essentially separate. One day I hope that answer is, 'No, it's all health"' (R_15).
Mental health data data should not be treated differently
"I don't think so. I mean, we usually do, but **I think it's a bit artificial**. I mean, mental health diagnoses in my mind are the same as neurological diagnoses and somehow don't fall in the same category as, I don't know, further protected data" (R_19).
"**There are people who separate the mind and the body in ways that I feel are arbitrary**. So if you have a mental health illness, it's really, in my view, a physical illness. It's a problem with your body, it's the part of your body that's located in the brain" (R_02).
"I would hope that we would be thinking about overall you know, human health now and not separating out mental health from the rest. But others would probably find that to be more sensitive than me, I don't know. **I try not to think about it in any different way than I would heart disease**" (R_09).
"I mean, I think psychiatric and neurological conditions are just different names for the problems in different systems of the same organs. So, **it seems arbitrary to me** to call something a mental health problem and something else a neurological problem and then say that one is more protected or sensitive than the other" (R_19).
"I think we need to treat our brain as we treat **every other organ of our body**" (R_22).

scientific discovery related to aDBS due to features of the field such as small sample sizes in most studies. They expressed support in particular for what is plausibly categorized as a *collaborative* or *team science* approach (Little et al., 2017). Such approaches have been employed successfully in the genomics context by the Psychiatric Genomics Consortium (Sullivan et al., 2018) and in neuroimaging by the SchizConnect initiative (Ambite et al., 2015), as well as the adoption of the Brain Imaging Data Structure (BIDS) standard (Gorgolewski et al., 2016) which is now being applied to intracranial electroencephalography data (Holdgraf et al., 2019). The genomics and neuroimaging contexts are therefore likely to offer important lessons that will ideally be transferable to the context of next-generation DBS research.

While researchers were generally optimistic about and supportive of data sharing as a way to promote advancement in the field, they also suggested that the full benefits of data sharing are not being realized. Technical barriers to maximally useful sharing include disparate measures and data formats, as well as lack of annotation that sufficiently contextualizes data for use by others. While these are important challenges that will need to be overcome, they are not different in kind than similar challenges that have been identified and adequately addressed in other research contexts. In genomics research, for example, there are lessons to be drawn from the eMERGE Consortium, such as the use of a coordination center to manage data flow (McGuire et al., 2011). In neuroimaging research, sophisticated annotation tools are available to help promote standardization (Poline et al., 2012). The FAIR principles (**f**indability, **a**ccessibility, **i**nteroperability, and **r**eusability) also offer general but useful guidance for the management and stewardship of scientific data (Wilkinson et al., 2016; FORCE 11, 2020). Lessons from other contexts will of course need to be tailored in such a way as to be responsive to specific features of the aDBS context. Features such as the small number of current research participants, reliance on video data that may include participants' faces (Girard et al., 2015; Provenza et al., 2019), and the sometimes highly specific nature of symptoms in disorders such as OCD and Tourette syndrome present additional privacy challenges that may make de-identification and aggregation more difficult. Nonetheless, researchers should share data to maximize social benefit and minimize risk to individual participants, and the small number of current research participants arguably strengthens this obligation.

Researcher-participants also raised important questions about what scientific investigators are properly entitled to for having generated these datasets, on the one hand, and what society is properly entitled to for having provided resources such as funding, on the other. These two interests have long been widely recognized as important ethical values in science. The U.N. Declaration of Human Rights affirms rights both "to share in scientific advancement and its benefits" and "to the protection of the moral and material interests resulting from any scientific... production of which [a person] is the author" (United Nations General Assembly, 1948). Researchers' perceptions regarding academic and professional fairness, as well as obligations to the public, are similar to those historically expressed in the field of genomics during the Human Genome Project. These concerns were met with solutions similar to what our researcher-participants proposed, notably with the implementation of the Fort Lauderdale Agreement and acceptance of the Bermuda Principles, which provided both rapid access to data and publication priority for researchers who generated a given dataset (Kaye et al., 2009; Contreras, 2011). The Bermuda Principles allowed for the achievement

of rapid sharing in the spirit of open science while remaining flexible and responsive to the needs of the scientific community (Jones et al., 2018).

The NIH Genomic Data Sharing Policy includes similar practices related to publication priority and seeks to ensure appropriate credit for data generators (National Institutes of Health, 2014). Policymakers in the aDBS research context would do well to attempt to replicate this model, which shows that the interests of society and the interests of scientific investigators may not in fact be in tension when it comes to data sharing.

aDBS research relies on device manufacturers to produce the systems used in these trials. Some researchers raised concerns about the involvement of commercial interests in aDBS research, especially when it leads to what they considered unacceptable uses of data, such as for neuromarketing, cosmetic neuromodulation, and commercially available predictive diagnostics. Strong governance structures are needed to address these concerns and should be informed by frameworks applied in other contexts—for example, Contreras's (2011) application of the *institutional analysis and development framework* (Ostrom, 1990; Ostrom and Hess, 2006; Madison et al., 2010) to genomic data sharing and Deverka et al.'s (2017) Ostrom-inspired principles for the governance of medical information commons in general.

Likewise, concerns raised about patenting invented systems but not scientific discoveries themselves are reminiscent of controversies involving Myriad Genetics, Inc.'s attempted patenting of BRCA1 and BRCA2 genes (see also Naufel and Klein, 2020, p. 7). In *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Supreme Court of the United States held that scientific work can be patented only when it "creates something new," and that "products of nature" therefore cannot be patented (Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 2013). This decision plainly allows an aDBS device to be patented but might seem to preclude the patenting of brain biomarkers of symptom states discovered in the course of aDBS research. However, strikingly broad method patents have already been obtained for applications of DBS and other methods of neuromodulation, and this overbreadth may in some respects approximate patents on the brain regions themselves (Roskams-Edris et al., 2017). Neuroethics debate on whether such patents are appropriate has already begun (Illes et al., 2019; Kuersten and Wexler, 2019). As a further complication, one might also wonder how courts in the U.S. and elsewhere would respond to arguments that a particular brain biomarker emerges only in response to the *interaction* of a patient's natural neurophysiological processes with an aDBS device.

In the aDBS context, research depends on a small number of private corporations for devices without which trials could not be conducted. This dependence is potentially problematic, including in the context of data sharing. One researcher directed us to the BRAIN Initiative's Public-Private Partnership Collaborative Research Agreement template, which includes the following clause regarding what should be included in quarterly progress reports made by BRAIN investigators to device manufacturers:

> *These reports will include all relevant PROJECT DATA. PROJECT DATA refers to all written and otherwise recorded information created or collected in service of the PROJECT PLAN. PROJECT DATA shall include, but are not limited to, raw and analyzed data signals (e.g., electrophysiological recordings) as well as any annotations and interpretations of the data necessary for appropriate analyses and interpretation of such PROJECT DATA (BRAIN Initiative, 2015, 1.6.ii).*

Because this is merely a template, it does not necessarily reflect the actual agreements entered into between investigators and device manufacturers. Nonetheless, it is instructive as an expression of a baseline or default norm for BRAIN's Public-Private partnerships. Data sharing of the kind described may provide device manufacturers with the kind of broad-scope access to data that members of the academic research community currently *lack* concerning one another's work, particularly if companies are receiving project data from multiple trials. Device manufacturers or other private companies involved in this research may thereby be benefitting from data sharing without similar benefits being made available to the broader community *via* sharing among academic researchers. If so, such a state of play may involve an unfair distribution of benefits and burdens, potentially favoring corporate interests at the expense of research advancement by impeding publicly-funded research from fulfilling an obligation to share benefits with society as a whole. As one possible solution to this sort of issue, stakeholders from the scientific community might consider being more vocal about the kinds of arrangements that they view as ethically preferable to the current state of play, potentially including data sharing by device manufacturers themselves.

Some researchers also believed that particular types of aDBS data raise distinct concerns, ones on which the data sharing experience in other fields does not yield clear lessons. The capacity to record as well as stimulate sets aDBS devices apart even from conventional DBS devices, which are themselves unlike most other implanted devices due to their presence in the brain. Recording capabilities allow for the collection of NAD as a key component of the closed-loop systems these researchers aim to develop. In light of the centrality of various cognitive capacities for prominent theories of personhood (Singer, 1993; Korsgaard, 1996; McMahan, 2002) and recent discussions about how the idea of the brain as the basis of the self applies to issues in DBS in particular (Byram and Reiner, 2014; Mecacci and Haselager, 2014; Racine et al., 2017), a natural question to ask about NAD is whether it may be especially sensitive on this or some other basis. This issue forms part of the broader question of *neuro-exceptionalism*: whether and to what extent neurotechnologies raise special ethical, legal, social, and policy issues (Illes and Racine, 2005; Schick, 2005; Alpert, 2007; Tovino, 2007; Wachbroit, 2008). Scholars have engaged in analogous discussions regarding HIV exceptionalism (Bayer, 1991; Ross, 2001; April, 2010; O'Hara,

2011) and genetic exceptionalism (Rothstein, 2010; Garrison et al., 2019; Martani et al., 2019). Recent commentators have stressed that some types of NAD, such as neural activation patterns related to attention, could be especially sensitive due to the wealth of information they potentially represent for hackers, corporations, and governments (Yuste et al., 2017, p. 161). While advances in data security may mitigate some of these concerns, emerging providers of such security are themselves for-profit corporations, potentially heightening concerns about data commodification (Kellmeyer, 2018, p. 6–7).

The researchers we interviewed were split on the sensitivity of this data, offering apparently competing views about the sensitivity of NAD, including whether it allows for the unique identification of a participant. As we describe in our results, nine researchers believed that NAD was equally or more sensitive than genetic data, nine believed it was less sensitive, four were unsure, and one did not express a view. Naufel and Klein (2020, p. 5–6) found that BCI researchers were also split on the related issue of whether neural data is medical data (thereby at least potentially containing sensitive information about an individual's health). They report 58% of their participants responding that it is, 22% disagreeing, and 20% holding a "neutral feeling" ($n = 122$).

At least for our participants, however, it is also possible that there is more consensus here than it would initially seem. Some of our respondents who took a neuroexceptionalist view did so because of the anticipated *future*, rather than present, informativeness of data, and some of our respondents who took an anti-neuroexceptionalist view did so because of the *present* lack of informativeness of data. Our results may therefore be partially explained by ostensibly neuroexceptionalist researchers focusing on problematic future uses of data and ostensibly anti-neuroexceptionalist researchers focusing on lack of problematic present uses. On the other hand, other of our respondents appeared to hold in-principle views that do not depend directly on how informative NAD is or even could be. Discerning the true degree of consensus among researchers on data sensitivity concerning current and potential future uses will require further investigation. Such work is pressing, as this issue will only grow in importance with the expansion of aDBS research in particular and research involving neural recording in general, as well as with technological advancements allowing for more efficient integration of data (Hendriks et al., 2019).

Data related to mental health emerged as another potentially sensitive data type. Researchers' views on whether mental health data should be treated differently in the context of data sharing resembled, in one important respect, scholarly debates about *mental health exceptionalism* (Tovino, 2012; Terry, 2015; Gelpi, 2017). Researchers who said that mental health data should be treated differently overwhelmingly believed that this data is especially sensitive due to stigma and potential discrimination. These researchers described harms of stigma such as the overall negative impact on stigmatized individuals' lives, unjustified assumptions by others, and potential threats to relationships and work opportunities. Treating mental health data the same as other data types risks overlooking how it may be perceived differently and should thus warrant greater privacy protections to avoid stigma or discrimination. Additional protections and tiered access for mental health data, suggested by some researchers, are broadly in line with recommendations by Dyke et al. (2016).

While a majority of researchers said that mental health data should *not* be treated differently in the context of sharing, it is notable that only one of these researchers explicitly mentioned stigma as a reason for this view. In this respect, our findings cut against recent discussions of mental health exceptionalism in which considerations of stigma often figure in arguments *against* treating mental health differently in addition to arguments *for* doing so. As expressed by one researcher, treating mental health data differently may perpetuate stigma by implying that mental health data is substantively or connotatively different than physical data, revealing a different *type* of illness with potentially worse stigmatization. Further research is necessary to determine whether researchers understood these considerations as implicitly invoking considerations of stigma, or whether they view them as not essentially depending on such considerations. For example, it is possible that researchers see these considerations as being philosophically prior to issues of stigma (believing, e.g., that mental health stigma is unjustified partly *because* there is no scientific or conceptual basis for singling out mental health), and took these considerations as sufficient on their own as a rationale for why mental health data should not be treated differently.

LIMITATIONS

These in-depth interviews were intended to identify the range of responses that researchers would offer when discussing ethical and policy aspects of data sharing. This approach is limited in the sense that it cannot and is not intended to provide generalizable results. In line with established principles of qualitative research, we conducted interviews until reaching theme saturation, understood as a point at which participant-researchers were no longer raising novel themes relative to previous interviewees (Saunders et al., 2018). Doing so allowed us to identify ethical and policy issues for further analysis and gain an understanding of the conceptual and argumentative resources that scientific experts deploy in considering and responding to these issues (Lázaro-Muñoz et al., 2019). Another potential limitation is that our snowball sampling strategy began with a convenience sample and relied on researchers being willing to discuss these issues with us. This recruitment strategy may therefore have limited the range of perspectives encountered. However, we mitigated this by employing NIH RePORTER to identify additional BRAIN-funded researchers conducting work related to aDBS.

CONCLUSION

Our researcher-participants offered a rich set of perspectives that are well-positioned to inform ethics and policy analysis

of issues related to data sharing in the aDBS research context. These perspectives are crucial for ensuring that normative neuroethics analysis and resultant policy guidance is grounded in an understanding of existing practices and expert knowledge. Some concerns and barriers, particularly those related to privacy, technical issues with the usability of shared data by others, and academic and professional fairness, have parallels in other research contexts. Policymakers and aDBS data generators should consider strategies that have been successful in other research contexts such as the Bermuda Principles and Psychiatric Genomics Consortium's approach to authorship and appropriate credit, as well as approaches to data standardization in neuroimaging, tailoring these as necessary to the aDBS context. However, researchers also raised distinct issues that existing ethics and policy frameworks useful for other research contexts may require amendment or extension to fully address. One of these is the commercialization of data derived from and utilized by aDBS and other devices utilizing neural recordings. Further empirical neuroethics research is needed to identify the full landscape of commercial involvement in aDBS and other invasive neuromodulation research and assess the ethical and policy implications of such involvement in a way that takes account of the perspectives of all stakeholders, including members of device manufacturing companies. Another issue requiring further empirical neuroethics research is the potential sensitivity of certain data types in the aDBS sharing context. Researchers were relatively split regarding whether NAD and mental health data raise special issues related to sharing. Additional research is needed to better understand the full complexity of aDBS researchers' views about and justifications for the relative sensitivity of NAD and mental health data. Because NAD and mental health data will increasingly constitute the currency of sharing in the decades to come, it is imperative that potential ethical and policy challenges associated with these data types be anticipated and managed now.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because full datasets must remain unavailable in order to ensure de-identification of interview participants. Requests to access the datasets should be directed to glazaro@bcm.edu.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by Institutional Review Board, Baylor College of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Verbal consent was obtained from each research participant before beginning interviews.

AUTHOR CONTRIBUTIONS

PZ, SO, LT, GL-M, RH, and DS-M contributed to data acquisition by conducting interviews. PZ, CS, KK, LT, and RH contributed to data analysis. PZ, CS, and GL-M conceptualized the manuscript. PZ drafted the manuscript. KK, BK, AM, and GL-M made substantial revisions to the manuscript. JR, BK, SP, AM, and GL-M served in senior leadership roles for the project. All authors contributed to the article and approved the submitted version.

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REVIEW
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International Legal Approaches to Neurosurgery for Psychiatric Disorders

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Neurosurgery for psychiatric disorders (NPD), also sometimes referred to as psychosurgery, is rapidly evolving, with new techniques and indications being investigated actively. Many within the field have suggested that some form of guidelines or regulations are needed to help ensure that a promising field develops safely. Multiple countries have enacted specific laws regulating NPD. This article reviews NPD-specific laws drawn from North and South America, Asia and Europe, in order to identify the typical form and contents of these laws and to set the groundwork for the design of an optimal regulation for the field. Key challenges for this design that are revealed by the review are how to define the scope of the law (what should be regulated), what types of regulations are required (eligibility criteria, approval procedures, data collection, and oversight mechanisms), and how to approach international harmonization given the potential migration of researchers and patients.

Keywords: neuroethics, regulation, law, deep brain stimulation, psychosurgery, neurosurgery for psychiatric disorders

INTRODUCTION

The history of neurosurgery for psychiatric disorders (NPD) is one of extremes running from celebration and expanded use to backlash and public condemnation. António Egas Moniz was awarded the 1949 Nobel Prize for the prefrontal leucotomy, and a form of this, known more often as the lobotomy, was pursued particularly but not exclusively in the US until the late 1960s. At this point, the availability of effective antipsychotic drugs, along with changes in social attitudes to psychiatry, the rise of the civil rights movement, and concerns about the application and side effects of the lobotomy all contributed to a strong shift away from what was then usually called psychosurgery (Pressman, 1998; Robison et al., 2012; Caruso and Sheehan, 2017). Cultural products such as Suddenly Last Summer (Williams, 1958; Spiegel and Mankiewicz, 1959), One Flew over the Cuckoo's Nest (Kesey, 1962; Douglas et al., 1975), and Hombre Mirando al Sudeste (Pflaum et al., 1986) reflect different societies' concerns in the 1960s to 1980s with the role of psychiatry, physical treatments involving the brain, and state control of behavior. An unusual law reflecting this kind of concern is the Utah Code provision stating that it is a criminal offense to give psychiatric treatment, including "lobotomy or surgery" to any person "for the purpose of changing his concept of, belief about, or faith in God"[1].

During this period of controversy, the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research conducted an evaluation of psychosurgery (1977). The National Commission, also known for the (United States National Commission for the Protection of Human Subjects of Biomedical Behavioral Research, 1979), issued a generally favorable report and provided guidelines for the ethical use and regulation of psychosurgery (Fins, 2003). Also in this period, multiple legal jurisdictions enacted their own laws that specifically regulate NPD. These laws often used the term psychosurgery, and some defined the term to include non-ablative interventions such as deep brain stimulation (e.g., Ontario, Canada). In some jurisdictions, NPD-specific laws have been recently amended, demonstrating continued regulatory interest in the topic. However, many locations do not have NPD-specific laws, leaving the field of practice to be regulated under general laws pertaining to medicine [e.g., Mexico, Argentina, Manitoba (Canada)].

Today, brain interventions intended to restore functions that are disrupted in psychiatric conditions are rapidly evolving. The technologies available, and the scope of targeted medical conditions potentially suitable for these interventions, are expanding swiftly. Rapid technological evolution presents a major challenge for legal systems. Poorly designed laws may impede or distort that evolution, and may also fail to achieve their key objectives of, for example, protecting the interests of vulnerable patients, promoting the public interest, and encouraging beneficial innovation. Another challenge for democratic legal systems is how to ensure that the perspectives and experiences of a broad range of stakeholders are reflected in the compromises that are struck in the eventual laws (statutes, regulations, and common law). The interests of patients, caregivers, researchers, medical practitioners, device manufacturers, and the public may diverge, and the laws adopted must appropriately balance these interests, although structural and political factors mean that certain interests may dominate.

The existing legal frameworks are patchy and have failed to keep up with scientific, technological and social change. The scope of applicability of the existing NPD-specific laws is often unclear and many are partly obsolete, reflecting old science, methods of intervention and social currents of decades past. The laws also reflect mind-brain dualism, with many restricted to interventions to treat mental illnesses, while excluding similar interventions intended to treat what are categorized instead as neurological or brain illnesses. The international discussion amongst clinical experts recognizes a need for some form of guidelines for the field (Wu et al., 2012; Nuttin et al., 2014; Bari et al., 2018; Doshi et al., 2019). Occasional calls for mandatory forms of regulation have been made by members of the relevant clinical community (Wu et al., 2012; Visser-Vandewalle, 2014).

Rules come in many forms, both legal and non-legal. Consensus guidelines produced by authoritative professional bodies, policies adopted by hospitals or medical regulators, and self-regulatory procedures created by groups of medical practitioners are examples of rules that may guide practice even though they do not constitute formal legal rules and principles developed by judges or enacted by government bodies. Each of these forms has pros and cons in terms of the ease with which they may be prepared and amended over time, their enforceability, their geographical applicability, and other features. It is not immediately clear which form would be best suited to regulating NPD, and different approaches may be preferable depending upon the type of intervention and the particular society and legal culture. In some jurisdictions clinicians have created forms of self-regulation. For example, psychiatrists and neurosurgeons in the Netherlands formed a review board in the 1970s that went on to review cases from Belgium and the Netherlands. It was endorsed by the Dutch Health Council as a "good example of self-regulation" (Cosyns et al., 1994). This body continues to operate (Gabriëls et al., 2008). Cultures and jurisdictions may also differ in their views of what those regulations should say–reflecting variation in underlying conceptual and ethical views as well as the social and economic realities that shape regional reactions to NPD.

Against this backdrop, six key questions are raised:

(1) Is there a need for specific rules addressing NPD, or can this be left to more general rules applicable to medical practice and research, and/or to mental health legislation?

If specific rules addressing NPD are needed, then:

(2) Which forms of current and anticipated intervention require specific rules (i.e., is "NPD" as a category for regulation too broad or narrow a target)?

[1]Utah Code § 17-43-308. This code provision remains intact after this section was amended in 2018. An interesting problem of legal interpretation arises in the case of mental disorders displaying religiously-oriented symptoms. Would treatment of the condition run afoul of the criminal legal restriction?

(3) Should the rules be the same for all forms of NPD, or is a different approach appropriate for particular interventional techniques (e.g., ablative or not, requiring surgical incision or not, investigational or established), indications, patient populations (e.g., children, incapable adults, or other vulnerable populations such as institutionalized people)?
(4) What form should the rules take (e.g., legal statutes, professional guidelines) and what form of oversight and enforcement is best (e.g., oversight committees, licensing bodies or tribunals; prior authorization of procedures or ex post reporting; advisory or mandatory decisions)?
(5) What issues should the rules address (e.g., eligibility of patients, consent procedures, reporting requirements, training and suitability of medical personnel or centers)?
(6) Should these rules be harmonized across different legal jurisdictions? To what extent is this possible, and what is the optimal process to achieve this?

We do not attempt to answer all of these questions in this article. Instead, we set the groundwork for answering them by offering a structured overview and assessment of existing legislation that specifically addresses NPD from a range of international jurisdictions. The overview illustrates the kinds of rules, procedures and enforcement mechanisms that have been enacted, and offers commentary on their current adequacy.

METHOD AND LIMITATIONS

Objective

The objective of this work is to examine a selection of NPD-specific legislation enacted around the world, and to consider the strengths and weaknesses of the approaches taken in those laws.

Data Collection

Legal systems vary greatly around the world, encompassing the civilian (i.e., Roman) tradition, common law tradition, customary and religious law, and mixed systems. We focus on primary legislative texts (e.g., statutes, codes, and decrees) enacted by government bodies as opposed to judicial decisions or doctrine. We took a three-tiered approach to selecting legislation for consideration in this study. First, drawing on the legal expertise within the authorship group, we conducted a comprehensive search for NPD-specific legislation in Canada (13 provinces and territories) and the United States (50 states). In a second step, we broadened this inquiry by searching the laws of certain Western Commonwealth countries (Australia, New Zealand, Ireland, Scotland, and England). We selected these because these countries reflect a common law tradition consistent with the legal expertise of the primary author. Finally, we drew on the full group of co-authors who collectively represent eight countries in South Asia, East Asia, South America, North America and Europe to help us to find legislation from their jurisdictions. This three-stage effort at data collection furnished a robust cross-section of statutes from which to comment on some of the ways that NPD legislation has been approached, but it does not necessarily represent all NPD-specific legislation that may exist around the world.

Analysis

We employed several analytical methods in this work. First, the rules of statutory interpretation includes principles according to which the meaning of the written text and its application in concrete scenarios is determined (Solan, 2010). In interpreting the statutes, we relied primarily on the "plain meaning" of the words used, as well as the inclusion of definitional or interpretive aids within the statutes themselves, and the placement of the provisions within the broader structure of the statute. Second, we conducted a thematic qualitative legal analysis, organizing the contents of the statutes into themes that we found to be repeated across multiple statutory examples. We took note of unusual approaches as well, given our interest in capturing a range of potential approaches to regulating NPD. Our author group included international and interdisciplinary representation from clinical neuroscience, psychiatry, neurosurgery, neurology and neuroethics, and we evaluated the statutory language in light of this medical and scientific expertise to determine the suitability of the statutory language to the field and its potential future evolution.

Results and Presentation

Our analysis revealed several cross-cutting themes raised by most or all of the examples of NPD-specific statutes considered here. We organized these as follows: (1) definition of the field and scope of the law (section Legal Definitions of NPD), (2) specific rules prescribed for the field (sections Regulations–Prohibitions Applying to Certain Procedures or Populations, Regulations–Independent Approval Procedures, and Regulations–Data Collection Requirements). The international and interdisciplinary authorship group also identified certain matters that were not addressed in the statutes we considered; we decided to include discussion of those following the summary of the statutes we examined (sections Experimental Forms of NPD and Regulatory Variation and the International Movement of Patients).

Limitations

A limitation of this work is that we cannot provide a comprehensive picture of all of the law related to NPD around the world or within any one jurisdiction, each of which has its own legal structure and broader body of laws that may apply concurrently with any NPD-specific laws. In addition, each jurisdiction has its own principles of legal interpretation, and judicial decisions interpreting the legislation, which we do not examine here. Therefore, our review should not be relied upon as an authoritative statement of the relevant law, which should be sought from locally licensed lawyers if needed. Instead we have collected a broad sample of NPD-specific laws around the world in order to identify patterns in these laws.

As we focus in detail on NPD-specific laws, we have not included laws regulating electroconvulsive therapy (ECT), although these also exist in many jurisdictions. Also we have focused solely on formal laws, and have not included consensus guidelines or any other forms of self-regulation.

Finally, many NPD procedures remain investigational, and so the rules applicable to medical research in human subjects

would apply along with any NPD-specific laws. We do not review those rules here, and it is important to note that the NPD-specific laws usually ignore the distinction between interventions that constitute established therapies and those that remain experimental.

LEGAL CHALLENGES POSED BY EVOLUTION IN PSYCHIATRIC NEUROSURGERY

The existing and potential future range of technologies available for neurosurgery and neuromodulation for psychiatric disorders is varied and rapidly evolving. This complicates an effort to determine when regulation is needed, what form of regulation is advisable, and how to define the scope of the laws. As will be discussed later, the laws that address specific psychiatric brain interventions focus primarily on one or more of the following: ablative neurosurgery, non-ablative surgical interventions such as deep brain stimulation (DBS), and electroconvulsive therapy (ECT). An important question is whether this focus is appropriate given the evolution in techniques of functional brain intervention. Here, we briefly survey the evolving range of techniques of psychiatric neurosurgery. Although not all of these would fit within the current laws governing NPD, it is important to consider the broader potential range of interventions in deciding on what the optimal law going forward would be.

Ablative neurosurgery can be performed using incisional and incision-less methods of accessing and lesioning targeted brain tissue [e.g., stereotactic radiosurgery, magnetic resonance image-guided laser interstitial thermal therapy (LITT) and magnetic resonance image-guided focused ultrasound thermal ablation (MRgFUS)] (Franzini et al., 2019). Ablative procedures continue to be provided on a small scale for serious treatment-resistant psychiatric disorders such as major depressive disorder (MDD) and obsessive compulsive disorder (OCD) (e.g., anterior cingulotomy, capsulotomy) (Nuttin et al., 2014). In most developed countries, NPD has shifted from ablative procedures to the neuromodulatory approach of DBS (Hariz and Hariz, 2013), although this is not the case for resource-poor contexts where access to medication, psychotherapy, and more expensive DBS is limited (Nuttin et al., 2014). DBS is being investigated for a broad and increasing range of neurological and psychiatric problems including MDD, OCD, addiction, Tourette's syndrome, eating disorders, pain, disorders of consciousness, aggression, post traumatic stress disorder (PTSD), and dementia (Nuttin et al., 1999; Mayberg et al., 2005; Schiff et al., 2007; Lee et al., 2019). Other forms of psychiatric neuromodulation requiring surgical access include epidural and subdural stimulation (Tronnier and Rasche, 2013, p. 343). Surgical neuromodulation for psychiatric conditions is not always applied directly to the brain but can also be delivered via the peripheral nervous system, as with vagus nerve stimulation. Multiple techniques for externally applied neuromodulation such as transcranial electric stimulation (tES) and transcranial magnetic stimulation (TMS) are now being explored. Some of these are in use clinically to treat certain psychiatric disorders and they are being actively explored for others (Cristancho et al., 2013; George et al., 2013; Lefaucheur et al., 2017, 2020). In the future, externally applied techniques may allow for the modulation of more precisely delimited structures deeper within the brain through electrical field interference (Grossman et al., 2017) or low-intensity focused ultrasound (Di Biase et al., 2019).

Another substantial technological change in neuromodulation is the move toward responsive or adaptive methods that monitor brain activity and deliver stimulation only when needed rather than continuously. This technique, known as responsive neurostimulation (RNS) is approved for adult epilepsy (FDA, 2020), and is being explored for broader use. The integration of machine learning to optimize modulation algorithms, as well as the incorporation into the algorithms of a broad range of markers to identify the need for neuromodulation (Hell et al., 2019) could produce more powerful, flexible, and complex neuroprostheses for the management of dysfunctional brain states.

Technological evolution may also cause some forms of treatment like psychotropic drug therapy that have not fallen within NPD laws in the past to fall within the scope of the laws. Methods to deliver drugs directly to the brain via a surgical approach (in a manner analogous to existing forms of intrathecal drug delivery) are possible in future (Fowler et al., 2020), and when used to address psychiatric disorders would constitute a form of neurosurgery that would fall outside some existing legal definitions of NPD but within others.

All of this means that laws may become ambiguous, obsolete, overly broad or under-inclusive over time as methods of intervention change. This poses a significant challenge to designing appropriate and useful regulation.

Multiple factors are relevant to the question whether some form of regulation is required and if so what it should say. Factors relevant to the method of intervention include safety, reversibility, effectiveness, side effects, and practicality. While all ablative techniques are intended to produce irreversible brain lesions, non-incisional ablative techniques such as focused ultrasound or radiosurgery may avoid risks like infection that are associated with incisional techniques. Neuromodulation techniques differ in whether they (a) are general, diffuse or precisely targeted in their stimulatory effects, (b) are able to affect superficial brain tissue or deeper structures, (c) require surgical incisional access or are applied externally, (d) are applied directly to the brain or rather to the peripheral nervous system, and (e) are adaptive.

In addition to characteristics of the techniques, other factors are relevant to the need for regulation. The context in which the interventions are applied and the degree of vulnerability of the specific patient group will also be relevant to the need for additional legal protections. For example, the existing laws demonstrate concern with the use of NPD in young, incapable, involuntarily hospitalized, or imprisoned people.

The following review of NPD laws should be read with the evolving technological landscape in mind. The current laws raise multiple questions. For example, some laws apply the same restrictive rules to ablative NPD and non-ablative interventions like psychiatric DBS. While both involve surgical risks, they differ in their degree of reversibility and adaptability. Some laws capture only ablative NPD, but appear to leave out psychiatric DBS, which some may view as posing sufficient risks as to

require specific legal protections. Although we focus on NPD and psychosurgery laws in this article, we note that an analogous question pertains to externally applied neuromodulation. ECT is subject to specific laws in some jurisdictions (e.g., India; South Australia; Portugal), raising the question as to whether other more novel forms of non-invasive neuromodulation like tES or TMS should also be similarly regulated.

EXISTING LAWS GOVERNING NPD

In this section, we provide examples of existing laws governing psychosurgery or NPD that are drawn from around the world. Many countries do not have NPD-specific laws, and instead regulate these procedures according to the general legal rules applicable to human subjects research, medicine and medical device regulation. Others have chosen to enact NPD-specific laws that cover some of these matters. Here we present the topics contained in these NPD-specific laws, noting and evaluating the range of approaches that are revealed on each topic.

Legal Definitions of NPD

Legal definitions are selected for a particular reason—namely to make it clear when the law applies and when it does not. A central question in selecting a legal definition is why legal regulation is required. Once this is determined, the definition can be tailored to try to capture only those situations requiring that regulation and leaving others outside the law. Definitions can be specific and narrow, or more broad and general, with each approach posing particular problems.

One of the challenges with specific definitions is that they are easier to circumvent by selecting procedures that fall outside the definitions. Specific definitions are also risky for rapidly evolving fields, like NPD, as the laws can more quickly become obsolete. One can instead adopt a general definition, but this would bring other problems. First, a general definition tends to capture too much thus requiring the law to include a list of specific exceptions. Overly broad definitions can also harm rapidly evolving fields like NPD by imposing unnecessary regulation on advances that may not need to be regulated as strictly. There are regulatory techniques that allow for updating or clarification, and these vary in their level of bureaucratic delay and difficulty. On the other hand, a cautious pace of regulatory adaptation is not always a bad thing if it helps to avoid error or irresponsible haste, to identify unintended longer-term harms, or to accrue experience that supports beneficial innovation.

Obsolescence is a serious problem for statutes because they are usually difficult and time-consuming to amend. For this reason, many legal systems use delegated or subordinate legislation (often called regulations) which are more easily amended. The legislature delegates the authority to make these regulations to a specified body, setting out the scope of this delegated authority within the statute. For example, the law may state that psychosurgery includes or excludes those interventions listed in a particular regulation, which itself can be amended as needed. This is an approach that might permit a definition of NPD to be more easily changed from time to time, as needed.

Existing Legislative Definitions of NPD

The existing laws typically use a three-part definition that describes psychosurgery as a set of (a) techniques used for a set of (b) included indications, but not for a set of (c) excluded indications. An example is offered by the province of Ontario (Canada) [s.49 (2)] (Mental Health Act R.S.O., 1990), which defines psychosurgery as:

> "any procedure that, by direct or indirect access to the brain, removes, destroys or interrupts the continuity of histologically normal brain tissue, or that inserts indwelling electrodes for pulsed electrical stimulation for the purpose of altering behavior or treating psychiatric illness, but does not include neurological procedures used to diagnose or treat organic brain conditions, intractable physical pain or epilepsy, if these conditions are clearly demonstrable."

Ontario's definition thus includes ablative neurosurgery (both incisional and incision-less techniques like radiosurgery) as well as forms of neuromodulation using implants. These techniques count as psychosurgery under the law only where they are used for specified purposes: altering behavior or treating psychiatric illness. They are not included if used to address organic brain conditions, intractable physical pain or epilepsy.

A less common definitional approach is to define the term for the purpose of the statute as any procedure listed in a subordinate regulation. Three jurisdictions that use subordinate regulations in various ways to define NPD are the United Kingdom and the states of Queensland and New South Wales in Australia.

Examples of legal definitions of NPD from around the world are included in **Table 1**.

Common Problems With the Existing Legislative Definitions

A particular problem in some legal definitions of NPD is the exclusion of interventions for "organic brain conditions." This reflects a problematic philosophical mind-brain dualism. First, if the goal of legislation is to protect vulnerable patients, it is not clear that a patient is any less vulnerable if there is a demonstrable organic or physical cause for their symptoms (e.g., neurodevelopmental conditions, dementia). Second, the nosological distinction between mental/behavioral and organic brain conditions is not a stable one, as the underlying neurobiology of mental disorders becomes better understood. Several psychiatric illnesses are now known to have structural, neurochemical and electrophysiological pathological substrates within the brain. Some conditions like Parkinson's disease are classified as neurological disorders yet involve not just motor symptoms, but also emotional and cognitive symptoms. It is difficult to understand why the treatment of the condition would fall outside NPD laws because of the Parkinson's disease diagnosis, and treatment of similar emotional and cognitive symptoms alone would fall within NPD laws in the absence of such a diagnosis. Finally, the distinction is conceptually muddled to begin with given that the symptoms of mental disorders can be understood simultaneously at the levels of the mind and the brain, and their causes might be a heterogeneous mixture of psychological, environmental, and intrinsic biological factors.

TABLE 1 | Legislative definitions of NPD.

Jurisdiction	Technique	Included indications	Excluded indications	Legal citation
Pacific				
New Zealand	"Brain surgery" Any surgery or other treatment intended to destroy any part of the brain or brain function	For mental disorder	N/A	Mental Health (Compulsory Assessment Treatment) Act, 1992 Sections 61, 88
South Australia	"Neurosurgery for mental illness" Leucotomy, amygdaloidotomy, hypothalamotomy, temporal lobectomy,[a] cingulotomy,[b] electrode implantation in the brain or any other brain surgery for treatment of mental illness by the elimination or stimulation of apparently normal brain tissue	For mental illness	N/A	*Mental Health Act, 2009* Sections 3, 43
Victoria (Australia)	"Neurosurgery for mental illness" (a) any surgical technique or procedure by which one or more lesions are created in a person's brain on the same or on separate occasions for the purpose of treatment; or (b) the use of intracerebral electrodes to create one or more lesions in a person's brain on the same or on separate occasions for the purpose of treatment; or (c) the use of intracerebral electrodes to cause stimulation through the electrodes on the same or on separate occasions without creating a lesion in the person's brain for the purpose of treatment	For the purpose of treatment "treatment" is defined as including steps to remedy a person's mental illness or to alleviate the symptoms and reduce the ill effects of a person's mental illness "treatment" is defined to include neurosurgery for mental illness.	N/A	*Mental Health Act, 2014a* Sections 3, 6
New South Wales (Australia)	"Psychosurgery" (a) the creation of 1 or more lesions, whether made on the same or separate occasions, in the brain of a person by any surgical technique or procedure, (b) the use of electrodes within the brain to produce such a lesion or lesions, whether on the same or separate occasions, or (c) the use on 1 or more occasions of electrodes within the brain primarily for the purpose of influencing or altering the thoughts, emotions or behavior of a person by stimulation through the electrodes without the production of a lesion in the brain of the person	Primarily for the purpose of influencing or altering thoughts, emotions or behavior	Does not include a technique or procedure carried out for the treatment of a condition or an illness prescribed by the regulations for the purposes of this definition. The regulation specifies that "psychosurgery" does not include neurological procedures carried out for the relief of symptoms of Parkinson's disease, Gilles de la Tourette syndrome, chronic tic disorder, tremor, dystonia and epilepsy.	*Mental Health Act, 2007* Section 83 *Mental Health Regulation, 2019* Section 11
Australian Capital Territory	"Psychiatric surgery" Specialized neurosurgery for psychiatric conditions "Neurosurgery" Surgery on the brain of a person for treating a pathological condition of the physical structure of the brain [c]	For psychiatric conditions	N/A	*Mental Health Act, 2015 A2015-38* Section 145
Queensland (Australia)	"Psychosurgery" A procedure on the brain, that involves deliberate damage to or removal of brain tissue, for the treatment of a mental illness. "Non-ablative neurosurgical procedure" A procedure on the brain, that does not involve deliberate	For the treatment of a mental illness	For the purpose of non-ablative neurosurgery, certain conditions do not constitute mental illness: chronic tic, dystonia, epilepsy, Tourette, Parkinson's, tremor, another neurological disorder prescribed by regulation	*Mental Health Act, 2016* Section 9, 10, Schedule 3 *Mental Health Regulation, 2017* No provisions in this regulation mention psychosurgery or non-ablative neurosurgical procedures.

(Continued)

TABLE 1 | Continued

Jurisdiction	Technique	Included indications	Excluded indications	Legal citation
	damage to or removal of brain tissue, for the treatment of a mental illness.			
Fiji	"Psychosurgery" (a) The creation of one or more lesions, whether made on the same or separate occasions, in the brain of a person by any surgical technique or procedure, when it is done primarily for the purpose of altering the thoughts, emotions or behavior of the person; (b) the use for such a purpose of intracerebral electrodes to produce such a lesion or lesions, whether on the same or separate occasions; or (c) the use on one or more occasions of intracerebral electrodes primarily for the purpose of influencing or altering the thoughts, emotions or behavior of a person by stimulation through the electrodes without the production of a lesion in the brain of the person	Primarily for the purpose of altering the thoughts, emotions or behavior of the person;	Does not include a technique or procedure carried out for the treatment of a condition or illness prescribed for the purposes of this definition.	*Mental Health Act, 2010* Section 52
Asia				
India[d]	"Psychosurgery" No interventions specified.	For mental illness	N/A	*Mental Healthcare Act, 2017* Section 96
Europe				
United Kingdom[e]	"Any surgical operation for destroying brain tissue or for destroying the functioning of brain tissue" and other forms of treatment specified by regulation The additional treatment specified in the Regulation is not relevant here (implantation of hormones to reduce male sexual drive).	For mental disorder	N/A	*Mental Health Act, 1983 1983 c.20* Section 57 *Mental Health (Hospital, Guardianship and Treatment) (England) Regulations, 2008, 2008 No. 1184* Section 27
Scotland	The law sets out rules for "medical treatment" falling within the definition of "certain surgical operations": any surgical operation for destroying— brain tissue; or the functioning of brain tissue; and such other types of medical treatment as may be specified in regulations for the purposes of this section. The regulation specifies "deep brain stimulation" which is defined as "the focal modulation of the activity of specific brain regions by direct electrical stimulation delivered by electrodes which are stereotactically implanted in the brain and attached to a programmable control unit inserted in the chest which delivers electrical stimuli. administered repeatedly, over an extended period." [f] The act also specifies special rules for electro-convulsive therapy and "such other types of	"Medical treatment" means "treatment for mental disorder"	N/A	Mental Health (Care Treatment) (Scotland) Act, 2003 Section 234, 329 *Mental Health (Medical treatment subject to safeguards) (Section 234) (Scotland) Regulations, 2005* *Mental Health (Medical treatment subject to safeguards) (Section 237) (Scotland) Regulations, 2005*

(Continued)

TABLE 1 | Continued

Jurisdiction	Technique	Included indications	Excluded indications	Legal citation
	medical treatment as may be specified in the regulations" (section 237) The regulation goes on to specify transcranial magnetic stimulation and vagus nerve stimulation. These are defined as follows: "Transcranial magnetic stimulation" means the focal modulation of the activity of specific brain regions, by the administration of a changing magnetic field repeatedly, over an extended period "Vagus nerve stimulation" means the intermittent electrical stimulation of the cervical portion of the left vagus nerve by a surgically implanted, programmable electronic device which administers electrical stimuli repeatedly, over an extended period.			
Ireland	"Psycho-surgery" Any surgical operation that destroys brain tissue or the functioning of brain tissue	For the purposes of ameliorating a mental disorder.	N/A	*Mental Health Act, 2001* 2001 No. 25. Sections 58.
Portugal	"Intervenção psicocirúrgica" Translation: psychosurgical intervention No further definition given in the statute.	N/A	N/A	*Lei de Saúde Mental Lei No. 36/98* Art 5
South America				
Brazil	"A neuropsicocirurgia e quaisquer tratamentos invasivos e irreversíveis para doenças mentais" Translation: neuropsychosurgery and any invasive and irreversible treatments for mental illness No further definition given in the Resolution.	Para doenças mentais Translation: for mental illnesses	N/A	*Resolução and no. 2.057/2013* Art 19, 20.
Chile	"Psicocirugía o cirugía aplicada al tejido cerebral" Translation: psychosurgery or surgery applied to brain tissue No further definition provided in these documents.	con el fin de suprimir o modificar funcionamientos o conductas del paciente Translation: in order to suppress or modify patient functioning or behavior	N/A	*Ley Numero 20.584, Regula los derechos y deberes que tienen las personas en relación con acciones vinculadas a su atención en salud.* 2012 Art. 24 Chile, 1998 Art. 25 Chile, 2002
North America				
Alberta (Canada)	"psychosurgery" Any procedure that, by direct or indirect access to the brain, removes, destroys or interrupts the continuity of histologically normal brain tissue, or that inserts indwelling electrodes for pulsed electric stimulation	For the purpose of altering behavior or treating psychiatric illness	But does not include neurological procedures used to diagnose or treat intractable physical pain or epilepsy where those conditions are clearly demonstrable	*Mental Health Act, 2000*, c M-13 s. 1
Saskatchawan (Canada)	"Psychosurgery" Any procedure that by direct access to the brain removes, destroys or interrupts the normal connections of the brain for the primary purpose of treating a mental disorder or involves the implantation of electrodes [h]	For the primary purpose of treating a mental disorder	But does not include neurosurgical procedures designed to treat reliably diagnosed organic brain conditions or epilepsy	*Mental Health Services Act, S.S., 1984-85-86*, c M-13.1 s. 2.

(Continued)

TABLE 1 | Continued

Jurisdiction	Technique	Included indications	Excluded indications	Legal citation
Texas (USA)	"Psychosurgery" A surgical intervention to sever nerve fibers connecting one part of the brain with another, or to remove or destroy brain tissue	With the intent of modifying or altering severe disturbances of behavior, thought content or mood	Surgery for the relief of intractable physical pain or to treat neurological disease or abnormality	*25 Texas Administrative Code §405.103(15), 1993*
California (USA[i])	"Psychosurgery" Those operations currently referred to as lobotomy, psychiatric surgery, and behavioral surgery and all other forms of brain surgery"	For the purpose of any of the following: (1) Modification or control of thoughts, feelings, actions, or behavior rather than the treatment of a known and diagnosed physical disease of the brain. (2) Modification of normal brain function or normal brain tissue in order to control thoughts, feelings, actions, or behavior. (3) Treatment of abnormal brain function or abnormal brain tissue in order to modify thoughts, feelings, actions or behavior when the abnormality is not an established cause for those thoughts, feelings, actions, or behavior.	Psychosurgery does not include "prefrontal sonic treatment" wherein there is no destruction of brain tissue.	*California Welfare and Institutions Code § 5325(g)* (introduced in the Lanterman-Petris-Short Act, 1967)
Missouri (USA)	"Psychosurgery" (a) Surgery on the normal brain tissue of an individual not suffering from physical disease for the purpose of changing or controlling behavior; (b) surgery on diseased brain tissue of an individual if the sole object of the surgery is to control, change or affect behavioral disturbances, except seizure disorders	In the case of normal brain tissue–for the purpose of changing or controlling behavior. In the case of diseased brain tissue—where the sole purpose is to control, change or affect behavioral disturbances.	In the case of diseased brain tissue, an exception is made for seizure disorders.	*Revised Statutes of Missouri 630.005(27)*
Utah (USA)	"Psychosurgery" A neurosurgical intervention to modify the brain	To reduce the symptoms of a severely ill psychiatric patient.	N/A	*Utah Administrative Code R523-8-5(1)(c), 2015*
Oregon (USA)	"Psychosurgery" Any operation designed to produce an irreversible lesion or destroy brain tissue	For the primary purpose of altering the thoughts, emotions or behavior of a human being.	Does not include procedures which may produce an irreversible lesion or destroy brain tissues when undertaken to cure well-defined disease states such as brain tumor, epileptic foci and certain chronic pain syndromes	*Oregon Revised Statutes § 677.190*

[a] *A potential ambiguity in the drafting of South Australia's law is that "temporal lobectomy" is used for treatment of epilepsy (Wiebe et al., 2001; Franzini et al., 2019). Its inclusion in the definition of the phrase "neurosurgery for mental illness" suggests that the law means it be included only when it is performed for mental illness, and not epilepsy, which is not today classified as a mental illness. However, any uncertainty in whether to classify a condition as a mental illness or not would create uncertainty about the scope of the law. For greater clarity, some of the other laws explicitly exclude interventions like epilepsy or pain.*

[b] *The statute actually uses the term "cingulectomy" and not cingulotomy.*

[c] *Note a possible legal drafting error in this definition. The legal definition of neurosurgery appears to restrict the meaning of neurosurgery to interventions to situations in which physical pathologies are known. This would appear to restrict the meaning of "psychiatric surgery," which incorporates the term. This is unlikely to be the intended interpretation of the law.*

[d] *See also the discussion of this law in Doshi et al. (2019).*

[e] *The UK Mental Health Act is presently being revised.*

[f] *Note that DBS programmable control units are not always implanted in the chest (e.g., Garg et al., 2010), revealing the peril of overly precise legislative drafting.*

[g] *In Brazil, the federal Lei 3268/1957 delegates to the Conselho Federal de Medicina (CFM), a self-regulatory body, the authority to regulate the professional practice of physicians and surgeons. The CFM Resolutions govern the practice of medicine in Brazil and have a binding effect for health care professionals.*

[h] *Note that there is a potential drafting error. The phrase "for the primary purpose of…" appears to qualify lesional interventions but not the implantation of electrodes. This would have the unusual effect of meaning that the implantation of an electrode would fall within the definition whether or not its primary purpose was to treat a mental disorder, whereas lesional interventions would fit within the definition only when the primary purpose was to do so.*

[i] *Note that California has three slightly different definitions of psychosurgery occurring in five different legislative provisions: Cal. Welf. & Inst. Code § 4503; 17 CCR § 50510; 22 CCR § 76525, Cal.Welf. & Inst.Code § 5325(g), 9 CCR § 836. Only one of these is definitions is presented here.*

Ultimately, this assumed distinction is an inadequate basis for defining the scope of a law governing NPD, and it would be better to return to the main question of why a regulation is required. Then a definition can be developed to ensure that those cases that should be regulated are in fact regulated, and those that should not are not.

Another problem is posed by statutes that limit the scope of NPD to procedures that have the purpose of treating mental illness or disorder. Many laws stipulate a definition of "mental illness" or "mental disorder" for the purposes of the legislation, and this is critical in setting the scope of the law. The legal definitions may not precisely match the main medical nosologies, introducing a source of ambiguity and confusion. An example of the problem is furnished by the legal variation in approach to NPD for addiction and for intractable aggressive behavior associated with certain disorders or syndromes that involve intellectual disability (Micieli et al., 2016). Whether or not interventions in these types of cases would fit within the NPD laws of Victoria (Australia), Ireland and India depends upon the legal definition of mental illness or disorder in their respective statutes. The law of Victoria (Australia) defines mental illness as "a medical condition that is characterized by a significant disturbance of thought, mood, perception or memory" (s. 4). It is unclear, but this definition appears to exclude addiction and aggressivity associated with intellectual disability. Ireland, on the other hand, defines mental disorder in a manner that clearly includes intellectual disability, but likely excludes addiction (s. 3). Finally, India regulates psychosurgery for the treatment of mental illness, which is defined to include addiction but to exclude cognitive disability [s. 2 (s)].

This review also raises questions about the technological obsolescence of the definitions. Some of the more recently updated statutes directly or indirectly regulate interventions like TMS that do not appear to fit within the older statutes, which instead focus on invasive neurosurgery. For example, Scotland does not include TMS in the rules governing psychiatric neurosurgery, but explicitly includes TMS and vagus nerve stimulation within a set of safeguards applicable to electro-convulsive therapy (Reg. 2005 No. 292). If it is advisable to regulate interventions like TMS, statutes that do not address it should be updated.

Another example of the challenge of adequately describing the changing field of neurological interventions is provided by Queensland (Australia), which regulates a class of interventions labeled "non-ablative neurosurgical procedures," defined as "a procedure on the brain that does not involve deliberate damage to or removal of brain tissue, for the treatment of mental illness" (Sched. 3). The problem with this definition is that it is potentially very broad. Non-invasive forms of neuromodulation via focused ultrasound or TMS are obviously "procedures on the brain." However, it is unclear whether these non-invasive procedures were meant to be treated as falling within the legal definition of "non-ablative neurosurgical procedures" even though they would appear to fall within the legal definition[2].

Finally, definitions that include only those interventions that are for the "primary" purpose of treating mental illness [e.g., Saskatchewan (Canada)] also raise legal questions. For example, if neurosurgery was being undertaken to address a non-psychiatric condition but could be performed in one of two ways, one of which could incidentally alleviate a psychiatric condition, should the choice of that method constitute a choice made primarily to treat mental illness? Mallet et al. (2002) describe the unexpected alleviation of long-standing OCD symptoms in two patients treated with DBS for Parkinson's disease. Their report illustrates that it may sometimes be difficult to identify the primary purpose of an intervention when multiple conditions can be addressed simultaneously. It is also difficult to identify a "primary" non-psychiatric purpose because a condition can include a mix of symptoms, some of which are classified as psychiatric and some as neurological in the prevailing dualistic understanding. Bandini et al. (2007) describe the strategy of switching to DBS in patients with Parkinson's disease to allow the reduction of medication that is causing pathological gambling. Since gambling disorder is classified as a mental disorder, would the selection of surgery to reduce that behavior be surgery for the primary purpose of treating mental illness? Ultimately, dualistic concepts and legal language are poorly-suited to our evolving understanding of mental and behavioral conditions.

Regulations—Prohibitions Applying to Certain Procedures or Populations

Many of the existing laws prohibit certain kinds of NPD altogether, or their use in certain populations. The laws of New South Wales (s. 83) and the Northern Territory in Australia [s.58 (2)] ban psychosurgery regardless of technique or patient population. An example of a non-legal ban is provided by Japan, where the Japanese Society of Psychology and Neurology passed a general resolution against psychosurgery in 1975 during a period of public controversy (Nudeshima and Taira, 2017).

Some laws prohibit NPD for specific populations defined by age, decisional capacity, or legal status (e.g., prisoners or patients who have been involuntarily hospitalized). These prohibitions appear to be based on concerns about patient vulnerability due to incapacity or the voluntariness of consent given the context.

Examples of complete and partial prohibitions on NPD are set out in **Table 2**. Note that some laws allow NPD but only where additional approval requirements are satisfied (e.g., approval by tribunals, ethics boards or courts) and these are discussed separately in the next section C. In **Table 3**, we also include other regulations related to emergencies and advance directives, which also affect eligibility for NPD.

Issues Raised by Legal Prohibitions on NPD for Vulnerable Patient Populations

It is an important ethical problem that the categorical exclusion of vulnerable groups can be both beneficial and harmful at

[2]Laws do not typically offer illustrative examples to aid in interpretation. However, the Queensland statute cites DBS as an example of what is meant by the phrase "non-ablative neurosurgical procedure." This offers some guidance for interpreting the law, but the example still serves to illustrate the potential problem of uncertainty about the precise scope of what constitutes a neurosurgical procedure.

TABLE 2 | Examples of different forms of prohibitions on NPD.

Jurisdiction	Prohibition	Statutory penalty	Notes	Legal citation
Examples of prohibitions on all or some procedures				
Queensland (Australia)	"Psychosurgery on another person" is prohibited	2 years imprisonment or "200 penalty units" or ∼AU$26,000 in 2019.	The law allows "non-ablative neurosurgical procedures" for mental illness (e.g., DBS) with consent and tribunal approval.	*Mental Health Act, 2016* s. 238-241
New South Wales (Australia)	"Psychosurgery" on another person is prohibited	Maximum penalty: "50 penalty units" or ∼AU$5500 in 2019.	The definition of psychosurgery includes DBS for psychiatric purposes.	*Mental Health Act, 2007* s. 83
Northern Territory (Australia)	"Psychosurgery on another person" is prohibited.	Maximum penalty: "85 penalty units" or ∼AU$13,345 in 2019.	The definition of psychosurgery includes DBS for psychiatric purposes.	*Mental Health Related Services Act, 1998* s. 58
Oregon (USA)	"Performing psychosurgery"	Oregon Medical Board "may refuse to grant, or may suspend or revoke a license to practice" where someone performs psychosurgery.		Oregon Revised Statutes § 677.190
Chile	"Psychosurgery" is only an option for those with major treatment-resistant depression or very severe obsessive compulsive disorder, which have been refractory to treatment of sufficient quantity, frequency and duration using the established therapies that are available in the country		This approach specifies the indications for which psychosurgery is permitted, and so by implication excludes others.	Resolucion 656 s.2
China	Only approved institutions may perform NPD, and only where certain criteria are met. NPD may be performed only for severe and refractory OCD, depression or anxiety disorder, and may not be performed for schizophrenia or related symptomatologies		In addition to the restriction on eligible indications for NPD, the notification also specifies additional eligibility criteria such as "cerebral pathological finding or frequent abnormal brainwave activity."	Notification regarding improvement of management and related issues in neurosurgery for psychiatric disorders from the General Office of the Ministry of Health Issue (2008) 70.[a]
Examples of direct and indirect prohibitions on NPD for incapable patients				
Ontario (Canada)	"Psychosurgery" shall not be performed on a person who is incapable of consenting	Maximum penalty: fine of CA$25,000	This is an example of direct exclusion of the class of incapable people.	Mental Health Act R.S.O., 1990 s. 49, 80
New Zealand	"Brain surgery" shall not be performed for mental disorder on patients without consent and Tribunal approval	Maximum penalty: fine NZ$500 unless another penalty is specified elsewhere.	New Zealand's law indirectly excludes incapable people by making it clear that first person rather than substitute consent is required.	*Mental Health (Compulsory Assessment Treatment) Act, 1992*. s. 61, 121
Connecticut (USA)	"Psychosurgery" shall not be performed without written informed consent by a patient in "any inpatient or outpatient hospital, clinic or other facility for the diagnosis, observation or treatment of persons with psychiatric disabilities."		This law offers another example of the indirect exclusion by insisting on first person rather than substitute consent. Note, however, that written informed consent is valid for 30 days, revocable at any time, raising the possibility of relying on earlier capable consent after a patient loses capacity.	Connecticut General Statutes § 17a-543(c)
India	"Psychosurgery" shall not be performed as a treatment for mental illness without informed consent of the patient and Board approval.	Maximum penalty for first contravention: Six months imprisonment and/or fine of 10,000 rupees. Subsequent contraventions: Up to 2 years imprisonment and/or a fine of 50,000 to 500,000 rupees.	This law indirectly excludes incapable people by requiring informed consent of the patient.	*Mental Healthcare Act, 2017* s. 96, 108

(Continued)

TABLE 2 | Continued

Jurisdiction	Prohibition	Statutory penalty	Notes	Legal citation
Examples of prohibitions for children or minors				
New Zealand	"Brain surgery" for mental disorder shall not be performed on any person under the age of 17 years	Maximum penalty: fine $500 unless another penalty is specified elsewhere.	Note that this law prohibits NPD for minors under 17 years regardless of whether they have capacity.	*Mental Health (Compulsory Assessment Treatment) Act, 1992*. s. 88
California (USA)	"Psychosurgery" shall in no circumstances be performed on a minor			Cal. Welf. & Inst. Code § 5326.6.
Western Australia	"Psychosurgery" shall not be performed on a person under 16 years of age.	Penalty: 5 years imprisonment.		*Mental Health Act, 2014b* s. 206, 207
South Australia	"Neurosurgery for mental illness" may only be performed if a patient is 16 years of age or older	Maximum penalty: $50,000 or 4 years of imprisonment	This law provides that written consent must be given by the patient, or by the Tribunal if the patient is incapable.	*Mental Health Act, 2009* s. 43
Ontario (Canada)	"Psychosurgery" shall not performed on a person who is incapable of consenting	Maximum penalty: fine of $25,000	The Ontario law is silent regarding minors. Given that the "mature minor doctrine" contemplates that minors may be capable to make treatment decisions, some capable minors but not incapable minors will be eligible in Ontario.	Mental Health Act R.S.O., 1990 s. 49
Examples of prohibitions applicable to other classes of person (e.g., prisoners, involuntary psychiatric patients)				
Canada	"Psychosurgery" may not be imposed upon an unfit accused person under the *Criminal Code*.		The Criminal Code of Canada allows a court to direct that an unfit accused person be treated to render them fit to stand trial. Psychosurgery is excluded from these orders.	*Criminal Code of Canada* s. 672.58, 672.61
Newfoundland & Labrador (Canada)	"Psychosurgery" shall not be performed on an involuntarily hospitalized patient.			*Mental Health Care and Treatment Act* SNL 2006 c M-9.1 s. 36

[a]*Wu et al. (2012) have published a translation of this government document.*

the same time. Exclusion protects them from coerced or otherwise improper treatment. However, it also denies them access to a range of potentially beneficial treatments that others are permitted to have. The 1977 US Commission noted this problem, suggesting that "fairness requires that individuals should not be denied access to potentially beneficial therapy simply because they are involuntarily confined or unable to give informed consent" (page 64). At the same time, the Commission noted their vulnerability to coercion and the possibility that psychosurgery might be proposed to modify their behavior for social or institutional purposes that may not coincide with the patients' own interests or desires (page 65). The Commission proposed that this tension be resolved by adopting a range of protections. First, court review of individual applications should be required. Second, no psychosurgical procedure should be provided to these vulnerable groups until a national psychosurgery advisory board had determined that the procedure showed demonstrable benefit for the psychiatric symptom or disorder.

The solution of limiting NPD to capable patients until there is clear evidence of its safety and efficacy would be workable for some applications of NPD, but might not assist for problems that are encountered primarily in incapable persons (e.g., disorders of consciousness, aggressivity associated with intellectual disability). For example, self-injurious and aggressive behavior co-occurs sometimes with cognitive disability in some conditions (Arron et al., 2011). DBS and ablative NPD are being actively explored to address these aggressive behavioral issues (Gouveia et al., 2019). Research into forms of NPD that are prohibited legally in some places may instead proceed in countries with less restrictive legal environments, although those countries may have alternative forms of oversight that are adequate (e.g., strong research ethics systems and good checks and balances in the surrogate consent rules). However, migration of research to jurisdictions without regulation or an adequate alternative could be a problem if regulatory oversight is in fact warranted. In addition, given the rarity of these procedures, systematic detailed data collection and sharing (with adequate privacy protection) on every single case is important. As a result, it would be better to encourage research on conditions associated primarily with such vulnerable populations to occur in jurisdictions where proper oversight, data collection and publication of results can be ensured. Jurisdictions currently lacking that oversight should work toward developing these mechanisms so that local research may be supported and participants protected.

TABLE 3 | Examples of types of additional rules regarding eligibility for NPD.

Jurisdiction	Rule	Legal citation
Rules for advance directives		
Western Australia	The informed consent of the patient is required for psychosurgery, in addition to Tribunal approval. An adult can give informed consent within an advance directive issued under the *Guardianship and Administration Act 1990.*	*Mental Health Act, 2014b* s. 208 (note 1)
Georgia (USA)	The powers that may be given to a surrogate in an advance directive for health care exclude the ability to consent to psychosurgery.	Ga. Code Ann. § 31-32-7.
Rules regarding emergencies		
United Kingdom	In the case of "urgent treatment," the patient consent and independent approval requirements for NPD are lifted. Four different rules are provided, depending upon the level of medical urgency and the degree of risk and permanence of the intervention. There is no consent or independent approval required if the intervention is immediately necessary to save life. If the intervention is reversible and it is immediately necessary to prevent a serious deterioration in the patient's condition, then consent and independent approval are not required. If the intervention is reversible and non-hazardous and it is immediately necessary to alleviate serious suffering, then consent and independent approval are not required. If the intervention is reversible and non-hazardous and it is immediately necessary to prevent the patient from behaving violently or being a danger to himself or others, then consent and independent approval are not required.	*Mental Health Act, 1983*, 1983 c.20 s. 62
Western Australia	"Psychosurgery" cannot be provided without patient consent in emergencies. Informed consent is not required for "emergency psychiatric treatment." However, the law states explicitly that "emergency psychiatric treatment" does not include "psychosurgery."	*Mental Health Act, 2014b* s. 202(2), 203

This remains an important tension to navigate today in light of the legislated restrictions on the books, particularly for forms of NPD that have a good benefit to risk ratio and that are used voluntarily by capable patients.

Regulations—Independent Approval Procedures

Multiple jurisdictions impose independent approval procedures in addition to informed consent. These procedures vary in three main ways. First, they vary in who must provide the independent review and approval (e.g., independent physicians, government-appointed physicians or laypeople, hospital ethics committee, specialized administrative tribunal or courts). Examples of all of these are provided in **Table 4**. Second, the procedures differ in the amount of detail specified about what the independent body is expected to verify and the conditions for the body's approval. Third, they vary in whether the same independent approval process is set for all cases, or different approval processes are required for certain patient populations (e.g., prisoners, children, incapable patients).

The *Mental Health Act (2014b)* of the state of Western Australia is an example of a regulation that includes considerable detail of the decision-making process and approval criteria to be applied by the Mental Health Tribunal. The patient's psychiatrist must apply to the Tribunal in writing, setting out (a) the reasons for recommending psychosurgery, and (b) the treatment plan for psychosurgery including a detailed description of the proposed psychosurgery, the name, qualifications and experience of the proposed neurosurgeon, and the name and address of the place where the psychosurgery is to be performed (s. 417). Parties to the proceeding before the Mental Health Tribunal include the patient, the applicant psychiatrist, and any other person the Tribunal feels has a sufficient interest in the matter to be included (s. 418). The Tribunal cannot approve unless it is satisfied of five things: the patient has given informed consent, the psychosurgery has clinical merit and is appropriate, all reasonably available alternative treatments likely to offer sufficient and lasting benefit have been tried without success, the proposed neurosurgeon is suitably qualified and experienced, and the proposed place for the performance of the psychosurgery is suitable (s. 419). The Tribunal must take into consideration a list of matters in reaching its decision on whether to approve the psychosurgery: (a) the views of any caregiver, close family member or personal support person of the patient, (b) the consequences for the treatment and care of the patient of not performing the psychosurgery, (c) the nature and degree of risk of the psychosurgery, (d) whether the psychosurgery is likely to promote and maintain the health and well-being of the patient, and (e) any other things the Tribunal regards as relevant to the decision (s. 420). Many other laws provide little or no detail of this kind, although the consideration of many of these matters is implicit in performing the function of an independent review tribunal.

Several jurisdictions apply different types of independent approval requirements depending upon the class of patient[3]. Court approval is required in Ireland when the patient is a child

[3]The California Penal Code discusses a court approval procedure for "organic therapy" including psychosurgery for at least some prisoners (California Penal Code §, 2670-2680), although the scope of the provision is confusing and it is

TABLE 4 | Examples of independent review procedures.

Jurisdiction	Approval body or individual	Approval process and requirements	Legal citation
Examples of approval by independent individuals			
Scotland (Approval where the patient is capable. See below for the approval process where the patient is incapable).	Independent medical practitioner and two people appointed by the Commission who are not non-medical practitioners.	Capable patients: An independent designated medical practitioner must certify in writing that the patient is capable, consents, and the treatment is in the patient's best interests. If the patient is a child, this practitioner must be a child specialist if the patient's responsible physician is not a child specialist. Two people appointed by the Commission who are not medical practitioners must certify in writing that the patient is capable and has consented.	*Mental Health (Care Treatment) (Scotland) Act, 2003* s. 235
United Kingdom	Independent appointed medical practitioner and two other appointees who are not medical practitioners.	The appointed independent medical practitioner and two other non-medical appointees must certify in writing that the patient is capable and has consented. The appointed independent medical practitioner must also certify in writing that the treatment is appropriate. Before doing so, the practitioner must consult with two people (other than the responsible clinician) who have been professionally involved with the patient's treatment. One must be a nurse and the other must be neither a nurse nor a medical practitioner.	*Mental Health Act, 1983*, 1983 c.20 s. 57
California	Three qualified physicians One must be appointed by the facility and two by the local mental health director. Two must be psychiatrists or neurosurgeons.	Three independent physicians must personally examine the patient and unanimously agree with the attending physician that the patient has capacity to consent, that all other appropriate treatments have been exhausted, psychosurgery is definitely indicated, and psychosurgery is the least drastic alternative available for the patient.	Cal. Welf. & Inst. Code 5326.6
Portugal	Psychiatrists appointed by the National Council of Mental Health	Favorable written opinion of two appointed psychiatrists.	*Lei de Saúde Mental Lei No. 36/98* Art. 5.
Chile	Independent psychiatric opinion	In addition to consent, the treating psychiatrist must complete a pre-operative protocol that specifies multiple medical details and is signed by an independent psychiatrist who confirms the treating physician's recommendation. As discussed below the file must also be sent for prior approval by the National Commission for the Protection of Persons Affected by Mental Illness	*Decreto 570* Art. 25 *Resolucion 656* s. 2, 3 *Ley* Art. 14, 15, 24
Examples of approval by specialized bodies (courts, mental health tribunals, medical commissions, ethics review boards)			
Western Australia	Mental Health Tribunal	In addition to informed consent by the patient, the psychiatrist must submit an application in writing for Tribunal approval. The application must contain reasons for recommending psychosurgery as well as a detailed treatment plan. The law specifies the conditions for Tribunal approval.	*Mental Health Act, 2014b* 2014 No. 024. Section 208, 384, 416-421.
Victoria (Australia)	Mental Health Tribunal	In addition to informed consent by the patient, the psychiatrist must apply for approval for approval to the Tribunal, which must hear the application and decide within 30 business days.	*Mental Health Act, 2014a* Section 100-103, 152-153
China	Medical Ethics Committee	Approval from the Medical Ethics Committee is required in each case of neurosurgery for psychiatric disorders.	Notification regarding improvement of management and related issues in neurosurgery for psychiatric disorders from the General Office of the Ministry of Health Issue (2008) 70.[a]
Ireland	Mental Health Tribunal Court	Adult patient: In addition to written consent by the patient, the responsible psychiatrist must notify the Mental Health Commission in writing of the proposed psychosurgery, and the Commission refers the matter to the Tribunal. An appeal to the Court. Is available from the Tribunal decision. Child patient: Psychosurgery may not be performed on a child who has been involuntarily hospitalized without Court approval	*Mental Health Act, 2001,* 2001 No. 25. s. 19, 25(12), 48-49, 58

(Continued)

TABLE 4 | Continued

Jurisdiction	Approval Body or individual	Approval process and requirements	Legal Citation
Brazil	Technical Chamber of Psychiatry and plenary session of the Regional Council of Medicine Judicial body in certain cases	In addition to the informed consent of the patient or legal guardian of the patient, the Chamber must prepare an opinion for approval by the Regional Council of Medicine. The Chamber may request advice from professionals in fields related to medicine in forming its opinion. The Regional Council of Medicine must consider and approve the Chamber's opinion in a plenary session. If the patient is involuntarily or compulsorily hospitalized, then prior judicial authorization is required.	Resolução and no. 2.057/2013, 2013 Art. 19
India	Mental Health Review Boards (constituted by the State Mental Health Authority under s. 73)	Approval from the relevant Mental Health Review Board is required to perform psychosurgery for mental illness.	*Mental Healthcare Act, 2017* s. 96
Chile	Comisión Nacional de Protección de las Personas Afectadas de Enfermedades Mentales Trans: National Commission for the Protection of Persons Affected by Mental Illness.	In addition to consent, the psychiatrist must complete a pre-operative protocol, containing a confirmatory opinion from an independent psychiatrist. The medical file must be sent to the Commission a minimum of 30 days before the proposed psychosurgery, in order for the Commission to verify that the patient satisfies eligibility criteria for psychosurgery set out in the Resolution and also to ensure the protection of the patient's rights.	*Decreto 570* Art. 25 *Resolucion 656* Section 3.3 *Ley* Art. 14, 15, 25
Scotland (Approval process where the patient is incapable. See above for the approval process where the patient is capable).	Independent medical practitioner, two people appointed by the Commission who are not non-medical practitioners and the Court of Session.	Incapable patients: Psychosurgery may be provided to an incapable patient who is not objecting to the treatment as long as an independent designated medical practitioner and two appointees who are not medical practitioners have approved and the Court of Session has approved An independent designated medical practitioner must certify in writing that the patient is incapable, does not object, and the treatment is in the patient's best interests. If the patient is a child, this practitioner must be a child specialist if the patient's responsible physician is not a child specialist. Two people appointed by the Commission who are not medical practitioners must certify in writing that the patient is incapable and does not object. The Court of Session may approve if it is satisfied that the patient does not object and the treatment is in the patient's best interests.	*Mental Health (Care and Treatment) (Scotland) Act, 2003* s. 236.

[a] *Wu et al. (2012) have published a translation of this government document.*

who has been involuntarily hospitalized [s. 25 (12)]. In Brazil, judicial approval is required if the patient is involuntarily or compulsorily hospitalized (Art. 19). In Scotland, court approval is required in the case of incapable patients [s. 236 (4)].

Advantages and Disadvantages of Approval Procedures

Independent review procedures have advantages and disadvantages. They can protect against improper conduct by clinicians or institutions by ensuring independent scrutiny of cases before NPD is provided. Clinicians and institutions might welcome this independent scrutiny as providing external assurance of the appropriateness of the treatment in a clinical context that is potentially controversial. Another advantage of specialized mental health tribunals is that they can ensure multidisciplinary input into decisions by regulating the composition of the tribunal, specifying the professional expertise of independent appointees, and requiring consultation of a broad range of individuals. On the other hand, additional approval procedures increase the burden on patients and clinicians, and also raise the possibility that capable patients may be refused a treatment that they want and that their own clinicians, who know them better than the review bodies, are recommending. Attendance by the treating physicians at the review body discussions may help to ensure that decisions are adequately informed.

The foregoing are all examples of mandatory independent review and approval procedures. It is worth noting that advisory, as opposed to mandatory, review procedures may also work. For example, in Belgium, the Flemish Stereotactic Neurosurgery for Psychiatric Disorders (SNPD) Committee includes members from the four unversities of Flanders and was established in the 1970s to review proposals for psychiatric neurosurgery, to ensure the appropriateness of the treatment and the patient's ability to give informed consent (Cosyns et al., 1994; Gabriëls et al., 2008). Its initial role was advisory, although its approval now appears to be legally required in at least some situations (Belgium, 2016).

inconsistent with a separate legal provision, which seems to prohibit psychosurgery for all prisoners (California Code of Regulations. 15 CCR § 3999.349).

Regulations—Data Collection Requirements

Some jurisdictions require that periodic reports on the performance of NPD be submitted to a government body or government-appointed individual. The legal reporting requirements vary in detail, some including patient information and others merely reporting on the number and type of procedures performed. The less detailed reports offer less valuable opportunities for oversight. Examples of reporting requirements are provided in **Table 5**.

Some laws regulate the data that must be included in medical charts. For example, California requires that the attending and treating physician(s) place a signed statement in the patient's treatment record of the reasons for the procedure, the fact that all other appropriate treatment modalities have been exhausted, that psychosurgery is definitely indicated and is the least drastic alternative available for the treatment of the patient [California, Cal. Welf & Inst. Code § 5326.6(c)]. In addition, three additional physicians (one must be appointed by the facility and two appointed by the local mental health director; and two must be psychiatrists or neurosurgeons) must personally examine the patient and agree with the attending physician's assessment of the patient's capacity to consent as well as with the appropriateness of the psychosurgery. This must be documented and signed by them in the treatment record [California, Cal. Welf & Inst. Code § 5326.6(d)].

Advantages and Disadvantages of Reporting Requirements

Regulatory reporting requirements offer a useful way to ensure that adequately detailed information is collected about what remains an infrequent and exceptional form of intervention, and it also offers a means of retrospective oversight. It is worth noting that experts in the field have argued for more data collection and sharing, viewing it as "crucial to realizing the potential of a number of neurotechnologies and their use in clinical practice" (Ramirez-Zamora et al., 2019). The 1977 US National Commission report recommended that a mechanism be created to collect data about: the nature, extent and outcomes of psychosurgical procedures performed in the USA, the indications for the procedures, and the populations on which they are performed.

One downside of this type of data collection is the invasion of patient privacy, and the risk that highly sensitive patient records might be inadvertently compromised. The US National Commission noted this risk, recommending that stringent privacy safeguards be used (United States National Commission for the Protection of Human Subjects of Biomedical Behavioral Research, 1977).

EXPERIMENTAL FORMS OF NPD

In this article, we have not reviewed the rules applicable to experimental NPD procedures. Many forms of NPD remain experimental, and so additional legal rules pertaining to when it is acceptable to attempt treatments that are not within the accepted standard of care will apply, in addition to the NPD-specific laws canvassed here. For example, where the regulatory regime prohibits psychosurgery for minors, any concurrent human subjects research rules that allow medical research in minors should not be taken to suggest that psychosurgery research in minors is permitted.

Most of the NPD-specific laws do not distinguish between experimental treatment and established clinical treatments, and will apply to both. A couple of laws do address the issue of whether the proposed NPD is an established treatment modality or not. For example, Chile (2002) Decree on Psychosurgery justifies strict regulations of psychosurgery on the basis of a general lack of scientific evidence, lack of consensus about the possible benefits and harms, and international ethical controversy. It allows psychosurgery only for severe treatment-resistant depression or OCD.

REGULATORY VARIATION AND THE INTERNATIONAL MOVEMENT OF PATIENTS

An issue that may arise as a result of variation in the NPD laws is that research activity and patients may move to jurisdictions that are more permissive. This possibility is illustrated by the tendency, documented by the former Psychosurgery Review Board of the state of Victoria in Australia,[4] for patients to move from Australian states that prohibit psychosurgery to those that permit it. The 2011–2012 report of the Psychosurgery Review Board observed that:

> "One of the applications received in 2011/12 concerned an individual from South Australia. This continued a pattern of previous years, in that five applications since 2007 have related to the treatment of individuals from interstate. This occurs because of restrictions or prohibitions on the availability of deep-brain stimulation for the treatment of mental illness in other Australian jurisdictions. New South Wales–where psychosurgery is banned–is examining this…" (Victoria Psychosurgery Review Board 2011/2012 Annual Report Melbourne:, 2012, p. 26).

Widespread migration of patients between countries seems unlikely at the moment given the expense and investigational status of much NPD. However, one can still find advertisements for medical tourism that mention ablative surgery, DBS and vagus nerve stimulation for psychiatric disorders, as well as a range of established functional neurosurgical procedures for other conditions (Neurosurgery in Mexico, 2020). Indeed, medical tourism for established neurosurgical treatments may occur due to lack of availability or cost in the home country (e.g., Idowu and Adewole, 2015). In addition, patients may migrate

[4]The Psychosurgery Review Board was established under s. 56 of the Victorian *Mental Health Act 1986* to hear applications by psychiatrists for a neurosurgeon to perform psychosurgery on patients. This Board ceased to exist in 2014, when its functions were assumed by the Mental Health Tribunal constituted under the *Mental Health Act (2014a)*.

TABLE 5 | Examples of regulatory reporting requirements.

Jurisdiction	Content	Reporting chain	Citation
California (USA)	Quarterly report of the number of involuntary, voluntary, capable and incapable patients who receive psychosurgery Quarterly report of any records or information from reports indicating violation of the law or regulations	Any doctor or facility administering psychosurgery and the State Department of State Hospitals must send quarterly statistics on numbers of patients to the local mental health director, who then transmits a copy to the Director of Health Care Services. The quarterly report of violations of the law must be sent by the Director of Health Services to the Medical Board of California	Cal.Welf. & Inst.Code § 5326.15
Texas (USA)	Quarterly report indicating the number of voluntary and involuntary patients who received psychosurgery as well as the number of involuntary patients for whom a guardian consented, the age, sex and race of the patients, the source of the treatment payment, as well as autopsy findings if death occurred within 14 days of the treatment. Other information required by Departmental rule must also be included.	Any doctor, mental hospital or facility that administer psychosurgery must submit quarterly reports to the department. The department is entitled to use this information to analyze, audit and monitor the use of psychosurgery. The department will file an annual report with the governor and the presiding officer of each house of the legislature summarizing this information.	Health & Safety Code § 578.007 and 578.008 25 TAC § 405.112
Western Australia	As soon as practicable, a report of the performance of psychosurgery in each individual case and a copy of the Mental Health Tribunal approval of the procedure. Annual statistics on performance of psychosurgery.	Patient's psychiatrist must report to the Chief Psychiatrist, and if the patient is a mentally impaired accused, the psychiatrist must also report to the Mentally Impaired Accused Review Board. Chief Psychiatrist must report annual statistics to the Minister, who must report to Parliament.	*Mental Health Act, 2014b* Section 209, 533-534
Victoria (Australia)	Written report to the Chief Psychiatrist on the results of the neurosurgery for mental illness within 3 months after the surgery and within 9–12 months after the surgery is performed.	The psychiatrist who applied for Tribunal approval or the treating psychiatrist must report to the Chief Psychiatrist, who may require further information.	*Mental Health Act, 2014a* Section 104
China	Provincial health administrative departments must inspect and supervise NPD, and provide a summary of previously performed NPD to the Ministry of Health.	The provincial health administrative department must report to the Ministry of Health	Notification regarding improvement of management and related issues in neurosurgery for psychiatric disorders from the General Office of the Ministry of Health Issue (2008) 70.[a]

[a]*Wu et al. (2012) have published a translation of this government document.*

between jurisdictions after they have received treatment, raising questions about access to ongoing care in their new countries.

To the extent that movement of patients to access NPD is occurring, an important issue relates to how to ensure appropriate follow-up and management of patients such as those with implanted DBS. Furthermore, migration would be troubling if the regulations in the receiving jurisdictions are inadequate. This is an important issue that should be monitored. It also suggests that governments and professional associations should take steps to harmonize regulatory standards and to ensure their enforcement.

CONCLUSION

This review of some of the NPD-specific laws enacted around the world reveals that diverse legal jurisdictions have viewed this area of medical intervention as warranting specific regulatory attention, and that this view persists today. Indeed, many laws have been recently enacted or amended particularly in countries in Asia, Europe, and Australia. The kinds of matters contained in these laws vary, but they usually relate to restrictions on eligibility for NPD, specialized approval procedures, and data collection and reporting requirements.

Substantial legislative challenges surround drafting appropriate laws in a context of rapid evolution in technology and medical practice. The challenge is not just one of defining the scope of the regulation appropriately, but even of identifying where regulation is presently required or may in the future be required.

Authoritative voices within the medical community see a need for consensus guidelines and some have called for mandatory regulation, as well as for greater data collection and sharing in this field. Work should now continue to answer the questions set out in the introduction to this article. First, is there a need for specific guidelines or rules addressing NPD? Multiple jurisdictions have decided that specific rules, rather than rules that apply generally to all medical research and practice, are needed for NPD. It is worth noting that this does not always have to take the form of formal legislation, but might emerge from self-regulatory initiatives by the profession.

A significant challenge will be to decide what forms of intervention ought to be regulated, and to select a legal definition that can survive change in technique and practice over time. Our

review has revealed how difficult this is, and suggests that the best approach is reflected by jurisdictions such as Scotland that do not attempt to exhaustively list the specific interventions to be regulated within the statute, but instead indicate that in addition to listed interventions, other types of treatment may be specified in regulations from time to time. This method or some version thereof would allow the system to be updated to add or remove types of interventions as the need for regulation becomes clear.

Another critical question is what the regulations should say. Multidisciplinary reflection on how best to promote and protect the interests of a vulnerable group of patients will be essential. Harms may flow from improper interventions but also from laws that exclude people from treatments. An important dimension for international reflection is how to handle the migration of research and patients among jurisdictions with different rules and oversight mechanisms. Finally, systems that allow for more robust data collection and sharing will help to protect patients and to advance the field, and a key role international regulatory harmonization could be to achieve this objective, in addition to addressing the potential risks of medical tourism for NPD.

We have not analyzed the suitability for NPD of existing systems of oversight and regulation of human subjects research or the possible inconsistencies between those systems and existing NPD laws. This should also be pursued in future work. Nevertheless, in our view, available information is sufficient to conclude that appropriate regulations are essential to the safe and ethical development of a promising field that may offer an option to patients with severe and intractable suffering.

AUTHOR CONTRIBUTIONS

JC researched, wrote and revised the manuscript. All other authors provided regional knowledge of relevant law and medical practice, and reviewed and revised the manuscript.

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CASE REPORT
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Case Report: Deep Brain Stimulation to the Ventral Internal Capsule/Ventral Striatum Induces Repeated Transient Episodes of Voltage-Dependent Tourette-Like Behaviors

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Deep Brain Stimulation (DBS) is an invasive device-based neuromodulation technique that allows the therapeutic direct stimulation of subcortical and deep cortical structures following the surgical placement of stimulating electrodes. DBS is approved by the U.S. Federal Drug Administration for the treatment of movement disorders and obsessive-compulsive disorder, while new indications, including Major Depressive Disorder (MDD), are in experimental development. We report the case of a patient with MDD who received DBS to the ventral internal capsule and ventral striatum bilaterally and presented with 2 weeks of voltage-dependent Tourette-like symptoms including brief transient episodes of abrupt-onset and progressively louder coprolalia and stuttered speech; tic-like motor behavior in his right arm and leg; rushes of anxiety, angry prosody, angry affect; and moderate amnesia without confusion. We describe the results of the inpatient neuropsychiatric workup leading to the diagnosis of iatrogenic voltage-dependent activation of cortico-subcortical circuits and discuss insights into the pathophysiology of Tourette as well as safety considerations raised by the case.

Keywords: DBS, neuromodulation, MDD, Tourette syndrome, PET, brain stimulation

INTRODUCTION

Deep Brain Stimulation (DBS) is an invasive neuromodulation technique that allows the direct stimulation of subcortical and deep cortical structures following the surgical placement of brain electrodes connected to an implantable battery-powered pulse generator. It aims to act as a neural pacemaker, improving function in diseased neuronal populations, and facilitating therapeutic adaptive changes in brain networks. The exact mechanism of action and optimal therapeutic parameters for each target and pathology are yet to be established, but a significant amount of research in animal models and humans is underway (Herrington et al., 2016).

Following successful engineering and clinical developments in the field of cardiac pacemakers, DBS emerged as an alternative to ablative neurosurgical procedures that provided several

advantages: its reversible nature, the capacity to modulate the parameters of stimulation, and its potential for placebo-controlled blinded studies. DBS is approved by the U.S. Federal Drug Administration (FDA) for the treatment of patients with severe and refractory movement disorders (including Parkinson's disease, Essential Tremor, and Dystonia) or Obsessive-Compulsive Disorder (OCD). Also, several experimental approaches are exploring the use of DBS for other treatment-resistant neuropsychiatric disorders, including Major Depressive Disorder (MDD; Kaur et al., 2013), Gilles de la Tourette Syndrome (GTS; Andrade and Visser-Vandewalle, 2016), and others (Arulpragasam et al., 2013).

Here, we report the case of a patient with MDD implanted with DBS on the ventral internal capsule/ventral striatum (VC/VS) who presented with 2 weeks of Tourette-like symptoms including brief transient episodes of stuttered and progressively louder speech with coprolalia; predominantly right-sided tic-like behaviors; rushes of anxiety, angry prosody, angry affect; and moderate amnesia without confusion. We describe the course of the admission and diagnostic workup, including structural and functional neuroimaging data to support a mechanistic pathophysiological hypothesis and discuss DBS safety considerations raised by the case.

METHODS

Case Report

The timeline of events can be found in **Table 1**. A 57-year-old right-handed single Caucasian male with a history of severe, treatment-resistant MDD since the age of 20 and a Deep Brain Stimulator implanted bilaterally in the VC/VS (**Figure 1A**) 32 months before admission, presented to the Emergency Room of the Massachusetts General Hospital complaining of 2 weeks of brief transient episodes, lasting 20 s to 2 min, of abrupt-onset and progressively louder coprolalia; tic-like motor behavior in his right arm or leg; rushes of anxiety, angry prosody, angry affect; and moderate amnesia without confusion. No obsessions or compulsions were reported. The patient's history also includes Panic Disorder without Agoraphobia in full sustained remission, Alcohol Dependence, Hypercholesterolemia, Hypertension, Peptic Ulcer Disease, and Lumbar Spondylosis.

Mr. N.'s psychiatric history started around the age of 20 in the form of a depressed mood with severe neurovegetative symptoms and panic attacks without agoraphobia. After the age of 25, the panic attacks resolved with medication, but he remained depressed and anxious. Early in his disease history, he started abusing alcohol to "self-medicate," per his report, developing significant dependency in his late 20 s. Through the course of his illness, he had a total of four psychiatric admissions and never attempted suicide. The current major depressive episode began in the early 1990s and he tried multiple medications without relief, including Fluoxetine, Paroxetine, Venlafaxine, Mirtazapine, Buproprion, Isocarboxazid, Tranylcypromine, and augmentation strategies including Buspirone, Lithium, Olanzapine, Thioridazine, and Liothyronine. He also failed outpatient Cognitive Behavioral Therapy administered by an experienced Ph.D. psychologist. The only medication that showed a good response was Phenelzine, but the effects faded after some years. In 2001, he had a Vagus Nerve Stimulator (VNS) implanted in the context of a clinical trial, and although the initial response was positive, he relapsed despite gradual increases in stimulation intensity. In 2005, he required a psychiatric admission to receive Electroconvulsive Therapy (ECT). He tolerated the first two sessions with mild post-ECT confusion, but after the 3rd session, he became markedly delirious. The confusion lasted for at least 5 days, at which point it was decided to terminate ECT treatment due to poor tolerability. Given the lack of efficacy, the VNS was explanted in 2006. Later that year he was enrolled in a DBS trial and had a stimulator implanted without complications and with good tolerability. See Malone et al. (2009) for details of the surgical procedure and study protocol. The treatment worked well initially and although he did not remit, he responded positively for approximately 2 years. During the 4–5 months before these events though, his depressive symptoms worsened again and he resumed drinking alcohol, up to four mixed drinks per day. The home medications at the time of admission were Phenelzine 15 mg four times a day, Alprazolam 0.5 mg four times a day, Atorvastatin 10 mg daily, and Omeprazole 20 mg daily.

The day before the admission, Mr. N. called the psychiatric neurotherapeutics team complaining of 2 weeks of bizarre transient episodes, lasting less than 1 min each, in which he was witnessed to suddenly engage in mumbled foul speech with occasional right leg twitching. The frequency and duration of these episodes increased progressively. In one of these episodes, the patient was speaking to his sister when he abruptly interrupted a normal conversation by raising his voice, stuttering incoherent random syllables, and swearing profusely, while also tapping his right leg. In a different event, Mr. N. was talking on the phone when he suddenly started a stuttered conversation with mumbled incoherent words but clear intense swearing. Coprolalia often interrupted speech and behavior, and it generally included a limited repertoire of swear words, though not always following a stereotyped pattern. It is significant that after these episodes, Mr. N. seemed anxious but did not remember what had happened. When he explained these episodes he did it according to what he had been told had occurred, but he had no episodic memories. That said, he was aware of a rush of sympathetic activation, psychological anxiety, and a negative emotional gestalt that he could not relate to concrete events. He never lost consciousness, had generalized or bilateral abnormal movements, or became disoriented. His post-event confusion seemed primarily related to transient amnesia in the context of sympathetic activation, his inability to contextualize the sudden anxiety and negative emotions, and the incapacity to make logical sense of what people described had just happened. Otherwise, he was alert and oriented.

After describing these new symptoms on the phone, the patient was advised to turn the stimulator off and present for evaluation. He was seen in the clinic, DBS parameters were Voltage 7 V (left) and 5 V (right), pulse

TABLE 1 | Timeline of events.

Time	Event	Description
35 years before admission	The onset of Major Depressive Disorder (MDD) and panic attacks.	Since the age of 20.
30 years before admission	Panic attacks resolved with medication.	
s ∼28 years before admission	Patient report of alcohol abuse and dependence.	Patient attempt to "self-medicate" mood.
7 years before admission	Vagus Nerve Stimulator (VNS) implanted for treatment-resistant MDD.	
3 years before admission	Received Electroconvulsive Therapy (ECT).	Tolerated 2 sessions with mild post-ECT confusion; encephalopathic, confused and disoriented for 5 days after 3rd session. ECT stopped.
2 years before admission	VNS device explanted.	Due to lack of efficacy.
2 years before admission	Deep Brain Stimulator (DBS) implanted for treatment-resistant MDD.	Bilaterally in ventral internal capsule/ventral striatum; positive response for ∼2 years.
∼1–2 years before admission	Patient scanned with Positron Emission Tomography (PET).	In the context of a neuroimaging research study; inhaled radiolabeled CO2 molecules. Images acquired while stimulating at different DBS electrode positions.
16 weeks before admission	Depressive symptoms worsened; resumed drinking up to four mixed drinks per day.	
11 weeks before admission	Radioablative treatment for lumbar spondylosis.	
2 weeks before admission	The onset of the patient presenting complaints.	Brief episodes (20 s-2 min) of garbled nonsensical speech with paraphrasias, neologisms, agrammatism, coprolalia, rushes of anger and anxiety without panic symptoms, motor automatisms on the right arm and right leg.
1 day before admission	The patient contacted the psychiatric neurotherapeutics team with presenting complaints.	The patient advised to turn the DBS device off and present it to the clinic.
Admission	The patient was seen at the outpatient clinic, referred to the Emergency. Department, admitted to Neurology service.	DBS device turned off, normal neurological exam.
During admission		Negative work up for TIA/stroke with CT of the brain, CTA of brain and neck, TTE, and 24 h Holter.
		Normal limits for lipid panel, hemoglobin A1C, Vitamin B12, Thiamine, TSH, urine drug screen, blood alcohol level.
		Negative work up for seizures with EEG when DBS device was off (and later on).
		Two possible but unclear events with no epileptiform activity during 24 h long-term monitoring EEG.
	DBS device turned on at original settings.	Short episodes of progressively faster and louder stuttering with coprolalia, neologisms, agrammatism, paraphrasias, right-sided tic-like motor automatisms, ego-dystonic "rush" of physical and psychological activation; the patient had minimal memory of these events after they occurred.
	The psychiatric neurotherapeutics team consulted.	The voltage of the DBS device increased from 7 to 8 V with no changes, then increased to 8.5 V. The event started immediately and ceased when the voltage was reduced to 7 V.
Discharge	Patient discharged and scheduled to follow up with neurotherapeutics team.	
1 day after discharge	The patient presented back at the outpatient clinic.	DBS device turned on. Decreased pulse width to 90 μs of the left electrode, voltage left at 9V. The Patient reported no side effects and left with a safety plan.
3 weeks after discharge	The patient called the neurotherapeutics team.	Reported having a few brief similar episodes; advised to turn the stimulator off.

(Continued)

TABLE 1 | Continued

Time	Event	Description
	The patient returned to the outpatient clinic.	Outpatient EEG with DBS device on at a higher intensity led to immediate induction of an event; no signs of epileptiform activity seen; EEG remained unchanged even when intensity reduced and behavioral effects disappeared.
		DBS device turned on and left at same low pulse width (90 μs) but with reduced voltage (5 V).
		Active leads on left stimulator were changed to a more dorsal position to match the position of right stimulator active leads; voltage slowly titrated up to 7.5 V bilaterally over several weeks.
	No side effects have since been reported but depressive symptoms worsened and the patient lost initial beneficial response to DBS.	

width 210 μs, frequency 130 Hz, electrode configuration 0 + 1−. He was referred to the Emergency Department that same day, from where he was admitted to the Neurology inpatient service. The patient presented with a normal neurological exam, except for bilateral lower extremity paresthesias which were chronic. He had not suffered any further episodes since turning the stimulator off. Toxicological screens including urine drug screen and blood alcohol were also normal.

The patient was worked up for a possible transient ischemic attack (TIA) or stroke with a head CT, CT angiography of the head and neck, transthoracic echocardiogram, and 24 h Holter, all of which were normal. The patient was initially started on 81 mg of Aspirin daily and continued on his home Atorvastatin, but given all the negative results a TIA was ruled out and Aspirin was discontinued.

Given the recurrent brief nature of these events, the patient was also worked up for seizures. An electroencephalogram (EEG) was obtained while the DBS was off and also when it was on: both were normal. The patient was subsequently studied with a 48 h long-term monitoring EEG, with video only for the first 24 h. Two possible but unclear events occurred during this time and the EEG showed no epileptiform activity. At that point, the stimulator was restarted at its original settings, which prompted new spells. The initial events were short and discrete, consisting of abrupt onset of progressively faster and louder mumbled stuttering with clear coprolalia. He also presented right-sided tic-like motor automatisms (right hand or foot abrupt-onset jerk-like movements or tapping-like behaviors that were more complex and not as fast as myoclonus) and an egodystonic "rush" of physical and psychological activation, "as if I were fighting with myself inside my head." The patient had minimal awareness or memory of the events after they occurred but knew one had just happened. He was always conscious and interactive though, before, during, and after the events. After the events, he was alert and oriented, but mildly confused and lacking a good recollection of the details. He had approximately six events per day while the stimulator was on. During one of the events, as he was completing his breakfast preferences in the hospital menu, an episode started and he continued drawing circles on the paper in what seemed to be a mix of jerk-like movements and transient perseveration (**Figure 2**).

At this point and with a negative diagnostic workup, the psychiatry neurotherapeutics team was consulted. To clarify a possible iatrogenic effect from the DBS stimulator, the voltage of the stimulator was increased from 7 to 8 V. A few minutes later the voltage was further increased to 8.5 V and an event started immediately. The stimulator voltage was then reduced back to 7 V and the event stopped abruptly. In the light of the previous negative workup and the observed dose-related response of the spells, an iatrogenic etiology related to DBS became the most likely explanation. The patient was discharged with the stimulator off and a follow-up appointment with the neurotherapeutics team the next day. No changes were made to his medications. He did not present any signs of alcohol withdrawal.

The patient presented for follow up. The stimulator was turned on and the left electrode was set to provide a lower charge density by decreasing the pulse width to 90 μs. Acutely, the patient described no side effects. Three weeks later though, he called to let us know he had had a few brief similar episodes. He was then advised to turn the stimulator off. He was seen a few days later to do an outpatient EEG with the stimulator on. When the patient was in the neurophysiology unit, the DBS voltage was increased eliciting an event. The EEG was carefully analyzed with particular emphasis on the period when the event was noted, but no signs of epileptiform activity were observed. The behavioral effects disappeared as the voltage was reduced, but the EEG remained unchanged. After this assessment, the stimulator was left at the same low pulse width (90 μs) but with reduced voltage (5.0 V).

On closer radiographic analysis of DBS electrodeposition, the left stimulator was observed to be more ventral and rostral than the right (**Figure 1B**). The active leads on the left stimulator were therefore changed to a more dorsal position, from 0 + 1− to 1 + 2−. In the following weeks, the voltage was slowly titrated up with close monitoring of mood symptoms and DBS tolerability in several outpatient visits. The voltage

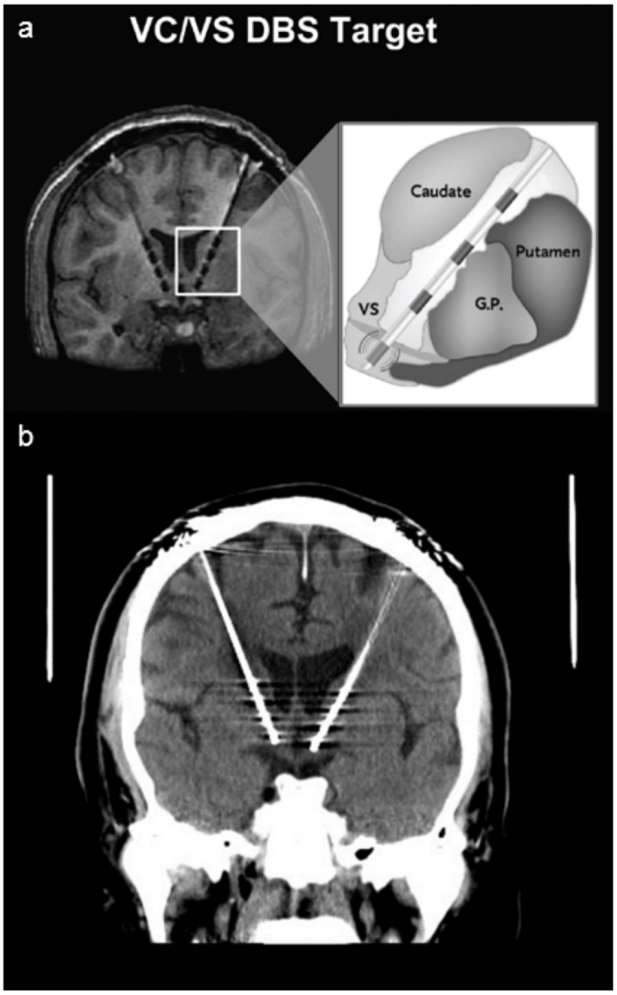

FIGURE 1 | Deep Brain Stimulator. Panel **(A)** shows a schematic of Deep Brain Stimulation (DBS) electrodes placed on the ventral capsule/ventral striatum with four different electrodes placed from ventral (0) to dorsal (3; image used with permission from Medtronics). Panel **(B)** shows the head CT of the patient, revealing the more ventral and anterior position of the left electrode.

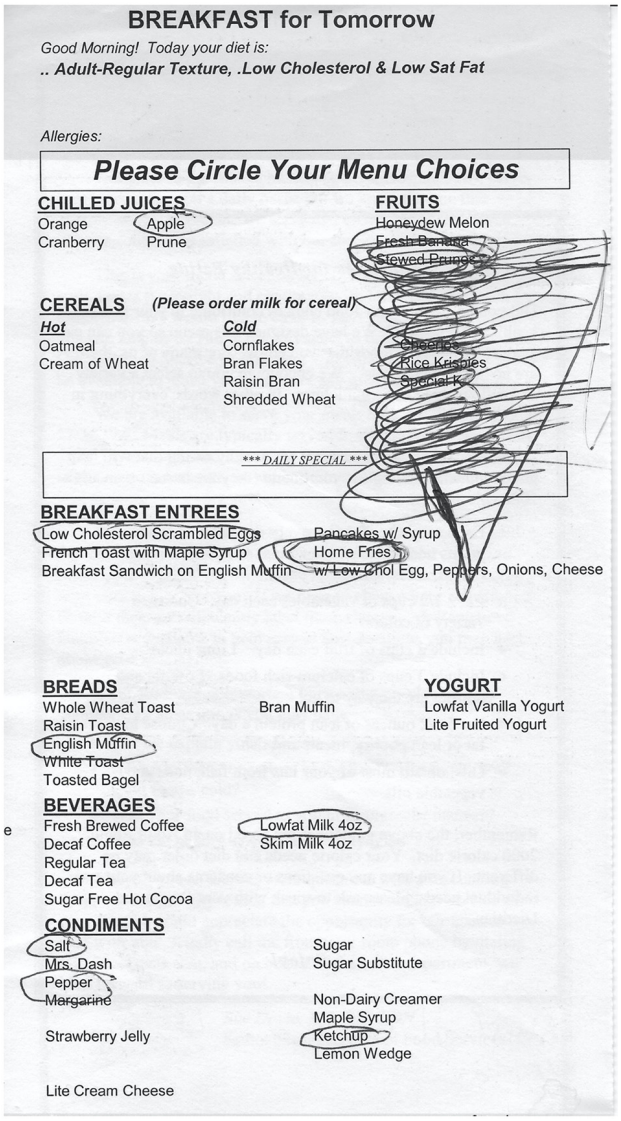

FIGURE 2 | Behavioral and motor manifestation. Drawings made by the patient on a hospital menu during one of the events with right-hand movements.

was increased sequentially up to 7.5 V bilaterally, but the pulse width and active leads were unchanged. No side effects were reported since, but the patient's depressive symptoms worsened and he lost the initial antidepressant benefit: in the first year after DBS implantation, Montgomery-Asberg Depression Rating Scale (MADRS) scores improved from 36 to 19 points, slightly worsening at the end of year 2 (8 months before these events) up to 23 points. After this event and with the new DBS settings, depression symptoms continued to worsen with a MADRS of 32 points at the end of year 3 (4 months after these events) and 36 points at the end of year 4.5, the last recorded score. The patient was eventually explanted given lack of efficacy, poor compliance with follow-up visits, and new medical comorbidities that could be more effectively and safely monitored using MRI without the limitations of a metallic foreign body.

Positron Emission Tomography Protocol

In the context of a neuroimaging research study, previous to the development of these symptoms, Mr. N. was scanned with Positron Emission Tomography (PET) to measure brain perfusion. We analyzed these data for him individually, aiming to identify specific brain perfusion patterns associated with the iatrogenic DBS location.

Images were acquired using a 15-slice whole-body tomography scanner (model 4096; Scanditronix, General Electric, Milwaukee, WI, USA) in stationary mode. The slice geometry consisted of contiguous slices with a center-to-center distance of 6.5 mm (axial field 97.5 mm) and an axial resolution of 6 mm full-width at half-maximum. Head alignment was made relative to the canthomeatal line. Once the head was in place, an

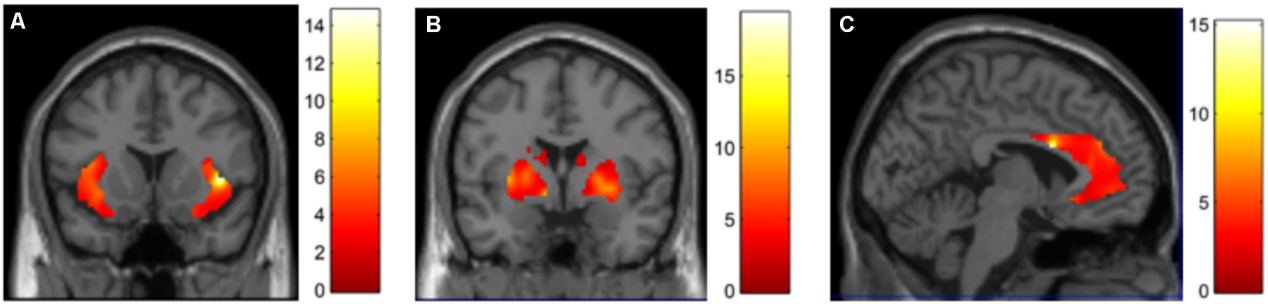

FIGURE 3 | DBS-evoked changes in brain perfusion with 15O CO2 PET. Contrasting DBS on at contact 0 + 1 (bipolar) > contact 3 (unipolar), we identified increases in perfusion in the **(A)** insula, **(B)** basal ganglia and **(C)** anterior cingulate.

overlying face mask attached to a vacuum and a nasal cannula which delivered the [O–15]-CO_2 (concentration 2,960 MBq/L; flow rate 2 L/min) was positioned.

Eight runs (with two runs of four conditions) were performed: (1) DBS off; (2) DBS on in monopolar configuration at contact 1; (3) DBS on in monopolar configuration at contact 3; and (4) DBS on in bipolar configuration between contacts 0(+) and 1(−). A 10 min rest period was imposed between each successive PET run, to allow for decay of O–15 radiation signal.

Data Analysis

The PET images were preprocessed using SPM5. We compared perfusion patterns when DBS was on in the bipolar configuration that induced these events (0 + 1−) and when DBS was on in monopolar configuration at contact 3, more dorsally like the post-discharge montage that did not elicit aberrant behaviors. Based on previous studies of GTS, we restricted our search territory to *a priori* regions of interest [the anterior cingulate, basal ganglia (caudate, putamen, pallidum), and insula] as defined by the Wake Forest University Pick Atlas (Maldjian et al., 2003). To correct for multiple comparisons, a false discovery rate (FDR) correction was applied with a significance threshold of $p < 0.05$.

RESULTS

DBS stimulation with the iatrogenic montage (0 + 1−) compared to stimulation with the monopolar configuration at contact 3 led to a significant increase in perfusion in the insula (peak cluster MNI coordinates = 42, 14, 2, k = 1,646 voxels, Z-score = 4.21, FDR corrected $p < 0.05$, **Figure 3A**), pallidum (peak cluster MNI coordinates = −8, 2, −4, k = 2,005 voxels, Z-score = 4.50, FDR corrected $p < 0.05$, **Figure 3B**), and the anterior cingulate (peak cluster MNI coordinates = −4, 10, 24, k = 2,494 voxels, Z-score = 4.24, FDR corrected $p < 0.05$, **Figure 3C**).

DISCUSSION

We report the case of a patient with treatment-resistant MDD who after 32 months of moderately effective DBS to the VC/VS presented with recurrent, brief, and discrete episodes of abrupt-onset and progressively faster and louder coprolalia with stuttered mumbled speech; tic-like motor behavior in his right arm and leg; rushes of anxiety, angry prosody, angry affect; and transient amnesia without confusion. These episodes could be replicated in a montage- and voltage-dependent manner, stimulating the most ventral electrodes at higher voltages, while more dorsal stimulation and/or lower voltage did not elicit these episodes and even terminated ongoing events.

The diagnostic workup ruled out cerebrovascular etiologies such as TIAs. The recurrent and episodic presentation in the context of electrical brain stimulation was suggestive of seizures. Complex partial seizures can present with coprolalia, particularly when affecting the frontal lobes (Daniel and Perry, 2016; Massot-Tarrús et al., 2016; Xu et al., 2020). It was unclear if the patient had premonitory urges or was able to suppress the motor symptoms or coprolalia, as he did not remember the events: this may have helped distinguish tics from motor stereotypies or complex motor seizures (Robertson et al., 2017).

The cognitive changes after the events were suggestive of generalized or complex partial seizures, but further examination revealed that it was not confusion as one may typically see in post-ictal states, but brief transient episodic amnesia leading to a discontinuous perception of both external and internal events. Although certain aspects of the phenomenology were indeed suspicious for complex partial seizures and deep frontal epileptic sources may be poorly detected in surface EEG, video-EEG recordings during several active episodes (including lateralized motor phenomena) did not identify epileptic activity despite careful analysis by the Epilepsy team. While these stimulation-dependent symptoms should be electrical, they did not seem to stem from epileptic patterns of neuronal firing, but more likely, from the non-epileptic artificial activation of circuits involved in cognition, behavior, affect, and movement.

It is reasonable to consider if the abnormal movements were indeed tics or stereotypies, but the co-occurrence of abrupt onset coprolalia that interrupts the flow of normal conversation (like in GTS) and does not seem to respond to pain or other factors that could trigger cursing led us

to hypothesize that we were activating a circuit of regions similar to that involved in GTS, and our analysis of the PET perfusion data seemed to confirm this hypothesis. In this context, we favored the use of tic-like (not tics) to describe the abnormal movements, though we acknowledge the symmetries with stereotypies.

The PET results support the hypothesis that maladaptive DBS activation of functional circuits caused these events: DBS of the ventral-anterior VC/VS (which elicited the aberrant behaviors) led to increased perfusion in a circuit of regions involving the insula, basal ganglia, and the anterior cingulate, compared to a more dorsal VC/VS configuration that did not elicit symptoms. Indeed, GTS has been associated with hyperperfusion in the striatum and anterior cingulate (Robertson et al., 2017). Further support for this iatrogenic hypothesis is given by the parameter-dependent nature of these symptoms: they were elicited when the stimulator was turned on, and remitted with lower voltages or switching to dorsal electrode positions or off. Of note, iatrogenic GTS symptoms have been reported with other therapies as well: Lamotrigine, an anticonvulsant and mood stabilizer, has been described to trigger vocal tics in an adult patient (Seemüller et al., 2006), and motor and vocal tics in five children (Sotero de Menezes et al., 2000). While our evidence does not offer answers regarding the role of white matter tracts, connections exist linking these regions and integrating motor control, cognitive and emotional processing (Testini et al., 2016), which have been proven effective for GTS and other neuropsychiatric syndromes when therapeutically modulated with DBS (Marano et al., 2019). We should note that while the clinical phenotype of GTS is heterogeneous, the symptoms we reported were Tourette-like but did not perfectly mirror the symptomatology observed in idiopathic GTS.

Two factors seemed to be related to the parameter-dependent aberrant behaviors: higher voltages and more ventral electrodes on the left side. Careful examination of neuroradiological images identified that the left electrode was slightly more ventral and more anterior than the right. This led to the clinical decision to move to more dorsal electrode configurations which resolved the Tourette-like events, but unfortunately also the antidepressant benefit. The VC/VS is a complex region that includes several behaviorally relevant white matter tracts and subcortical gray matter structures. Such dense functional and structural diversity could explain how small spatial variations in electrode placement or electric field size and topography may lead to unintended physiological activation of circuits leading to maladaptive behavior, cognition, affect and movement, instead of the intended therapeutic adaptive effects. This case highlights the critical importance of a careful understanding of the patient-specific functional anatomy of DBS targets and the use of individualized strategies guided by imaging, physiology, or both for target selection, not only to optimize efficacy but also to avoid complications. Complications which, in functional neurosurgery, are not always traditional surgical side-effects such as bleeding, infection, trauma, etc., but can also result, like in our patient and others (Widge et al., 2016), from the maladaptive activation of behaviorally-relevant nodes and circuits.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Partners Healthcare IRB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JAC and DDD led the clinical management. TC analyzed the PET data. JAC wrote the main draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Intraoperative Characterization of Subthalamic Nucleus-to-Cortex Evoked Potentials in Parkinson's Disease Deep Brain Stimulation

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a clinically effective tool for treating medically refractory Parkinson's disease (PD), but its neural mechanisms remain debated. Previous work has demonstrated that STN DBS results in evoked potentials (EPs) in the primary motor cortex (M1), suggesting that modulation of cortical physiology may be involved in its therapeutic effects. Due to technical challenges presented by high-amplitude DBS artifacts, these EPs are often measured in response to low-frequency stimulation, which is generally ineffective at PD symptom management. This study aims to characterize STN-to-cortex EPs seen during clinically relevant high-frequency STN DBS for PD. Intraoperatively, we applied STN DBS to 6 PD patients while recording electrocorticography (ECoG) from an electrode strip over the ipsilateral central sulcus. Using recently published techniques, we removed large stimulation artifacts to enable quantification of STN-to-cortex EPs. Two cortical EPs were observed – one synchronized with DBS onset and persisting during ongoing stimulation, and one immediately following DBS offset, here termed the "start" and the "end" EPs respectively. The start EP is, to our knowledge, the first long-latency cortical EP reported during ongoing high-frequency DBS. The start and end EPs differ in magnitude ($p < 0.05$) and latency ($p < 0.001$), and the end, but not the start, EP magnitude has a significant relationship ($p < 0.001$, adjusted for random effects of subject) to ongoing high gamma (80–150 Hz) power during the EP. These contrasts may suggest mechanistic or circuit differences in EP production during the two time periods. This represents a potential framework for relating DBS clinical efficacy to the effects of a variety of stimulation parameters on EPs.

Keywords: electrocorticography, deep brain stimulation, evoked potential, subthalamic nucleus, Parkinson's disease, high-frequency stimulation

INTRODUCTION

High-frequency deep brain stimulation (DBS) in the subthalamic nucleus (STN) has been commonly used to treat symptoms of advanced Parkinson's disease (PD) since the late 1990s (Wichmann and DeLong, 2016), but its basic mechanisms remain debated. Pathophysiology of PD at the cortical level, particularly the primary motor cortex (M1), is well-established from electroencephalography (EEG) and electrocorticography (ECoG) recordings of PD patients and includes high-amplitude beta oscillations (Mallet et al., 2008; Crowell et al., 2012) and tight phase-amplitude coupling between beta and gamma frequencies (De Hemptinne et al., 2013). Some studies have observed reduction of these pathological oscillations with clinically effective DBS (Kühn et al., 2008; De Hemptinne et al., 2015), suggesting that such abnormal activity is suppressed by STN stimulation. However, our understanding of basal ganglia-cortical interactions, their role in PD, and how they are altered by DBS is limited, and these observations have not yet contributed significantly to clinical treatment (Devergnas and Wichmann, 2011).

The structural and functional circuits connecting the basal ganglia and the cortex are classically grouped into three pathways – the direct, indirect, and hyperdirect pathways. Of these, STN DBS may directly modulate the latter two (Wichmann and DeLong, 2016). The indirect pathway is a cortico-basal ganglia-thalamo-cortical loop that connects the primary input structure of the basal ganglia, the striatum, to the primary output structure, the internal segment of the globus pallidus (GPi), via the external segment of the globus pallidus (GPe) and the STN. From the GPi, the pathway then projects through motor areas of the thalamus to feed back on the motor cortex (Wichmann and DeLong, 2016). The hyperdirect pathway consists of fibers descending from motor cortical areas directly to the STN (Monakow et al., 1978; Miocinovic et al., 2018).

The ascending portions of these circuits are implicated in both the pathophysiology of PD and the therapeutic efficacy of DBS. Many hypotheses exist as to how high-frequency stimulation affects the output of the basal ganglia and how these changes improve PD symptoms (Devergnas and Wichmann, 2011). The "informational lesion" hypothesis posits that DBS activates outgoing axons of the STN, thus preventing the transmission of pathological basal ganglia activity to the cortex without disrupting the structural connectivity (Grill et al., 2004). The "selective filter" hypothesis suggests a more limited disruption that leaves some functional information transmission between STN and cortex intact while specifically blocking high amplitude, low frequency activity patterns from the basal ganglia (Agnesi et al., 2013; Zimnik et al., 2015), leading to an overall enhancement of activity in cortico-basal ganglia-thalamo-cortical loops (Fukuda et al., 2002). A third, increasingly popular hypothesis suggests that DBS disrupts pathological synchrony within the basal ganglia, thus disrupting abnormal cortical oscillations and phase-amplitude coupling entrained and propagated through cortico-basal ganglia-thalamo-cortical loops (De Hemptinne et al., 2015; Wilson and Moehlis, 2015). Further exploration of the functional impacts of STN stimulation on cortical physiology could help elucidate subtle differences between these theories.

An extensive literature has explored evoked cortical activity (e.g., EEG, ECoG) in response to single stimulation pulses in the STN (Devergnas and Wichmann, 2011). Both short- and long-latency evoked potentials (EPs) are observed at the cortex after single stimulation pulses in the STN and GPi (Devergnas and Wichmann, 2011). The short-latency (∼2–10 ms) EPs elicited by STN stimulation are temporally consistent with antidromic activation of the hyperdirect pathway, implying this circuit may be activated and/or modulated by DBS (Miocinovic et al., 2018). Longer latency (18–25 ms or longer) EPs are thought to reflect multisynaptic, orthodromic transmission through the indirect pathway (Ashby et al., 1999; Devergnas and Wichmann, 2011). While the exact significance of these EPs remains debated, it is thought that they reflect changes in cortical excitability in response to STN stimulation (Ashby et al., 1999).

One limitation of these subcortical-to-cortical EP studies is that they typically look at responses to single DBS pulses, delivered at a low frequency (typically 5–30Hz) to allow for long-latency responses uninterrupted by further stimulation pulses, which would also introduce stimulation artifacts that could obscure cortical signals (Devergnas and Wichmann, 2011). However, low frequency stimulation of STN is typically ineffective at treating symptoms of PD (Wichmann and DeLong, 2016). To better understand how therapeutic DBS impacts cortical activity, a characterization of cortical evoked activity in response to high-frequency (>100 Hz) stimulation is necessary.

This study begins to address this gap in our understanding of the functional subcortical-cortical interactions at play in high-frequency STN DBS. We combine ECoG in an intraoperative setting and a recently published artifact removal method that *post hoc* subtracts artifacts from recordings (Caldwell et al., 2020) to reveal physiological signals during ongoing DBS. We then examine cortical EPs during and immediately after trains of high-frequency stimulation that resemble clinical DBS protocols.

MATERIALS AND METHODS

Subjects

Six subjects (6 M, ages 63–77) undergoing clinical STN implantations for DBS underwent additional, temporary placement of unilateral or bilateral subdural ECoG strips and intraoperative DBS for research purposes. All research methods were conducted in accordance with a University of Washington Institutional Review Board-approved protocol with informed consent obtained from participants. Of the 6 patients, 4 received bilateral DBS implants, 1 received only a right implant, and 1 received only a left implant. The ECoG strip was placed ipsilaterally to the electrode used for stimulation (4 left, 2 right). One patient (Subject 4) was bilaterally implanted with ECoG strips, but only the strip ipsilateral to stimulation (right) was analyzed. Subject demographics, implant information, and medications are summarized in **Table 1**.

For several reasons, we did not seek to directly examine data in relation to the therapeutic effects of DBS for

TABLE 1 | Subject demographics.

	Age	Sex	Preoperative PD medication	Disease duration	Implant hemisphere	Recording hemisphere
Subject 1	77	M	Carbidopa-levodopa	11 years	Bilateral	L
Subject 2	76	M	Carbidopa-Levodopa; Entacapone	20 years	L	L
Subject 3	69	M	Pramipexole; Carbidopa-Levodopa; Rasagiline	5 years	R	R
Subject 4	71	M	Carbidopa-Levodopa; Rasagiline; Ropinirole	8 years	Bilateral	R
Subject 5	63	M	Carbidopa-Levodopa	35 years	Bilateral	L
Subject 6	78	M	Carbidopa-Levodopa	5 years	Bilateral	L

individual subjects due to limited and/or inconsistent clinical follow-up data: (1) Not all patients underwent DBS programming at the University of Washington, making it difficult to obtain accurate records with extensive mapping of clinical response, (2) Patients that we do have records for were often assessed using monopolar or novel stimulation configurations, rather than the bipolar configuration used here, and (3) In at least one subject, the clinical team re-positioned the DBS electrodes after the research team collected data.

Clinical Procedures for DBS and ECoG Placement

All patients were under total intravenous anesthesia as well as PD medication (see **Table 1**) for the duration of the implantation and research protocols. Once in the operating room and deeply anesthetized, patients' heads were fixed at three points using a skull clamp and long DORO Transitional Member Radiolucent headrest system (Pro Med Instruments GmbH). After affixing bone fiducials (Medtronic Inc.) to the skull, a pre-implant CT scan was obtained (see below) and registered to a pre-operative MRI using FrameLink (Medtronic Inc.). The co-registered imaging was used to form a surgical approach plan to the STN (unilaterally or bilaterally, as described above). A Stimloc burr hole cover (Medtronic Inc.) was secured to the skull and the dura mater was opened widely in a cruciate fashion over the hemisphere(s) where the ECoG strip(s) was to be placed. An eight contact macro-scale ECoG strip (2.3 mm diameter exposed surface per electrode, 1 cm inter-electrode spacing, Ad-Tec Medical Instruments Corp.) was slipped underneath the dura posteriorly, parallel to the midline, so as to approximately cross the hand/upper extremity region of primary motor cortex. A Nex-Frame frameless stereotactic system (Medtronic Inc.) was then positioned and DBS lead (1.5 mm inter-contact spacing, Medronic Inc., model 3387) placement continued as previously described (Herron et al., 2017). A second, post-implant CT was then acquired in order to confirm the position of the DBS lead. This CT was subsequently used to localize surface ECoG electrodes. For one subject (Subject 2), the clinical team repositioned the DBS lead three times in response to imaging examination, but only recordings obtained with the original implant position were analyzed. See **Figure 1** for positions of ECoG (**Figure 1A**) and DBS (**Figure 1B**) electrodes for all subjects.

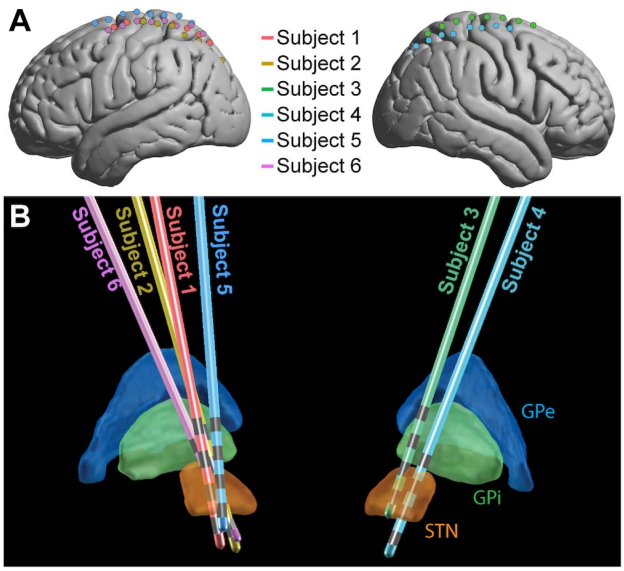

FIGURE 1 | Electrode placement. ECoG **(A)** and DBS **(B)** electrode locations shown for the 6 subjects in MNI space. For ECoG strips, electrode 1 was the most posterior and electrode 8 was the most anterior. The 4 gray bands on each DBS contact **(B)** represent the contacts, with electrode 0 the deepest and electrode 3 the most superficial (Medtronic naming conventions). GPe, globus pallidus external segment; GPi, globus pallidus internal segment; STN, subthalamic nucleus.

Intraoperative Stimulation and Recording

All stimulation and recording for research purposes was performed with a Tucker David Technologies (TDT, Alachua, Florida, United States) acquisition system. A TDT IZ2H-16 stimulator with LZ48-400 battery pack was used to stimulate through DBS electrodes, and both STN and cortical electrodes were recorded using a System 3 RZ5D and PZ5 Neurodigitizer. A scalp EEG electrode was used as a reference for all recordings. No stimulation parameters used in this study exceeded a charge density of 60 $\mu C/cm^2$/phase to ensure patient safety and avoid tissue damage (Cogan et al., 2016).

The stimulation protocol delivered a series of high-frequency stimulation trains, each of 180 (n = 4) or 185 (n = 2) Hz. Each train was 0.5 s in duration with an inter-train interval of 2.5 s (**Figure 2A**). Stimulation pulses were monophasic and delivered in bipolar configurations between contacts on the DBS electrodes, with pulse widths of 60 μs. 60 stimulation bursts were delivered in

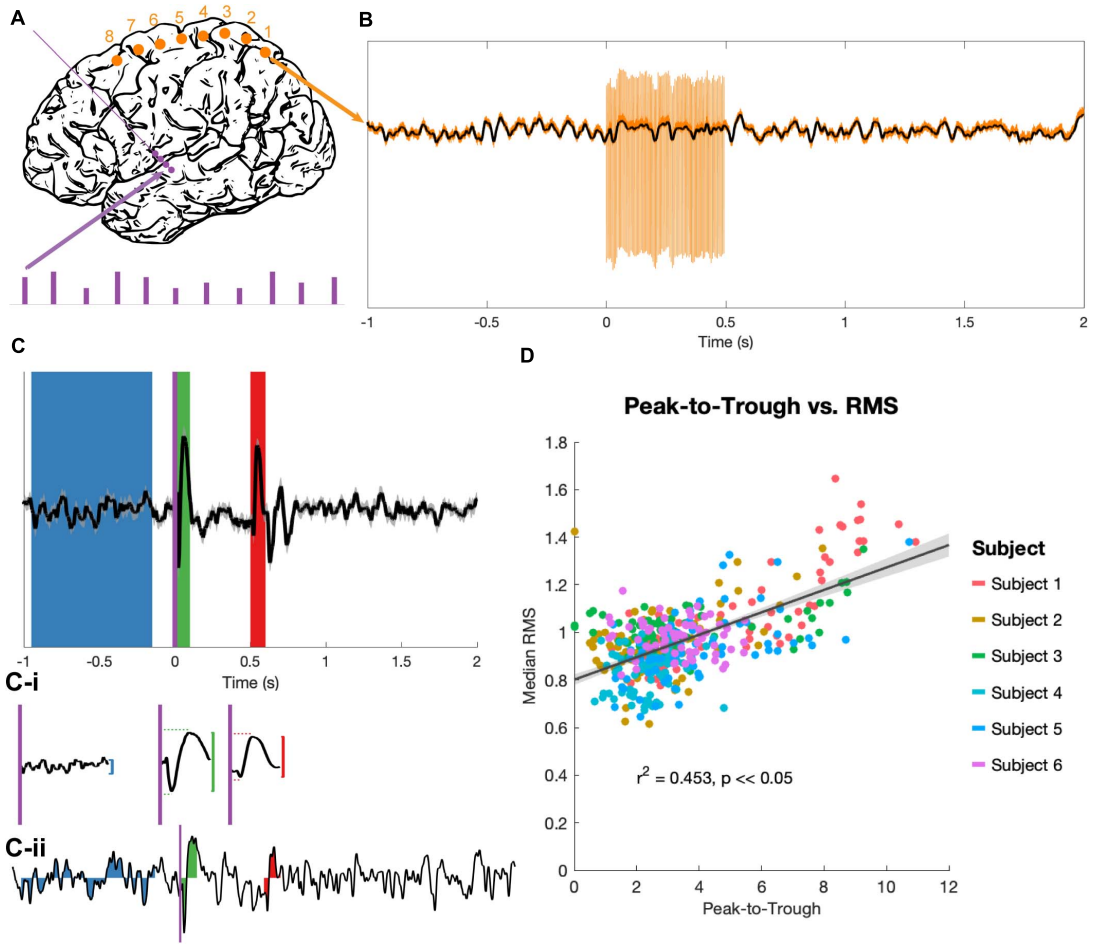

FIGURE 2 | Stimulation and evoked potential measurement. **(A)** Monophasic stimulation was delivered in a bipolar configuration to DBS electrodes (purple dots). Stimulation occurred in 5 s bursts at 4 amplitudes (purple bars), though only EPs evoked by 3 V stimuli were analyzed. Signals were recorded at cortical electrodes (orange dots). **(B)** Raw trial (orange) shows stimulation artifacts, which were removed by an unsupervised dictionary-based learning algorithm (black). **(C)** The average of 30 trials (top trace, ±SEM, z-scored) was used to identify EPs. A long baseline period (blue) prior to stimulation onset (purple vertical line) and the 100 ms windows immediately after stimulation onset (t = 0 s, green) and offset (t = 0.5 s, red) were the regions of interest. The peak-to-trough amplitude was computed for each period (vertical red and green lines), as well as the latency to peak and trough components for the two EPs (horizontal red and green dashed lines, **C-i**). The RMS amplitude was extracted for these time periods for each z-scored individual trial (example trial shown in **C-ii**). **(D)** The peak-to-trough of the average trace and the median RMS of all trials (separate medians for the start and end EPs) were highly correlated across subjects in a non-parametric test (generalized linear model in black with confidence intervals in gray, r^2 and p from Spearman correlation).

blocks to each consecutive bipolar configuration on the DBS lead (0–1, 1–2, 2–3), with trains divided evenly among 4 voltage levels (determined individually for each subject based on the trained clinical team's [AK] recommendations). Each DBS electrode pair was tested in both possible bipolar configurations (i.e., anodic first and cathodic first), for a total of 360 bursts per subject. Only the 90 of these bursts delivered at 3 V (the highest stimulation voltage that all subjects had in common) were considered for analysis, yielding 30 bursts per DBS electrode pair. While DBS stimulation was delivered, recordings were obtained from the 8 cortical strip electrodes at 48 kHz.

Imaging and Electrode Localization

Preoperative clinical Magnetic Resonance Imaging (MRI) and intraoperative Computerized Tomography (CT) were used for electrode localization and anatomical computations. A Philips 3T Achieva scanner with a standard 8 channel SENSE head coil was used to acquire high-resolution 3D T1 magnetization prepared rapid gradient echo (MRPAGE) sequence (repetition time (TR)/echo time (TE)/flip angle: 4.17/51/8°). Slice thickness was 0.750 mm, and the scan included 640 × 640 FOV matrix with 214 overlapping slices, resulting in in-plane resolution of 0.4 × 0.4 mm^3. Intraoperative CT scans were acquired on a CereTom scanner (NeuroLogica Inc.), resulting in a 512 × 512 × 88 matrix and an in-plane resolution of 0.5 × 0.5 mm with 1.25 mm slice thickness.

The MRI and CT were co-registered using a standard affine transform in Freesurfer (http://surfer.nmr.mgh.harvard.edu/) and surface electrodes were manually identified. The electrode coordinates were then transformed into 152MNI space

(1 × 1 mm). Brodmann areas were determined manually using an MNI-based atlas.

LEAD-DBS (Horn and Kühn, 2015) was used to localize DBS electrodes on co-registered MRI and CT scans and project them into MNI space. The DISTAL atlas (Ewert et al., 2018) was used in LEAD-DBS to visualize the location of electrodes relative to the thalamus and STN (**Figure 1**).

Data Pre-processing

For EP analysis, minimal pre-processing was used in an attempt to preserve the shape and latency of the complex, multiphasic responses. No re-referencing was performed, as many (if not all) cortical electrodes in each subject exhibited simultaneous EPs of different sizes but similar shapes, so bipolar or common average referencing would have reversed the polarities of some of these EPs. EPs were averaged over trials during the periods of interest.

The collected time-series data were first segmented into 2.5 s epochs, each containing 1 s of rest, 0.5 s of stimulation, and another 1.5 s of rest. Epochs were then run through an unsupervised, dictionary-based artifact rejection pipeline as previously described (Caldwell et al., 2020) (**Figure 2B**). Briefly, this clusters each ECoG channel's artifacts based on shape to create a dictionary, matches each individual artifact to its closest dictionary entry, and subtracts a scaled version of this template from the trace to flatten the artifact and approximate the underlying signal. Residual artifact (which was minimal) and additional high-amplitude spike-like noise (not uncommon in the intra-operative setting) lasting less than 0.5 ms were removed and the resulting gaps were linearly interpolated. Each trial was then visually examined, and trials with remaining high-amplitude noise were removed. An average of 1.67/90 trials were removed per subject.

After artifact removal, time-series epochs were lowpass filtered at 200 Hz using a fourth order Butterworth filter and down-sampled by a factor of 8, for an ultimate sampling rate of approximately 6 kHz. 60 Hz line noise and harmonics were removed with fourth order Butterworth notch filters. Finally, the data were baseline corrected by subtracting the mean voltage of a 0.5 s period before the start of each stimulation burst.

Evoked Potential Analysis

90 stimulation trains delivered at 3 V were processed for each subject, then grouped by bipolar stimulation pair. Average EPs from the 30 traces for each recording pair and stimulation condition were calculated (for example, see **Figure 2C**). The 100 ms period immediately following stimulation onset (t = 0 to 0.1 s) and the 100 ms period immediately following stimulation offset (t = 0.5 to 0.6 s) were extracted as the "start" and "end" EP windows respectively. For statistical contrast, an 800 ms period prior to burst onset (t = −0.95 to −0.15 s) was defined as a baseline. A z-transform over the entire EP period was used to standardize amplitudes across subjects, then the largest amplitude difference between a consecutive peak-to-trough or trough-to-peak pair was taken ("peak-to-trough measure," **Figure 2C-i**). The latencies between the start of the EP period (stimulation onset or offset) and the positive and negative peaks were also noted.

Individual trials were too variable to get a reliable peak-to-trough measure, so the root mean square (RMS) of the EP was used to quantify deflection from the zero for individual trials (Prime et al., 2017; Shimada et al., 2017). RMS values of the z-scored trials were computed for the three time windows identified above (**Figure 2C-ii**). Because RMS is an average-based measure, having a longer baseline period did not inflate the values as compared to the EP periods, and a longer baseline allowed for a more stable estimate of "baseline" activity despite high trial-to-trial variability.

Spectral Analysis

Low gamma (30–80 Hz) and high gamma (80–150 Hz) power series were also constructed for each artifact-free trial, following the pre-processing steps described above. Fourth order Butterworth bandpass filters for the low and high gamma frequencies were applied to individual trials, then the square of the analytical amplitude from the Hilbert transform was taken as power time series. These were then baseline normalized to a period 0.5 to 0.1 s prior to stimulation onset using a z-transform (the median rather than the mean was used for the average because of the unstable baseline) to correct 1/f scaling. Using this baseline rather than the 800 ms baseline used in EP analysis allowed us to better avoid edge artifacts, leaving a 500 ms buffer on the front end of each trial. The median of the gamma-filtered series was taken over each set of trials to construct a single power series for each stimulation-recording electrode pair.

Statistics

To identify non-zero EPs, the distributions of RMS measures for each trial of the EP period were compared to the RMS distribution of the corresponding trial's baseline using a non-parametric, paired (signed rank) test. EPs that differed significantly ($p < 0.05$, FDR-corrected) from the baseline period were counted as "significant EPs" The median RMS of all trials for each significant EP, along with the latency values recorded from the average trace, was contrasted between the two EP periods using a non-parametric, unpaired (Wilcoxon rank-sum) test (significance cutoff of $p < 0.05$, FDR corrected).

RMS and latency values were then split by the Brodmann area (BA) of the corresponding cortical electrode. Only BAs with consistent coverage among subjects (1/2/3, 4, 6, and 7) were included in these analyses, although values for all other BAs (19, 39, 40) were pooled together and shown for transparency. Evoked activity for all recording electrodes and stimulation conditions, not just significant EPs, were included in this analysis. The start and end EP values for each metric were compared within each BA using Wilcoxon rank-sum test, and then the effect of BA on each metric within the start and end EPs was determined using a non-parametric, one-way analysis of variance (Kruskal-Wallis test). For metrics and EPs for which a significant ($p < 0.05$, FDR-corrected) effect was detected, *post hoc* testing (using MATLAB's *multcompare* command) was performed to reveal significant differences between individual BAs.

A mixed linear model was used to assess the relationships between high and low gamma and EP magnitude (RMS), adjusting the intercept and slope for random effects of subject on

EP and spectral data. From the high and low gamma power series for each stimulation-recording electrode pair (3 stimulation electrodes and 8 recording electrodes for 24 pairs per subject, see Section 2.7), the median power during the start (0–0.1 s after stimulation onset) and end (0.5–0.6 s after stimulation onset) EP periods was extracted. This was regressed against the median RMS over all trials for each stimulation-recording electrode pair. We adjusted our model to control for random effects of subject on EP RMS and gamma power.

RESULTS

After removing stimulation artifacts from cortical recordings obtained during DBS, we quantified EPs during ongoing stimulation and compared them to EPs following stimulation offset.

Measures of EPs

The peak-to-trough measurement of the average EP (computed from the average of 30 trials) and the RMS measurement of the same EP (the median of the RMS measures over the same 30 trials) correlated tightly ($r^2 = 0.453$, $p < 0.05$; **Figure 2D**). Because the RMS provides a magnitude distribution rather than a single magnitude value for each EP, it was used as the primary measure of EP size for all statistics.

Characterizing Start and End EPs

23/90 and 21/90 stimulation conditions produced EPs during the first 100 ms of stimulation and immediately following stimulation offset, respectively, that differed significantly from baseline (**Figures 3A,B**). Start EPs were observed in only two subjects, with the majority (∼75%) seen in Subject 1. Conversely, at least one significant end EP was observed in 5/6 subjects. Most EPs (start and end) had a characteristic biphasic shape with a narrow negative deflection followed by a longer positive deflection (**Figure 3E**). We noted similar features in other stimulus-triggered averages during the start and end windows that did not meet the statistical criteria. For example, Subject 3, channel 7, stimulation condition 2-3 and Subject 5, channel 6, stimulation condition 1-2 may have small start and end EPs respectively.

No discernable pattern was seen connecting the location of the stimulated electrodes to any features of the EPs. Of the 12 cortical electrodes with significant start EPs, 8 had significant EPs in more than one stimulation configuration, while 11/16 cortical electrodes had significant end EPs in multiple conditions. 9 cortical electrode-STN stimulation site pairs had significant start *and* end EPs.

Among the significant EPs, the magnitude (as measured with RMS) of start EPs were significantly larger than that of end EPs (median start RMS = 1.38, median end RMS = 1.18, $p = 0.018$; **Figure 3C**). Additionally, relative to stimulus onset and offset respectively, the positive deflection of start EPs occurred significantly later than that of end EPs (median start latency = 61.19 ms, median end latency = 44.56 ms, $p = 2.32e\text{-}4$; **Figure 3D**). No significant difference in negative deflection latency was observed between EPs, although there was a trend toward the start EP having a shorter latency to the negative deflection (median start latency = 23.51 ms, median end latency = 23.27 ms, $p = 0.055$ **Figure 3D**). This was likely driven by the much greater degree of variability in this latency for the end EP.

EPs by Brodmann Area

BA1/2/3 (primary sensory cortex, S1), BA4 (primary motor cortex, M1), and BA6 (premotor and supplementary motor areas, PMA/SMA) all had a >10% chance of producing a significant start and/or an end EP in response to STN stimulation (**Figure 4A**). All subjects had one or more electrodes on each of these BAs. BA7 (visuo-motor coordination area) also had a relatively high likelihood of producing a start EP and a non-zero likelihood of producing an end EP. In other BAs represented (BA19, associative visual area; BA 39, angular gyrus; and BA40, supramarginal gyrus – areas not primarily associated with sensorimotor function), no start EPs and few end EPs were elicited that differed significantly from baseline. The averages of significant EPs (**Figure 4E**) was generally similar between BAs, following the overall patterns seen in **Figure 3E**. The exception was in BA6, where the characteristic biphasic EP shape was less clear.

Within individual BAs, RMS and deflection latencies of start and end EP periods were not statistically distinct, despite the overall differences seen in the pooled EPs, except in one case – in BA 7, the positive deflection of the start EP occurred significantly later than that of the end EP (median start latency = 42.02 ms, median end latency = 38.01 ms, $p = 0.0034$; **Figures 4B–D**). Across BAs, there was a significant effect on both the positive ($p = 6.4204e\text{-}5$) and negative ($p = 0.0043$) latency of the end EP only. *Post hoc* testing revealed that this was driven by statistical differences between BAs 6 (median negative deflection latency = 55.87 ms, median positive deflection latency = 38.01 ms) and 7 (median negative deflection latency = 29.25 ms, median positive deflection latency = 55.13 ms) in the case of both the negative ($p = 0.0026$) and positive ($p = 2.3087e\text{-}5$) deflections. These data are summarized in **Table 2**.

High and Low Gamma Power During EPs

Using a linear mixed effects model with subject as a random variable, we tested the relationship between low and high gamma power with RMS during the start and end EP windows. Statistically significant relationships were observed between low gamma power during the 100 ms EP windows and magnitude of both the start (slope = 2.56, $p = 2.56 \times 10^{-4}$) and end (slope = 6.875, $p = 0.00217$) EPs (**Figures 5A,B**). High gamma power during the same windows correlated significantly with the magnitude of the end (slope = 3.199, $p = 5.88 \times 10^{-9}$), but not the start (slope = 1.405, $p = 0.0547$) EP (**Figures 5C,D**).

DISCUSSION

With acute, intraoperative subdural ECoG implants, we measured evoked potentials and power spectra at a number of

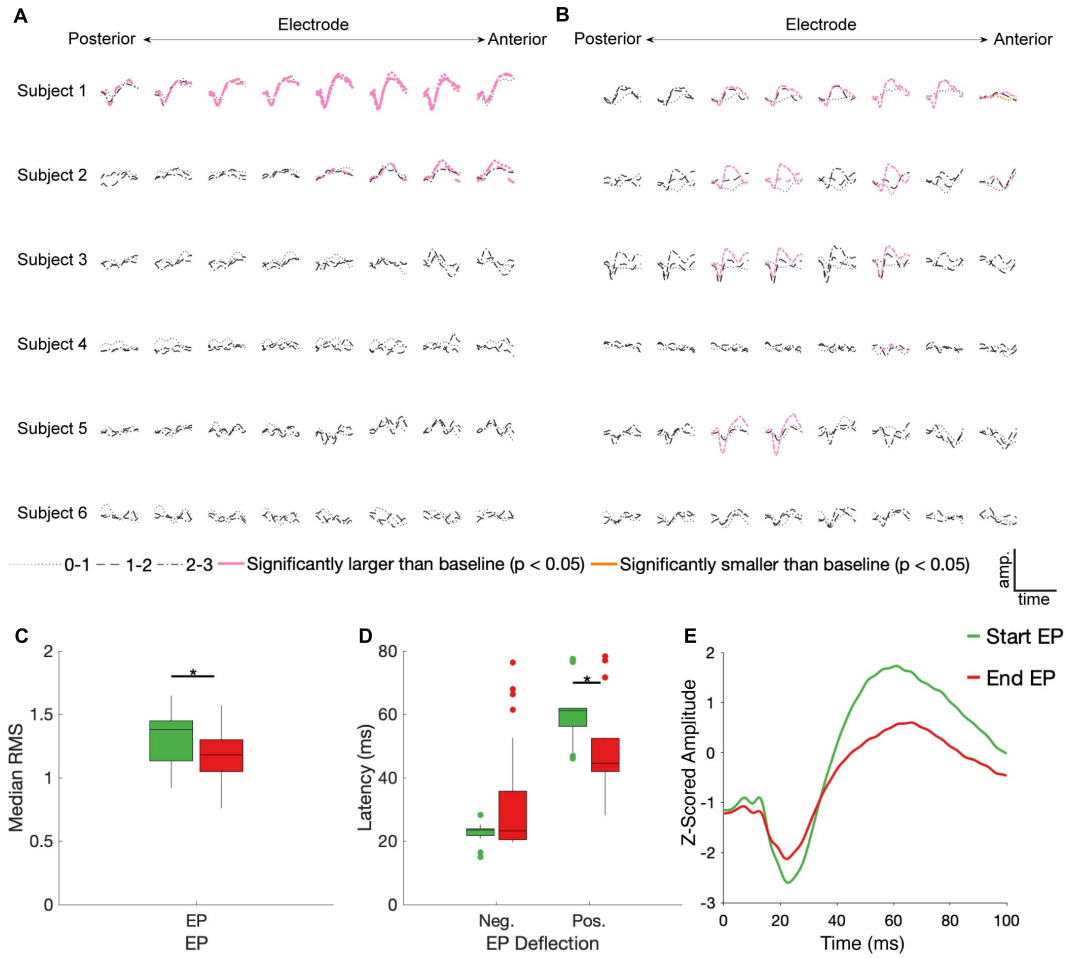

FIGURE 3 | STN DBS evokes start and end EPs. Z-scored start **(A)** and end **(B)** EPs (average of 30 trials) are shown for each electrode (columns, contacts were in different BAs for each subject – see **Figure 1**), subject (rows), and DBS stimulation electrode pair (line type). EPs in pink had a statistically significantly larger magnitude than baseline deviations ($p < 0.05$, FDR corrected by subject). The one trace in yellow was also statistically different than baseline, but it had a lower magnitude. Median RMS **(C)** and latencies to negative and positive deflections on the average traces **(D)** were compared between the start and end EPs; significant ($p < 0.05$, FDR corrected) differences indicated by stars. **(E)** The average of all significant start (green) and end (red) EPs.

cortical sites in response to high-frequency stimulation of the STN in PD patients. After reliable removal of the stimulation artifact (Caldwell et al., 2020), we observe two distinct responses that resemble canonical subcortico-cortical EPs – one during the first 100ms of a high-frequency, 500 ms stimulation train ("start EP") and one during the 100ms immediately following the offset of these trains ("end EP"). This provides additional characterization of EPs in cortex during ongoing, continuous and clinically relevant DBS. Within the framework of classic informational lesioning or transmitter depletion theories of STN DBS, the novel end EP may be indicative of a "rebound" in cortical activity after high-frequency DBS is turned off.

Responses at the cortex in response to high frequency STN DBS have previously been reported in EEG (Baker et al., 2002), but have not been quantified due to lack of sufficient artifact removal techniques. Although Baker and colleagues noted slow wave oscillations during stimulation artifact of 100ms of stimulation, their primary focus was on slower EPs that occurred after termination of the stimulation artifact (Baker et al., 2002). Our observed deflections during ongoing stimulation are more pronounced than previously reported. This discrepancy potentially may be due to a closer proximity to the dipole source and resulting higher fidelity of ECoG recordings with respect to EEG. It is unclear whether the slow oscillations (∼140–230 ms after stimulation onset, or ∼40–130 ms after stimulation offset) in the EEG is similar to the end EPs described here. Although there is some overlap in the time window, the first component of the observed end EP is still faster than the earliest component reported by Baker et al. More work is necessary, including varying the length of stimulation period, to elucidate these discrepancies.

The start and end EPs are grossly similar in shape (i.e., wave morphology) and are consistent with previously reported subcortico-cortico EPs (Hartmann et al., 2018; Miocinovic et al., 2018). We do, however, note some quantitative differences between the two EPs. The start EPs tend to be larger and longer than the end EPs. Additionally, start EP magnitude correlates

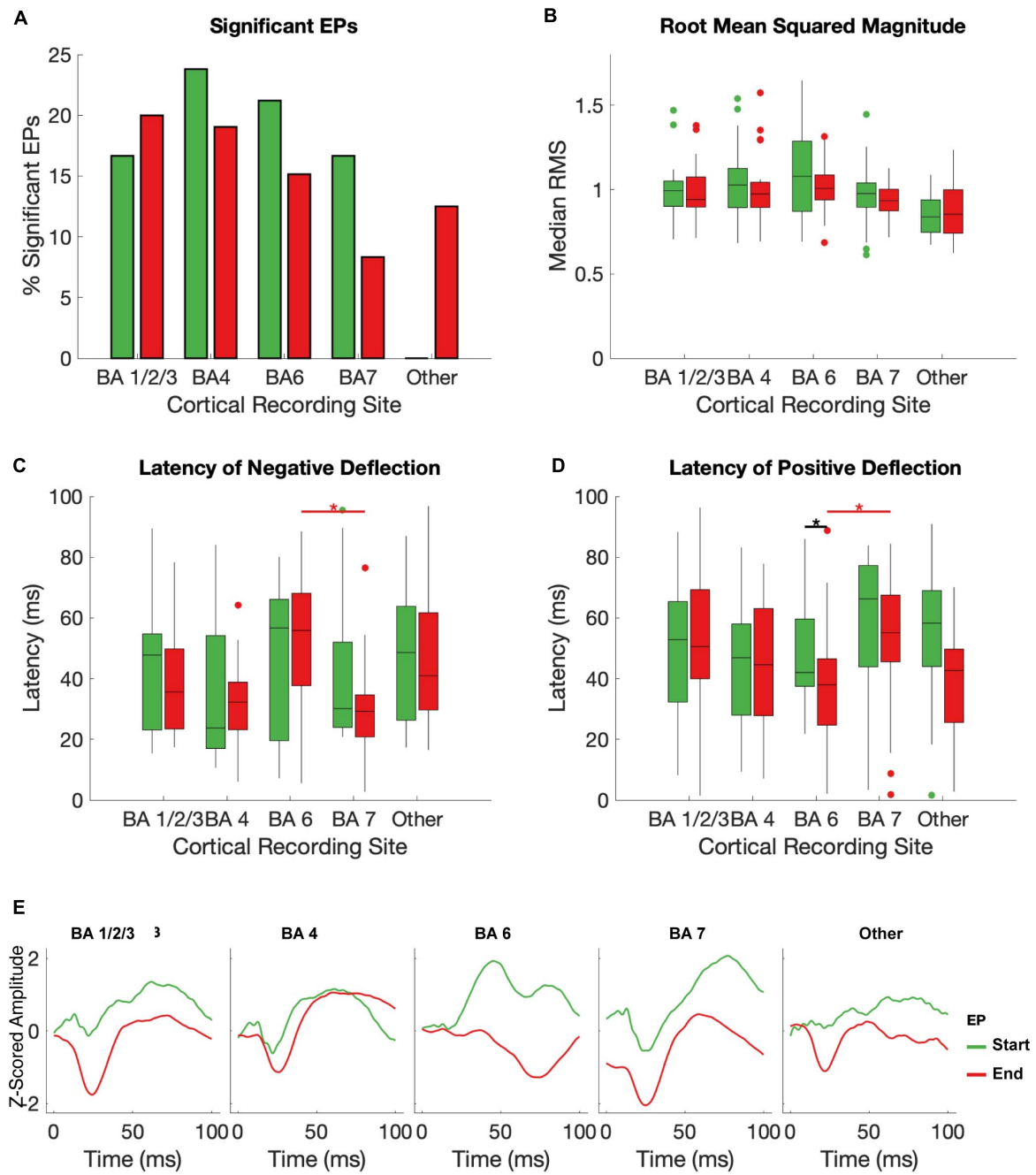

FIGURE 4 | Effects of brodman Area on EPs. The median RMS **(A)**, percent of EPs that differed significantly from baseline amplitudes **(B)**, latency to negative deflection **(C)**, and latency to positive deflection **(D)** were compared between start and end EPs with recording electrodes grouped by Brodman area across subjects. Brodmann areas with inconsistent coverage across subjects were pooled and shown for comparison but not included in statistical analysis. Black stars indicate significant ($p < 0.05$, FDR corrected) differences between start and end EP measures within each BA. Red stars indicate significant ($p \leq 0.05$, FDR corrected) *post hoc* comparisons between end EPs in different regions after a Kruskal-Wallis test revealed dependence of both latency measures on BA. The mean of all start (green) and end (red) EPs for each electrode in each BA are shown in **(E)**.

with both high and low gamma power, while end EP magnitude correlates only with low gamma power. These differences may be attributed to several unique and/or overlapping possibilities, including, (1) residual DBS artifacts surviving our artifact removal process, (2) evoked responses within distinct pathways and mechanisms, or (3) modulation of EP elements from ongoing high-frequency DBS.

We further note that, consistent with previous DBS studies, medium- to long-latency EPs are seen primarily in cortical areas corresponding to sensorimotor function and integration,

consistent with the signals traveling through known cortico-basal ganglia-thalamo-cortical loops of the indirect pathway. The site of stimulation in relation to the STN did not have a significant effect on EP magnitude or on the likelihood of producing a statistically significant (larger than baseline) EP, which may indicate that current spread within any given bipolar electrode configuration may play a role in the transmission of these signals from the STN to the relevant tracts.

Start vs. End EPs

The EPs we observe immediately following stimulation onset and offset resemble previously described STN-to-cortex EPs in shape and latency – a negative deflection around 20–30 ms and a positive deflection around 40–60 ms following stimulation onset or offset (Hartmann et al., 2018; Miocinovic et al., 2018). These canonical EPs are observed in ECoG (Miocinovic et al., 2018), magnetoencephalography (Hartmann et al., 2018), and electroencephalography (Walker et al., 2012). Their timing is consistent with orthodromic, multisynaptic transmission (Walker et al., 2012; Hartmann et al., 2018). The circuits through with this occurs are, as of yet, not fully understood, but modeling and experimental evidence have suggested that high-frequency stimulation activates STN efferents to the GPi and/or directly activates pallido-thalamic fibers (McIntyre et al., 2004; Miocinovic et al., 2006), indicating propagation through the indirect pathway.

Our ability to generalize the findings about start EPs is limited because the majority of start EPs (∼75%) were seen in a single subject (Subject 1). Classic EP-like waveforms that did not achieve statistical differences in magnitude over baseline periods were, however, seen in other subjects during both EP periods. Larger sample sizes and ranges of stimulation amplitude and quantification of EP thresholds are clearly needed to determine the relative prevalence of start and end EPs and determine if large, consistent start EPs like those seen in Subject 1 are associated with electrode position, disease process, or any other factors.

Interestingly, we do not see any evidence for short-latency EPs, like those previously reported (Miocinovic et al., 2018), after individual stimulation pulses within a stimulation train. These are generally attributed to antidromic activation of the hyperdirect pathway and have expected latencies of 2–10 ms. With the high frequency (180–185 Hz) stimulation used in this study, responses longer than ∼5 ms would be obscured by the next stimulation pulse in the train, so responses of the expected length may not be visible in our data. More work will need to be done to see if the long-latency start and end EPs have an impact on short-latency EPs following individual stimulation pulses.

Effect of Broadmann Area on EPs

Overall, we observed a greater likelihood of seeing an EP with a significantly larger magnitude than baseline in Brodmann Areas (BAs) associated with sensorimotor function than in any other BAs. This is consistent with the hypothesis that EPs are propagated through motor cortico-basal ganglia-thalamo-cortical loops, of which the STN is a part (McIntyre et al., 2004; Miocinovic et al., 2006; Devergnas and Wichmann, 2011).

TABLE 2 | Start and end EPs by BA.

		BA 1/2/3	BA 4	BA 6	BA 7	Other	*p*-value (Effect of BA, *post hoc* tests for significant effects)
RMS	Start EP	0.993	1.027	1.054	0.976	0.838	0.348
	End EP	0.941	0.974	0.978	0.934	0.854	0.327
	p-value (Start vs. End)	0.309	0.715	0.159	0.414	–	–
Negative deflection latency	Start EP (ms)	47.759	23.757	56.689	30.147	48.579	0.047
	End EP (ms)	35.635	32.276	55.951	29.245	40.960	0.004* BA 1/2/3-4: 0.962 BA 1/2/3-6: 0.0362 BA 1/2/3-7: 0.268 BA 4-6: 0.018 BA 4-7: 0.675 BA 6-7: 2.31×10^{-5}
	p-value (Start vs. End)	0.805	0.903	0.016	0.096	–	–
Positive deflection latency	Start EP (ms)	52.838	46.858	42.844	66.273	58.245	0.312
	End EP (ms)	50.545	44.564	38.093	55.132	42.680	6.42×10^{-6} BA 1/2/3-4: 0.896 BA 1/2/3-6: 0.0485 BA 1/2/3-7: 0.849 BA 4-6: 0.356 BA 4-7: 0.463 BA 6-7: 0.0026*
	p-value (Start vs. End)	0.159	0.715	0.411	0.003*	–	–

*Median RMS (**Figure 4B**) and median latency to negative (**Figure 4C**) and positive (**Figure 4D**) deflections by Brodmann area (BA). For each measure and BA, the p-value from a sign rank test for difference between start and end EP is shown. Additionally, the results of a Kruskal-Wallis test for effects of BA on EPs are given for all measures and for both the start and end EPs. For tests with significant ($p < 0.05$, FDR corrected) values, the p-values obtained from post hoc testing is listed for all pairs of BAs.*

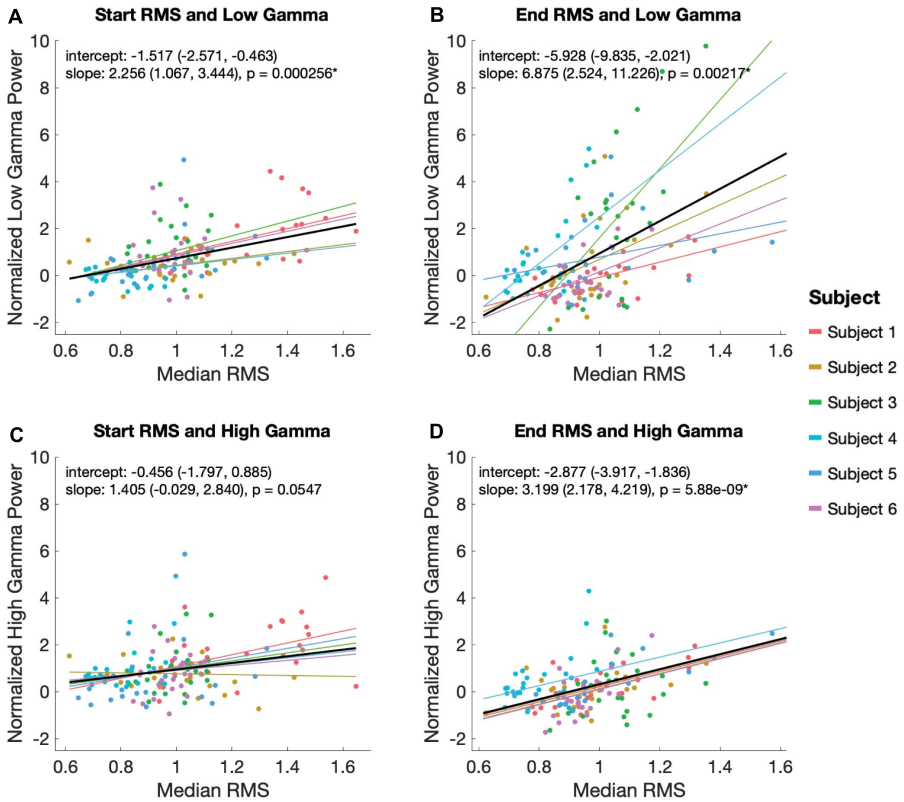

FIGURE 5 | Relationship between EP magnitude and gamma power. A mixed linear model was used to assess the relationship between EP magnitude low (30–80 Hz; **A,B**) and high (80–130 Hz; **C,D**) gamma power during the start **(A,C)** and end **(B,D)** EP intervals. The model controlled for random effects of subject, adjusting for intercept and slope. Each plot shows the model's predicted fits for each subject as well as the overall model in black. Overall model and slope are reported along with 95% confidence intervals.

Magnitude of EPs did not vary significantly with the BAs from which the EPs were recorded, nor did latency to either peak of the start EP. There was a significant effect of BA on end EP peak latencies, which was revealed by *post hoc* testing to be a result of differences between BA6 and BA7. The EPs observed in BA6 are less like the consistent biphasic EPs seen in S1, M1, and BA7, and the start and end EPs have approximately opposite polarities – the positive deflection comes before the negative deflection in the end EP of BA6, whereas negative comes before positive in all other EPs over sensorimotor areas. This polarity shift is responsible for the significant differences seen between start and end latencies within BA6, and likely also contributes to the overall effect of BA on EP latency without greatly impacting EP magnitude.

Relationship Between EP Magnitude and High and Low Gamma Power

In addition to measuring time-locked evoked potentials during the periods immediately following stimulation onset and offset, we also extracted high-frequency power responses. Average low gamma (30–80 Hz) power during both time windows correlated significantly with the magnitude of EPs seen in the same windows, but a similar correlation with high gamma (80–150 Hz) power was only seen for the end EP. The functional distinction of low gamma activity in the cortex is debated. Some reports have associated low gamma power with cognitive function and stimulus dependence (Başar, 2013), while others have found that the lower end of this frequency range more closely resembles canonical beta oscillations in movement-related amplitude modulation (Unterweger et al., 2020). High gamma power is known to correlate tightly to firing rates of local neural populations and is therefore often interpreted as a measure of local activity (Ray et al., 2008). The findings here suggest that the impact of high-frequency electrical stimulation of STN may be associated not only with EP production, but also with higher stimulus-dependent activity – in this case, some variant of motor processing. However, a higher rate of cortical neuronal activity seems unique (with respect to the selected windows used in our analysis) to the period at the end of ongoing high-frequency stimulation. The mechanisms giving rise to observed distinctions in RMS-high gamma power associations between analysis windows are unclear. Among other possibilities, it is conceivable that this association is an effect of DBS entrainment or evoked processing within local circuitry. Additionally, there is a trend in the data toward a relationship between start EP RMS and high gamma power that might reach statistical significance if we had additional trials.

Study Limitations

Many aspects of this study limit our ability to firmly draw conclusions. One limitation is that all subjects were anesthetized for the duration of this study, which has been found to change cortical oscillation patterns and lower evoked potential thresholds. Additionally, due to restricted time with each subject in the operating room, the number of trials we were able to run for each subject was highly limited. Our EPs are the average of only 30 trials, but we expect that we would see similar results but greater consistency if more trials were added, enhancing our statistical power. ECoG EPs are regularly characterized clinically with only 10s of trials, and studies have been published using as few as 20 trials per EP (e.g., Matsumoto et al., 2007; Keller et al., 2014).

As noted previously, our inability to relate our data to clinical follow-up is a significant limitation. Further behavioral work must be performed before the clinical relevance of these findings is established. Our predictions of potential relevance to clinicians are outlined below but are entirely speculative.

Potential Clinical Relevance of EPs in Response to High-Frequency DBS

While DBS is often effective in treating PD, symptom relief varies from patient to patient. Personalizing a DBS treatment plan to fit an individual's needs and best treat their symptoms is a time-consuming process for both clinicians and patients during which multiple stimulation parameters are tuned via behavioral testing. Better understanding how high frequency stimulation affects patterns of transmission between the STN and upstream cortical areas may provide insight into more efficient ways of individualizing therapies. If measurable events at the cortex during ongoing high frequency STN stimulation correlate with therapeutic efficacy of the stimulation parameters, these events could serve as a biomarker to more rapidly test a series of stimulation parameters without exhaustive behavioral testing. Doing this intraoperatively or postoperatively would narrow the parameter space for behavioral testing.

Additionally, better understanding basal ganglia-to-cortex functional connections could contribute to engineering new DBS devices, such as devices that pair cortical recording and/or stimulation with traditional STN stimulation to try to maximize efficacy in all patients. In order to determine how cortical and subcortical devices could work synergistically, we need a quantitative metric of their functional connectivity to test how the neural circuits respond to different types of stimulation. Previous high-frequency STN DBS efforts for example has examined EMGs modulation (Weaver et al., 2020). The EPs we observe during high-frequency DBS may represent the basis for this kind of metric.

CONCLUSION

We demonstrate the existence of two cortical evoked potentials in response to high-frequency stimulation of the STN similar to that used clinically for DBS to treat PD. One EP occurs immediately after stimulation starts and is, to our knowledge, the first long-latency cortical EP reported during ongoing stimulation. A lack of effective artifact removal methods has made measuring activity during continued stimulation difficult up until recently. The second EP occurs after the offset of high-frequency stimulation, and intriguingly suggests some sort of cortical "rebound" when DBS is turned off. Significant further work will be required to elucidate the mechanisms by which these EPs are produced and if and how they are related to the therapeutic efficacy of DBS. Here, we provide a foundation for that work by describing this cortical evoked activity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Washington Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DC, JC, KW, and AK conceptualized and designed the experiment. AK performed all clinical procedures. DC, JC, BH, and KW collected data. LL analyzed the data, with guidance from SP, KW, JH, JO, and AK. LL, SP, KW, JH, JO, and AK interpreted the data. LL prepared the manuscript. SP, KW, JH, JO, and AK edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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