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EDITED AND REVIEWED BY
Michael Denker,
Jülich Research Centre, Germany

*CORRESPONDENCE
Peter A. Tass
✉ ptass@stanford.edu

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Editorial: Neuromodulation using spatiotemporally complex patterns

Peter A. Tass^{1*} and Hemant Bokil²

¹Department of Neurosurgery, Stanford University, Stanford, CA, United States., ²Boston Scientific Neuromodulation, Valencia, CA, United States

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Editorial on the Research Topic

Neuromodulation using spatiotemporally complex patterns

Standard high-frequency deep brain stimulation (DBS) is an established therapy for the treatment of Parkinson's disease (PD) (Lozano et al., 2019). However, there is still a significant clinical need for further improvement, as DBS may cause side effects and its therapeutic effects may be limited, in particular, regarding axial symptoms (Baizabal-Carvallo and Jankovic, 2016; Lozano et al., 2019). The articles in this Research Topic highlight that stimulation with spatiotemporal patterns may engage the nervous system in fundamentally different ways than can be achieved with conventional single-frequency stimulation.

Theta burst stimulation (TBS) was initially developed for transcranial magnetic stimulation, especially to induce long-lasting modulation of motor networks (Huang et al., 2005). Later, this stimulus pattern was also applied to DBS. In a randomized, double-blind, clinical short-term trial, Horn et al. (2020) compared two types of TBS unilaterally delivered to the STN with standard unilateral DBS. Their results demonstrated safety and efficacy in this acute (20-30 min) setting, but no long-lasting aftereffects. Sáenz-Farret et al. (2021) studied safety and efficacy of chronically applied bilateral low intra-burst frequency TBS [as introduced by Horn et al. (2020)] in eight PD and one essential tremor patient. In seven patients TBS had to be discontinued due to side effects. Gülke et al. performed an analogous short-term study to test bilateral STN TBS under the same acute conditions and retrospectively combined their data with the data by Horn et al. (2020). Both unilateral and bilateral STN TBS reduced motor scores, where bilateral TBS did not lead to significant additive benefit. Note that the parameters for TBS used in these studies were not all the same which may explain the differences in results. In particular, Sáenz-Farret et al. (2021) utilized a lower intra-burst frequency and twice the inter-burst period as that used in Gülke et al.

Coordinated Reset (CR) stimulation is a patterned multi-site stimulation technique that was computationally developed to specifically counteract abnormal neuronal synchrony by demand-controlled delivery of stimuli that cause robust desynchronization, thereby overcoming limitations of phase-dependent stimulation (Tass, 2003). Using spike-timing dependent plasticity (STDP) (Markram et al., 1997)

in a variety of neuronal network models, CR stimulation turned out to induce cumulative and long-lasting desynchronizing effects, by inducing an unlearning of abnormal synaptic connectivity (Tass and Majtanik, 2006; Hauptmann and Tass, 2009). These computationally predicted, cumulative and weeks-long stimulus after-effects, very different compared to what was known from standard DBS, were verified in MPTP Parkinsonian monkeys (Tass et al., 2012; Wang et al., 2016, 2022; Bore et al., 2022) and human PD patients (Adamchic et al., 2014). Bosley et al. study the impact of CR-DBS delivered to the STN specifically on impaired gait in MPTP Parkinsonian monkeys. Their results show that CR-DBS can improve Parkinsonian gait. Kromer et al. present a computational model of the STN-GPe circuit and investigate how connectivity changes affect evoked responses and, hence, can be used to probe functional channels in the basal ganglia by means of a suggested two-site stimulation protocol. These results may lead to calibration techniques for CR-DBS enabled by implantable pulse generators that are able to sense.

In their review article, Najera et al. summarize alternative DBS stimulation approaches and their potential clinical applications. By the same token, in a review article, Cota et al. discuss standard and alternative brain stimulation techniques, including non-periodic stimulation. Different plasticity as well as compensatory mechanisms appear to play crucial roles in Parkinson's disease (Blandini et al., 2000; van Nuenen et al., 2012; Madadi Asl et al., 2022). Accordingly, in an opinion article, Asp et al. stress the importance of neuroplasticity as a key target for the development of novel stimulation techniques.

Adaptive deep brain stimulation (aDBS) has a long history, dating back to the 1980s (Krauss et al., 2021). One goal of aDBS is to reduce side effects by reducing stimulation current. In a computational study, Bahadori-Jahromi et al. compare standard DBS with aDBS with amplitude modulation in a cortico-BG-thalamic network. In their model, aDBS outperformed standard DBS with respect to reduction of beta band oscillations, restoring fidelity of thalamic throughput and overall stimulation current.

As shown computationally, properly timed multi-channel and multi-site stimulation can significantly reshape connectivity, thereby inducing long-lasting activity changes (Khaledi-Nasab et al., 2022; Kromer and Tass, 2022; Madadi Asl et al., 2023). Depending on the condition, restoring function may require to up- or down-regulate specific connections within and/or between brain areas and corresponding patterns of synchrony. In an N-of-1 case report study, Omae et al. use amplitude-modulated transcranial alternating current stimulation (AM-tACS) (Witkowski et al., 2016; Negahbani et al., 2018) to enhance low beta phase synchrony between Broca's area and the right homotopic area with the intend to improve language function in a patient with chronic post-stroke aphasia. Favorable electrophysiological outcomes and clinical benefits indicate that this approach deserves further clinical testing.

In mouse models of Alzheimer's disease, entrainment by gamma (40 Hz) rhythmic light flicker enabled to attenuate pathological processes associated with Alzheimer's disease (Iaccarino et al., 2016; Adaiikkan et al., 2019). To computationally study the electrophysiology of gamma flicker entrainment, Wang et al. propose a neural network model for thalamocortical

oscillations (TCOs) and computationally studied the impact of light flicker stimulation with different parameters in dependence on different thalamocortical oscillatory states. They revealed state-dependent stimulus responses that may inform future experiments.

EEG plays an important role in monitoring treatment effects and providing feedback for closed-loop stimulation techniques. Motivated by deep learning and stack generalization theory, Zhang et al. propose a novel method for the recognition of epileptic EEG signals: deep extreme learning machine (DELIM) which consists of several independent, hierarchically aligned extreme learning machine (ELM) modules. They compared DELIM with ELM alone, by applying it to the publicly available EEG data set from the Department of Epileptology at Bonn University, Germany (Andrzejak et al., 2001). In this comparison DELIM outperformed ELM regarding accuracy and computing time.

Modern neuromodulation devices, increasingly capable of complex stimulation patterns, and modern tools for data analysis may pave the way for leveraging the potential of novel patterned and multichannel stimulation approaches for clinical use.

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Conflict of interest

HB is an employee of and owns stock in Boston Scientific.

The remaining author declares 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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