frontiers | Research Topics

Combined therapeutic approaches to neurological rehabilitation

Edited by
Elizabeth Rochon, Carolee Winstein, Gail A. Eskes and Elizabeth Skidmore

Published in
Frontiers in Rehabilitation Sciences

ISSN 1664-8714
ISBN 978-2-88976-469-3
DOI 10.3389/978-2-88976-469-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Combined therapeutic approaches to neurological rehabilitation

Topic editors

Elizabeth Rochon — University of Toronto, Canada
Carolee Winstein — University of Southern California, United States
Gail A. Eskes — Dalhousie University, Canada
Elizabeth Skidmore — University of Pittsburgh, United States

Citation

Rochon, E., Winstein, C., Eskes, G. A., Skidmore, E., eds. (2022). *Combined therapeutic approaches to neurological rehabilitation*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-469-3

Table of contents

frontiers | Frontiers in Rehabilitation Sciences

EDITORIAL
published: 08 June 2022
doi: 10.3389/fresc.2022.918005

Editorial: Combined Therapeutic Approaches to Neurological Rehabilitation

Elizabeth Rochon[1,2]*, *Gail A. Eskes*[3], *Elizabeth R. Skidmore*[4] and *Carolee J. Winstein*[5,6]

[1] Department of Speech-Language Pathology and Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada, [2] Toronto Rehabilitation Institute, The KITE Research Institute, University Health Network, Toronto, ON, Canada, [3] Departments of Psychiatry, Psychology & Neuroscience, Dalhousie University, Halifax, NS, Canada, [4] School of Health and Rehabilitation Sciences, Department of Occupational Therapy, University of Pittsburgh, Pittsburgh, PA, United States, [5] Division of Biokinesiology and Physical Therapy, Herman Ostrow School of Dentistry, University of Southern California, Los Angeles, CA, United States, [6] Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States

Keywords: rehabilitation, neurological disorders, rehabilitation technology, multidisciplinary interventions, motor learning, cognition, communication, pharmacology

Editorial on the Research Topic

Combined Therapeutic Approaches to Neurological Rehabilitation

In this Frontiers special Research Topic we feature studies that combine intervention approaches to leverage improved rehabilitation outcomes in one or more domains. Studies examine varied combinations of neurophysiological, behavioral and pharmacological interventions, to address a range of cognitive, motor, and communication outcomes. Studies span a variety of neurological populations, functional domains, rehabilitation disciplines, and designs. By their very nature, these multi-component interventions all acknowledge the complexity of functional recovery in rehabilitation, while attempting to uncover underlying neurological and behavioral mechanisms of recovery, capitalize on the opportunity for neuroplasticity and maximize rehabilitation outcomes. The studies have implications for both theoretical, mechanistic accounts of experience-dependent neuroplasticity and for new approaches to interventions in rehabilitation. Several themes emerge from the 10 papers in this special issue.

First, researchers are investigating the effects of combining brain stimulation with cognitive or motor treatments to improve outcomes. Pastore-Wapp et al. describe a study protocol in which repetitive transcranial magnetic stimulation (rTMS) will be combined with video-game-based skill training compared to a video-game-based skill training alone condition. The hypothesis is that the combined condition will better improve dexterity in participants with Parkinson's disease in both the short and long term, leading to improvement in activities of daily living and quality of life. Hildesheim et al. review the factors affecting the use of rTMS for enhancing motor recovery post stroke. This group, The Canadian Platform for Trials in noninvasive Brain Stimulation (CanStim) network, aims to advance the use of rTMS to enhance post stroke recovery by encouraging standardized research protocols in clinical and pre-clinical studies. As such, their paper reviews existing clinical trials for demographic, clinical, and neurobiological factors that predict treatment response. Their review highlights several potential predictive factors. It also highlights the high variability in rTMS protocols and study designs and points to the need to better understand a number of factors, including the mechanisms by which rTMS might enhance recovery and the need for a better of understanding of the combinatorial approach. In a case study combining another neuromodulation technique with speech-language treatment, Figeys et al. employ transcranial direct current stimulation (tDCS) paired with script training for a stroke survivor with aphasia. Although they found a large effect size for the script training alone, the addition of tDCS did not improve script accuracy. However, there was a significant change in the rate of script acquisition. This study's careful single subject design and analysis

OPEN ACCESS

Edited and reviewed by:
Shuo-Hsiu Chang,
University of Texas Health Science Center at Houston, United States

***Correspondence:**
Elizabeth Rochon
elizabeth.rochon@utoronto.ca

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *11 April 2022*
Accepted: *20 May 2022*
Published: *08 June 2022*

Citation:
Rochon E, Eskes GA, Skidmore ER and Winstein CJ (2022) Editorial: Combined Therapeutic Approaches to Neurological Rehabilitation. Front. Rehabilit. Sci. 3:918005. doi: 10.3389/fresc.2022.918005

lead the authors to suggest factors that should be considered in the application of tDCS to aphasia therapy and in future research.

Additional studies examined the use of interactive technologies to promote rehabilitation outcomes. Volk et al. investigated the benefit of an intensive combined electromyography and visual feedback training program for patients with postparalytic facial synkinesis. They showed that facial grading was improved by reducing synkinesis and that effects were durable over 6 months. They suggest that these findings warrant a comparison to other approaches in a future randomized controlled trial; further they highlight the importance of incorporating patient-reported outcome measures in future research. In a similar vein, self-reports from stroke survivors and informal caregivers regarding the use of Socially Assistive Robots in physical therapy were collected in focus groups by Dembovski et al.. Several themes emerged from these very rich, qualitative data, that included both similarities and differences between stroke survivors and caregivers regarding the motivational capabilities of robots in therapy, whether robots are seen as replacements or adjuvants to the clinician, as well as aspects related to technical/ personalization of robots.

Another theme evident in several papers in this issue is combinatorial rehabilitation interventions based upon purported coherent functional networks, domains or systems, resulting in improved performance or outcomes. Vangilder et al.'s secondary analysis of clinical trial data shows that global cognition scores in participants with Parkinson's disease predicted follow up performance in an upper extremity motor task. The implications of this proof-of principle study point to the relationship of cognitive to motor deficits in recovery, and it raises the question of which cognitive deficits might be most related to motor abilities and how combinatorial interventions might best be structured. With the aim of targeting both mood and cognition, Sathananthan et al.'s VaLiANT trial combines cognitive rehabilitation with psychological therapy. This protocol paper outlines a Phase II trial to evaluate a multi-domain intervention for individuals with acquired brain injury. The study will evaluate feasibility as well as a primary outcome of wellbeing and several secondary outcomes, such as cognition, mood and quality of life. Two other studies, both targeting word retrieval in aphasia, focus on a combination of content and process in their respective interventions. In another single subject design, Martin et al. contrast the performance patterns in patients who respond differentially to the linguistic component (i.e., words) vs. the processing component (i.e., response delay) of their treatment, suggesting that personalized treatment based upon accurate diagnosis most likely will lead to better outcomes and provides support for models of speech production that incorporate a verbal short-term memory component of word processing. Simic et al. investigate the feasibility and preliminary efficacy of combined working memory training and targeted anomia therapy in individuals with aphasia, showing that this combination treatment is feasible overall and appears to show transfer to communication contexts beyond single word naming. These authors also suggest that further research is warranted regarding the cognitive abilities that are at play in aphasia therapy at different stages of recovery.

Lastly, Plummer et al. combine a pharmacological intervention (dalfampridine) with physical therapy in individuals with multiple sclerosis in their proof-of-concept study. Results showed that physical therapy combined with medication tended to improve walking function (i.e., gait speed) more than when physical therapy was provided alone. The authors conclude that physical therapy that is based upon motor relearning principles, such as was provided in their study, combined with dalfampridine, warrants further investigation.

This special topics issue well illustrates not only the potential merits of combinatorial approaches, but also the diversity of designs ranging from single-subject, focused reviews, detailed protocols, and small-scale single-site to planned multi-site randomized clinical trials, each reflecting the diverse stage of knowledge development and exciting future trajectory in this topic area. The range of article types reflects perhaps the rather early stage of this effort to move research from a silo perspective to a more multidisciplinary conceptual and collaborative one. If carried forward with the care and thoughtfulness of the projects described here, the combined approach is likely to not only promote new knowledge pertaining to neural and behavioral recovery-supportive mechanisms of neuroplasticity, but also promote more feasible application to current multidisciplinary team approaches. This multidisciplinary team of Guest Editors hopes that this special topics issue triggers new and creative conceptual thinking and sound research in this much-needed area of rehabilitation.

AUTHOR CONTRIBUTIONS

ER wrote the first draft of the editorial. GE, CW, and ES contributed to manuscript revision, read and approved the final manuscript. All authors contributed to the conception of the special Research Topic and took individual responsibility for editing separate articles.

Conflict of Interest: CW serves as a member of the DSMB for Enspire DBS Therapy, Inc., and as a member of the DSMB for Syntactx; a consultant for MicroTransponder, Inc. and receives royalty payments from Human Kinetics, Inc. (6th edition of Motor Control and Learning), and Demos Medical Publishers (2nd edition of Stroke Recovery and Rehabilitation). GE has a patent application pending for an intervention for improving cognitive function.

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.

frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 14 October 2021
doi: 10.3389/fresc.2021.746188

Effect of an Intensified Combined Electromyography and Visual Feedback Training on Facial Grading in Patients With Post-paralytic Facial Synkinesis

*Gerd F. Volk[1,2], Benjamin Roediger[1], Katharina Geißler[1,2], Anna-Maria Kuttenreich[1,2], Carsten M. Klingner[2,3], Christian Dobel[1,2] and Orlando Guntinas-Lichius[1,2]**

[1] Department of Otorhinolaryngology, Jena University Hospital, Jena, Germany, [2] Facial Nerve Center, Jena University Hospital, Jena, Germany, [3] Department of Neurology, Jena University Hospital, Jena, Germany

OPEN ACCESS

Edited by:
Carolee Winstein,
University of Southern California,
United States

Reviewed by:
Taslim Uddin,
Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh
Ana Lucila Moreira,
University of São Paulo, Brazil

***Correspondence:**
Orlando Guntinas-Lichius
orlando.guntinas@med.uni-jena.de

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: 23 July 2021
Accepted: 21 September 2021
Published: 14 October 2021

Citation:
Volk GF, Roediger B, Geißler K, Kuttenreich A-M, Klingner CM, Dobel C and Guntinas-Lichius O (2021) Effect of an Intensified Combined Electromyography and Visual Feedback Training on Facial Grading in Patients With Post-paralytic Facial Synkinesis. Front. Rehabilit. Sci. 2:746188. doi: 10.3389/fresc.2021.746188

Background: There is no current standard for facial synkinesis rehabilitation programs. The benefit and stability of effect of an intensified 10-day facial training combining electromyography and visual biofeedback training was evaluated.

Methods: Fifty-four patients (77.8% female; median age: 49.5 years) with post-paralytic facial synkinesis (median time to onset of paralysis: 31.1 months) were included in retrospective longitudinal study between January 2013 and June 2016. Facial function was assesses at baseline (T0), first days of training (T1), last day of training (T2), and follow-up visit (T3) at a median time of 6 months later using the House-Brackmann (HB) facial nerve grading system, Stennert index (SI), Facial Nerve Grading System 2.0 (FNGS 2.0), and Sunnybrook Facial Grading System (SFGS). Pairwise comparisons between the time points with *post-hoc* Bonferroni correction were performed.

Results: No significant changes of the gradings and subscores were seen between T0 and T1 (all $p > 0.01$). The 10-day combined and intensified feedback training between T1 and T2 improved facial symmetry and decreased synkinetic activity. Facial grading with the FNGS 2.0 or the SFGS were most suited to depict the training effect. FNGS 2.0, regional score, FNGS 2.0, synkinesis score, and FNGS 2.0 total score improved significantly (all $p \leq 0.0001$). Both, the FNGS 2.0 and the SFGS showed the strongest improvement in the nasolabial fold/zygomatic and the oral region. Neither the age of the patient ($r = 0.168$; $p = 0.224$), the gender ($r = 0.126$; $p = 0.363$) nor the length of the interval between onset of the palsy and training start ($r = 0.011$; $p = 0.886$) correlated with the changes of the SFGS between T1 and T2. The results remained stable between T2 and T3 without any further significant change.

Conclusion: Intensified daily combined electromyography and visual biofeedback training over 10 days was effective in patients with facial synkinesis and benefits were stable 6 months after therapy.

Keywords: facial nerve paralysis, synkinesis, biofeedback, electromyography, rehabilitation, physical therapy

INTRODUCTION

Post-paralytic facial synkinesis is a disfiguring condition characterized by involuntary contraction of one or more facial muscles during voluntary movement of other facial muscles (1). About 30–40% of patients with acute facial palsy do not recover completely and develop synkinesis (2). Problems with eye closure and eating, the inability to smile and affected face-to-face communication are the major motor impairments and non-motor symptoms leading to decreased quality of life (3). Nevertheless, many patients with synkinesis are never referred to a specialist or with significant delay (4). Besides botulinum toxin treatment, physical rehabilitation therapy is the most often prescribed measure (1, 5). The efficacy of physical therapy is very heterogeneous within the same study and between studies (6), because physical therapy types, schedules, frequency, and duration are highly variable and not standardized (5). Furthermore, facial palsy can be caused by a variety of diseases influencing the outcome and also the effect of physical therapy (7, 8).

The primary aim of a neuromuscular facial biofeedback training is that the patient learns how to change facial muscle activity of the affected side for the purpose of improved facial function (9). Facial biofeedback training mainly uses surface electromyography (EMG) recording of facial muscle activity and a feedback by visualization or acoustic signals (10–14). Astonishingly, the daily training periods in the literature take only 30–60 min distributed to a few sessions per week. Pathological recovery after deefferentation without deafferentation in case of facial paralysis is a complex disorder (15). From constraint-induced movement rehabilitation programs for patients after stroke, it is well-known that a daily forced use of an affected extremity for several hours per day over 2–3 weeks is needed to overcome corticomotor suppression and mismatch (16–18).

Therefore, we established in 2012 an intensified combined electromyography and visual feedback training program for patients with post-paralytic facial synkinesis after various etiologies of facial palsy (9). A pilot study with 20 patients using instructed raters revealed significant improvements of facial movements after the training (19). Here, we wanted (1) to confirm these encouraging results based on validated facial grading systems and additionally to test the hypotheses that (2) facial grading does not improve during the waiting time to facial training, and that (3) facial grading shows stable therapy effects over 6 months after facial training.

METHODS

Study Design and Inclusion Criteria

This retrospective observational and longitudinal study included patients with post-paralytic facial synkinesis after various etiologies of facial palsy who presented in the Facial Nerve Center, Jena University Hospital, between January 2013 and June 2016. All facial palsy related data and questionnaires were collected in the Facial Nerve Center. The inclusion criteria were: (a) a unilateral peripheral facial palsy; (b) an interval between onset and assessment of at least 6 months; (c) facial electromyography (EMG) confirmed voluntary activity in the affected facial muscles including synkinetic activity (20).

Intensified Combined Electromyography and Visual Biofeedback Training of Facial Movements

The training was carried out over a period of 10 days (two times for 5 days, the weekend in between without therapy). In the mornings, under the guidance of a therapist, 3 h of intensive facial training with (EMG) biofeedback combined with elements of constraint induced movement therapy was performed (9, 17–19). Biofeedback training was performed using the Nexus 10 biofeedback system, with Bio Trace software animations (Mind Media BV, Netherlands). Briefly, the patient was trained to control a defined and isolated facial muscle movement (for instance, pursing the lips by activation of the orbicularis oris muscle) without moving other facial muscles (for instance, without synkinetic activity of the ipsilateral orbicularis oculi muscle). To give another example, a specific activation of the zygomatic muscles on one or on both sides was performed while avoiding or at least minimizing synkinetic activation of the ipsilateral orbicularis oculi muscle. Surface EMG was recorded simultaneously and bilaterally from the target muscle for the intended movement and the most important muscle of an unintended movement (**Figure 1**). More details are given in **Supplementary Table 1**. Together with a video-generated mirror image, the patient could then simultaneously track the muscle activity on a screen during her/his movement exercises. The muscle activity was visualized with EMG feedback bars. The feedback signal was always proportional to the muscle activity. Due to the EMG feedback, the patient could track very fast voluntary and involuntary facial muscle activities even in their smallest forms. In this way, even unconscious movements were shown to the patient. A conscious relaxation of the muscles before and between every movement exercise was promoted on that way. The therapist was sitting opposite to the patient. So, the therapist could directly observe the patient and at the same time sees on the computer screen the video picture of the patient and the EMG feedback bars in the same way as the patient itself sees it on her/his screen. Thereby, the therapist could see the feedback, progress and deficits easily and could fast adapt the movement exercises if needed. The aim was that the patients developed new movement patterns in order to reduce synkinesis, control muscles independently and in this way balance their activity. Each afternoon, the patients performed an independent training for 2 h using a hand mirror. The patient documented the afternoon training on an exercise sheet (**Supplementary Material**). This was based on tasks and exercises first trained with the therapist. These exercises were inspired by a facial training booklet visualizing a standard set of facial exercises (21). The patients were encouraged to continue the exercises they had learned at home for at least 30 min daily for the following 6 months. No facial-palsy specific training was allowed during the waiting time before the training. Furthermore,

FIGURE 1 | Combined visual and EMG biofeedback setting. The patient (1) is sitting in front of a screen (2) showing himself via a camera on top of the screen. The therapist (3) is sitting in opposite to the patient allowing a direction view on patient's face. Beyond the face of the patient, the screen of the therapist (4) is showing the same information as the patient's screen: Bars are showing the surface EMG activity of the recorded muscles, in this examples the EMG activity is recorded symmetrically from both zygomatic muscles to control lifting the corner of the mouth on the affected side symmetrically to the contralateral side.

no facial surgery or botulinum toxin injections were allowed between T0 and T3.

Measurement Times and Facial Grading

Patients' charts were reviewed for demographic characteristics, patients' history, and prior treatment. All grading assessments were performed at four points in time: T0 = screening day and inclusion; T1 = start of facial feedback training; T2 = last day of the training, and T3 = follow-up examination at a minimum of 6 months later. **Figure 2** shows the examination workflow. Uniform series of photos were taken for all 54 patients for an objective assessment of facial function (22). Briefly, a sequence of static posed nine expressions was always photographed: (1) at rest, (2) closing both eyes, (3) closing both eyes with maximal effort, (4) frowning, (5) wrinkling the nose, (6) lifting both corners of mouth with closed mouth, (7) showing the teeth, (8) pursing the lips, and (9) pull down both corners of mouths. Hence, nine images were taken as a set per patient per time of assessment. Before evaluation, all photographs were blinded for the measurement time. The rater (BR) was not involved in the recruiting nor the training of any of the patients. He is a medical doctor in the training to a maxilla-facial surgeon with several years of experience in grading facial paly patients.

As shown in **Supplementary Table 2**, four different facial grading systems were used to classify facial nerve motor function based on the photographs described above. Grading was performed by the House-Brackmann (HB) facial nerve grading system, Stennert index (SI), Facial Nerve Grading System 2.0

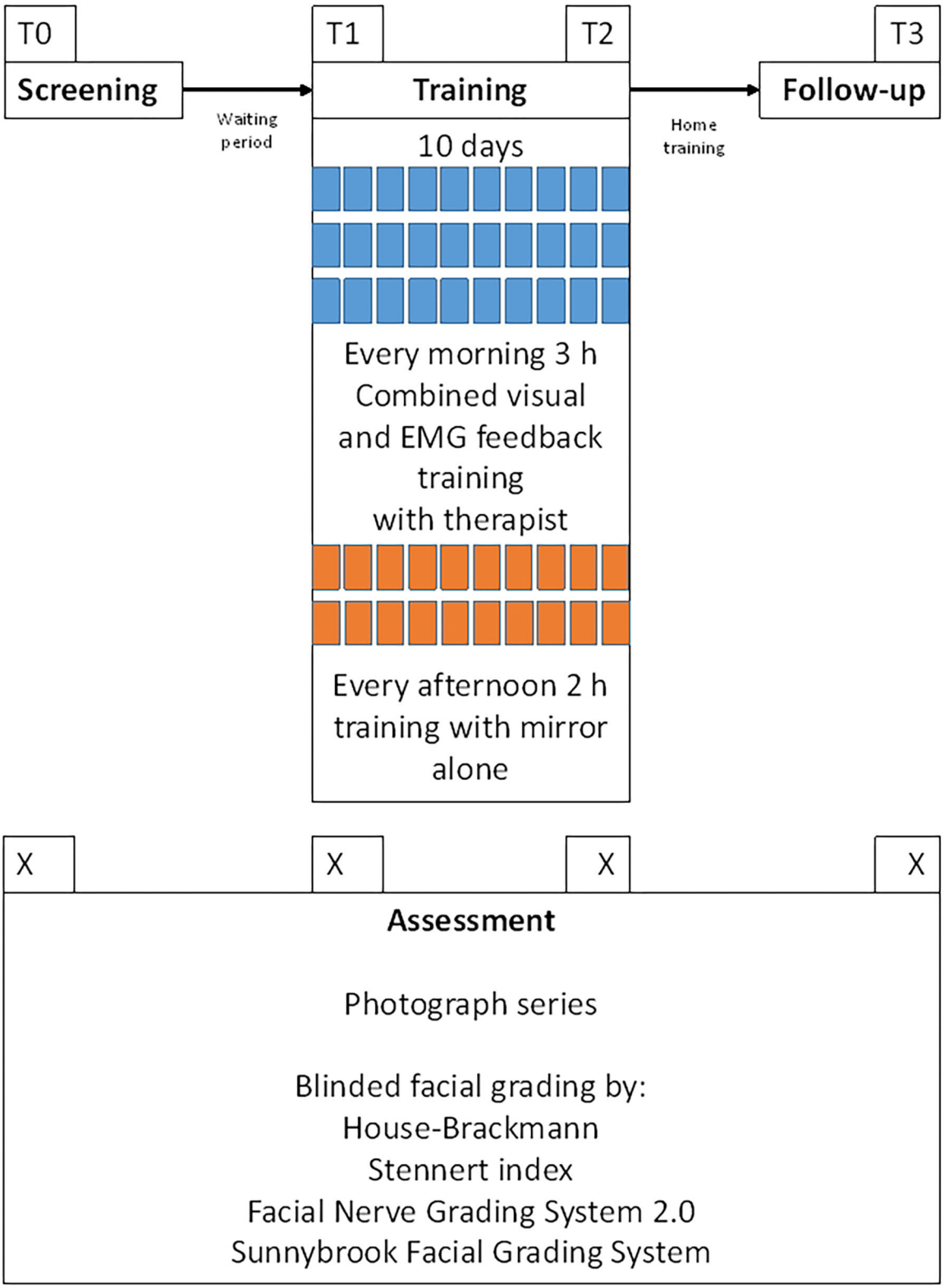


FIGURE 2 | Workflow of the examinations. T0 = day of the screening and inclusion into the training and the study. T1 = first day of the facial training. T2 = last day of the facial training (10th day). T3 = follow-up examination. Median interval between T0 and T1 (waiting period) was 4.4 months. Median interval between T2 and T3 (home training period) was 6 months.

(FNGS 2.0), and Sunnybrook Facial Grading System (SFGS). The HB ranges from grade I (normal function) to grade VI (complete paralysis) (23). In contrast, the SI is a double-weighted system (24). The observer judges facial symmetry at rest in four categories (0 =normal resting tone/symmetry up to 4 = no resting tone/gross asymmetry) and the motility of the facial muscles in six categories (0 =normal motility up to 6 = complete paralysis). The total score of the Stennert index summarizes both subscores. The FNGS 2.0 is a further development of the House-Brackmann facial nerve grading system (25). The FNGS 2.0 determines the final grade by adding regional assessments (score from 1 to 6) of the brow, eye, nasolabial fold, and oral regions to the score assessing the impact of synkinesis (score from 0 to 3). Summation of scores gives a final score of 4–24. Finally, the SFGS is a regional weighted system that rates three subscores (26): resting symmetry, the degree of voluntary facial muscle movement, involuntary muscle contraction (synkinesis). The three subscores are used to calculate a composite score (0 = total paralysis; 100 = normal function).

Statistical Analysis

The statistical analysis was performed with SPSS version 25.0 (IBM, Armonk, NY, USA). If not indicated otherwise, data are presented with mean values and 95% confidence intervals (CI). The comparisons between T0 and T1 (changes in the waiting period without any facial palsy specific intervention), between T1 and T2 (therapy effects), and T2 and T3 (changes during follow-up with active daily self-training) were performed with the non-parametric Wilcoxon test for paired data. These three, i.e., multiple comparisons were corrected with the Holm-Bonferroni method. Therefore, the corrected significance level was set at $p < 0.0001$. Cohen's d for paired data was calculated to evaluate the effect size between means of two measurement points. A large effect size was defined as $d \geq 0.8$. The Spearman test was used bivariate correlation analyses between different facial grading systems as well as to analyze the correlation of the changes of facial grading between T1 and T2 vs. age, gender, or duration of the palsy. The significance level was set at $p < 0.0001$.

RESULTS

Patients' Characteristics

A total of 54 patients were included (77.8% female; median age: 49.5 years). More details are shown in **Table 1**. The median interval between onset of the facial paralysis and training start was 31.1 months. The median interval between screening (T0) and start of the training (T1) was 4.4 months. Median interval between end of the training (T2) and follow-up examination was 6.0 months.

TABLE 1 | Patients' characteristics.

Parameter	Absolute (*N*)	Relative (%)
All	54	100
Gender		
Female	42	77.8
Male	12	22.2
Localization		
Left	30	55.6
Right	24	44.4
Etiology		
Idiopathic	23	42.6
traumatic/post-surgical	18	33.3
Inflammatory	12	22.2
Stroke, brainstem	1	1.9
	Mean ± SD	**Median, range**
Age, years,	42.8 ± 1.5	49.5, 14–77
Interval onset of facial palsy to training, months	62.3 ± 66.9	31.1, 12–302
Interval T0–T1 (waiting period), months	4.8 ± 2.4	4.4, 0.7–10.5
Interval, T2–T3 (follow-up period), months	6.3 ± 1.3	6.0 ± 5.0–11.8

Facial Nerve Grading in the Time Course From T0 to T3

All four grading systems confirmed the notable chronic facial movement disorder of the patients at baseline (**Table 2**) Grading with the FNGS 2.0 and the SFGS confirmed the detection of relevant synkinesis. No significant changes of the gradings and subscores were seen between T0 and T1. On average, the 10-day combined and intensified feedback training between T1 and T2 improved facial symmetry and decreased synkinetic activity. This was statistically most significantly obvious when using the FNGS 2.0 or the SFGS for facial grading (**Figure 3**). FNGS 2.0, regional score, FNGS 2.0, synkinesis score, and FNGS 2.0 total score improved significantly (all $p \leq 0.0001$). The median improvement between T1 and T2 using the SFGS was 7 points (range: −4 to 21). Strong effect sizes could be calculated when analyzing the changes measured by the SFGS ($d = 1.36$) and the FNGS 2.0 ($d = 1.15$) (**Table 2**).

On the individual level, 46 patients (85.2%) showed an improvement between T1 and T2 due to the SFGS results. Six patients (11.1%) showed no change, and two patients (3.7%) showed a deterioration. Both, the FNGS 2.0 and the SFGS showed the strongest improvement in the nasolabial fold/zygomatic and the oral region. No further change of facial grading was seen in the follow-up between T2 and T3, neither a further improvement nor a deterioration.

Correlation Analyses

A correlation analysis was performed for the changes between T1 and T2 for the total/composite scores in relation to the SFGS. The FNGS 2.0 showed the highest correlation ($r = 0.812$, $p \leq 0.001$), followed by the House-Brackmann grading ($r = 0.511$; $p \leq 0.001$). The correlation of the SFGS to the Stennert index was the lowest ($r = 0.318$; $p = 0.09$). Neither the age of the patient ($r = 0.168$; $p = 0.224$), the gender ($r = 0.126$; $p = 0.363$) nor the length of the interval between onset of the palsy and training start ($r = 0.011$; $p = 0.886$) correlated the changes of the SFGS between T1 and T2.

TABLE 2 | Comparison of facial grading at the initial screening (T1), start (T1), and end (T2) of therapy, and at follow-up (T3)*.

Parameter	T0		T1		T2		T3		T0–T1	T1–T2	T2–T3
	Mean	CI	Mean	CI	Mean	CI	Mean	CI	p; d	p; d	p; d
House-Brackmann	3.1	2.9–3.3	3.1	2.9–3.3	2.8	2.8–3.0	2.9	2.7–3.1	0.046; 0.29	**≤0.001**; 0.68	0.156; 0.19
Stennert, rest	1.4	1.2–1.6	1.4	1.1–1.6	1.2	1.0–1.4	1.2	1.0–1.4	0.532; 0.09	0.021; 0.46	0.766; 0.04
Stennert, motion	2.6	2.2–2.9	2.6	2.2–2.9	2.4	2.1–2.9	2.4	2.1–2.4	0.766; 0.77	**≤0.001**; 0.72	0.485; 0.10
Stennert, total	3.9	3.5–4.4	3.9	3.5–4.4	3.6	3.1–4.1	3.6	3.2–4.1	0.857; 0.04	0.007; 0.54	0.821; 0.03
FNGS 2.0, brow	4.4	3.9–4.9	4.4	4.0–4.9	4.3	3.8–4.7	4.4	3.9–4.8	0.010; 0.38	0.002; 0.64	0.058; 0.26
FNGS 2.0, eye	1.7	1.4–1.9	1.6	1.4–1.9	1.6	1.3–1.8	1.5	1.3–1.8	0.444; 0.11	0.160; 0.28	0.569; 0.08
FNGS 2.0, NLF	3.1	2.7–3.4	2.9	2.6–3.2	2.5	2.2–2.8	2.4	2.1–2.7	0.038; 0.30	**≤0.001**; **0.84**	0.419; 0.11
FNGS 2.0, oral	2.2	2.0–2.4	2.2	2.0–2.4	1.9	1.7–2.1	1.9	1.7–2.1	0.766; 0.04	**≤0.001**; 0.70	0.709; 0.05
FNGS 2.0, regional	11.3	10.4–12.2	11.2	10.3–12.0	10.2	9.4–11.0	10.2	9.4–11.0	0.597; 0.08	**≤0.001**; **1.13**	0.830; 0.03
FNGS 2.0, synkinesis	1.5	1.4–1.7	1.5	1.3–1.7	1.2	1.1–1.3	1.3	1.1–1.4	0.659; 0.06	**≤0.001**; 0.70	0.419; 0.11
FNGS 2.0, total	12.8	11.9–13.7	12.7	11.8–13.5	11.4	10.6–12.2	11.4	10.7–12.2	0.909; 0.02	**≤0.001**; **1.15**	0.569; 0.08
SFGS, resting symmetry	9.4	7.9–10.9	9.6	8.2–11.1	8.5	7.2–9.9	8.4	7.0–9.8	0.799; 0.04	0.003; 0.60	0.821; 0.03
SFGS, frontalis	2.3	1.9–2.6	2.2	1.9–2.5	2.4	2.0–2.7	2.3	2.0–2.6	0.010; 0.38	0,005; 0.57	0.322; 0.14
SFGS, orbicularis oculi	4.4	4.2–4.7	4.4	4.2–4.7	4.5	4.3–4.7	4.5	4.3–4.7	07.85; 0.03	0.261; 0.22	0.569; 0.08
SFGS, zygomaticus, risorius	3.1	2.8–3.4	3.2	3.0–3.5	3.6	3.3–3.9	3.7	3.4–4.0	0.006; 0.40	**≤0.001**; **0.81**	0.013; 0.35
SFGS, levator labii superior	3.1	2.8–3.4	3.2	3.0–3.5	3.6	3.3–3.9	3.6	3.3–3.9	0.051; 0.28	**≤0.001**; **0.91**	1.000; 0.00
SFGS, orbicularis oris	3.9	3.7–4.1	3.9	3.7–4.1	4.4	4.0–4.4	4.2	4.1–4.4	0.532; 0.09	**≤0.001**; 0.72	0.419; 0.11
SFGS, movement symmetry	67.0	63.1–70.9	68.0	64.4–71.6	73.0	69.3–76.6	73.5	69.8–77.1	0.243; 0.16	**≤0.001**; **1.15**	0.212; 0.17
SFGS, synkinesis frontalis	0.9	0.7–1.1	0.9	0.7–1.1	0.7	0.6–0.9	0.7	0.6–0.9	0.766; 0.04	0.021; 0.46	0.742; 0.05
SFGS, synkinesis orbicularis oculi	0.6	0.4–0.7	0.6	0.5–0.7	0.4	0.3–0.6	0.5	0.4–0.7	0.742; 0.05	0.003; 0.60	0.013; 0.35
SFGS, synkinesis zygomaticus, risorius	1.3	1.2–1.5	1.3	1.1–1.5	1.1	1.0–1.3	1.1	0.9–1.3	0.420; 0.12	0.021; 0.46	0.410; 0.11
SFGS, synkinesis levator labii superior	1.3	1.1–1.5	1.3	1.1–1.5	1.0	0.9–1.3	1.0	0.8–1.2	0.322; 0.14	**≤0.001**; 0.68	0.532; 0.09
SFGS, synkinesis orbicularis oris	1.0	0.7–1.2	0.9	0.7–1.2	0.5	0.3–0.7	0.5	0.4–0.7	0.532; 0.09	**≤0.001**; **0.89**	0.485; 0.10
SFGS, synkinesis	5.1	4.4–5.8	5.0	4.4–5.6	3.8	3.3–4.4	3.9	3.3–4.4	0.424; 0.11	**≤0.001**; **1.04**	0.808; 0.03
SFGS, composite	52.5	48.1–56.9	53.4	49.2–56.6	60.6	56.5–64.7	61.2	57.0–65.4	0.520; 0.13	**≤0.001**; **1.36**	0.322; 0.13

**Significant/strong effects in bold; FNGS 2.0, Facial Nerve Grading System 2.0; NLF, nasolabial fold; SFGS, Sunnybrook Facial Grading System.*

DISCUSSION

Synkinesis typically becomes clearly apparent about 6 months after pathological reinnervation and the full picture is reached after about 12 months (1, 27). Although the median time to onset in the present sample was already 31.1 months, 85% of the patients profited from the training. Furthermore, the waiting time analysis clearly showed that synkinesis remained unchanged before training. The follow-up showed that the effects of the training remained stable for at least 6 months. Of course, a randomized trial is needed to confirm the effectiveness of this short but very intensive training. The presented combined EMG and visual biofeedback training differs significantly in the number of hours per day from other biofeedback-based therapy concepts for patients. Other concepts are typically less intense but are performed over several weeks and months (14, 28–30). The structure of the presented intensified combined electromyography and visual feedback training was based on the established training concept of a constraint-induced movement rehabilitation program for patients after stroke. In accordance to the present results, it has already been shown that compact intensive training over a period of 2 weeks results in an improvement in function in stroke patients with paretic body parts mismatch (16–18). So far, no comparative studies on optimal training frequency and duration of an EMG-feedback approach for patients with synkinesis have been performed (5). This should be the subject of future research.

There are only a few other studies which included an EMG biofeedback element and investigated patients with synkinesis. The treatment time was always much longer than in the present study. The effectiveness of a complex EMG biofeedback and mirror feedback training in comparison to mirror feedback training alone was examined by Ross et al. (11). Training took place every 1–2 weeks for a total of 1 year. Both groups showed statistically significant improvements in facial motility compared to a control group but outcome in-between both therapy groups was not different. Cronin et al. examined an EMG biofeedback training that took place every 1–2 weeks for several months. Their therapy was associated with significant functional improvements of the face, including an increase in symmetry and motility, as well as a reduction in synkinesis (13). Both studies did not include follow-up examination after end of therapy. Long-term effects were only studied after mime therapy. Mime therapy includes massages, relaxation exercises, inhibition of synkinesis, and emotional expression exercises but not EMG-feedback elements (31). The mime therapy effects remained stable even 1 year after

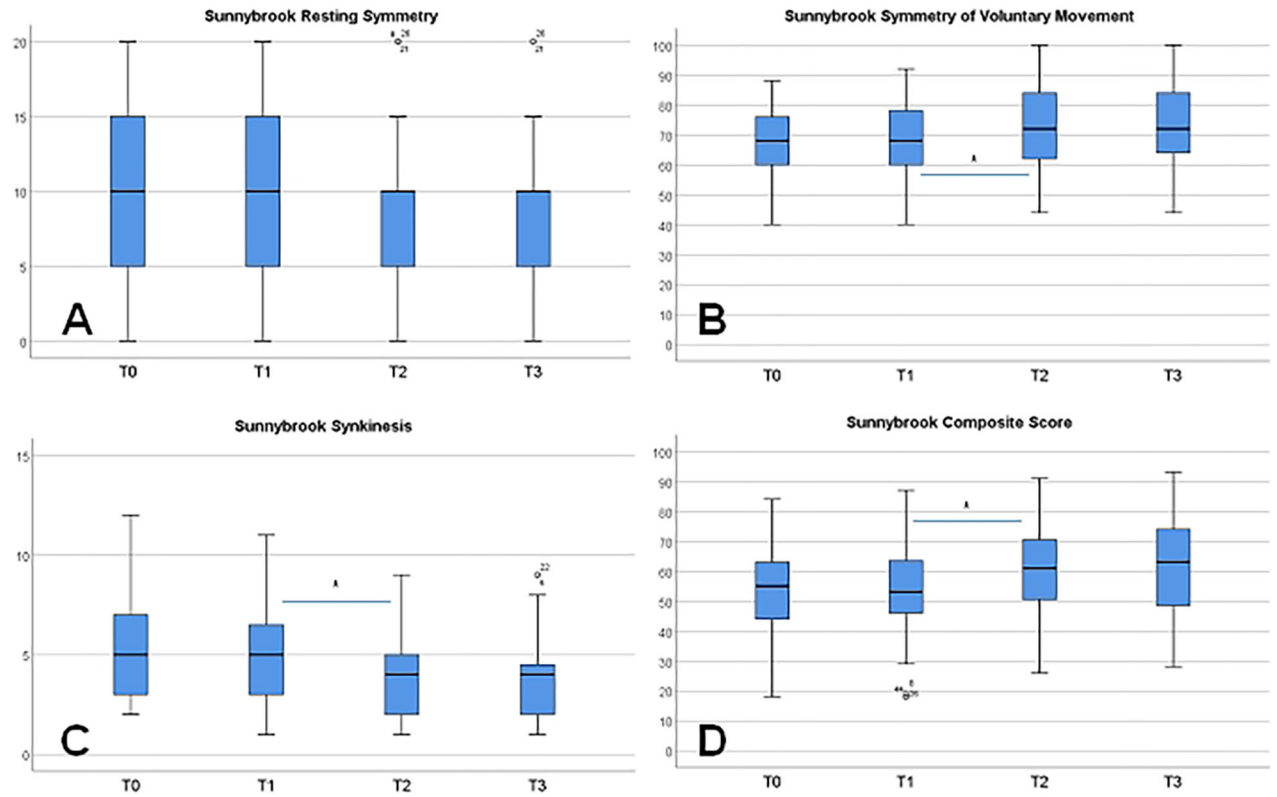


FIGURE 3 | Changes of the facial grading from T0 to T3 using the Sunnybrook grading scale and its subscores. **(A)** Symmetry of the face at rest. **(B)** Symmetry of voluntary movements. **(C)** Synkinesis. **(D)** Composite score. Significant changes (*$p \leq 0.001$) are only seen between T1 and T2 as a training effect, except for symmetry at rest.

therapy. According to Fitts and Posner (32), the learning of motor skills is divided into three stages. At the cognitive level, the trainee, here the patients with synkinesis, must first understand the type of task and learn to perform it (e.g., in the present training: lifting of the affected corner of the mouth). Therefore, the visual feedback and the control by the therapist is important. In the subsequent association stage, this ability must be refined by repeating it and combining it with other abilities (e.g., smiling, i.e., lifting of the affected corner of the mouth together with the contralateral corner). Here, especially the EMG feedback is very important. The level of autonomy is reached when the patient is finally able to integrate the learned ability freely into complex actions (e.g., speaking and smiling with integrated abduction of the corner of the mouth) in activities of daily live. Finally, the intensity of the training with repetitions over hours is very important. The ability or the training effect remains stable if this form of autonomous use is continued permanently (33, 34). Patients with facial palsy are typically extremely motivated to improve their restricted facial motor skills and to integrate what they have learned into their everyday lives (31).

Beyond physical therapy, botulinum toxin is a mainstay of synkinesis therapy (5, 35). Botulinum toxin treatment can also be combined with biofeedback rehabilitation (36). It might be an option to combine our treatment approach with botulinum toxin injection to facilitate specific movement tasks, but this has not yet been evaluated.

Furthermore, we need to introduce objective measurement tools to evaluate the outcome. The SFGS is a very robust but subjective facial grading tool (37). Like in many other studies, the scales were evaluated in the present study only by one examiner. First automated tools feasible for the use in clinical routine are published (22, 38). Such tools should be applied for SFGS or any other grading in future studies. As the present therapy is dependent on the surveillance of a trained therapy, it will also be of interest to develop a remote rehabilitation concept. Therefore, we will need remote EMG devices and especially a simplification of the camera technology using conventional smart phones or, for instance, special remote activity eye wear (39, 40).

CONCLUSION

This longitudinal study on 54 patients with post-paralytic facial synkinesis over four points in time showed that facial nerve function did not change during the waiting time before start of the training. An intensified daily training over 10 days using a combined EMG and visual biofeedback setting improved facial grading especially by reducing synkinesis. Finally, the effects remained stable over 6 months. Future studies should validate

the results in an external cohort of patients and compare the presented treatment to other approaches at best in randomized controlled trial. Furthermore, it has to show that the treatment is also effective from the patients' perspective, i.e., by the use of patient-related outcome measures using facial paralysis related quality of life assessment tools.

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 Ethics Committee of the Jena University 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

GV, OG-L, and CD: design of the work. BR, A-MK: data acquisition. GV, OG-L, KG, and CK: analysis. GV, BR, OG-L, CD, and KG: interpretation. All authors draft contribution, approval of the final version to be published, agreement 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.

FUNDING

OG-L acknowledges support by a Deutsche Forschungsgemeinschaft (DFG) grant GU-463/12-1.

ACKNOWLEDGMENTS

We thank Wolfgang H. R. Miltner for the collaborative development of the facial biofeedback therapy setting when we established the Facial Nerve Center in 2012. We thank Eva Miltner and Hendrik Möbius for their engaged training of the patients with post-paralytic facial synkinesis in the Facial Nerve Center, Jena University Hospital, Germany.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fresc.2021.746188/full#supplementary-material

REFERENCES

1. Husseman J, Mehta RP. Management of synkinesis. *Facial Plast Surg.* (2008) 24:242–9. doi: 10.1055/s-2008-1075840
2. Urban E, Volk GF, Geissler K, Thielker J, Dittberner A, Klingner C, et al. Prognostic factors for the outcome of Bells' palsy: a cohort register-based study. *Clin Otolaryngol.* (2020) 45:754–61. doi: 10.1111/coa.13571
3. Van Veen MM, Quatela O, Tavares-Brito J, Robinson M, Baiungo JH, Werker PMN, et al. Patient-perceived severity of synkinesis reduces quality of life in facial palsy: a cross-sectional analysis in 92 patients. *Clin Otolaryngol.* (2019) 44:483–6. doi: 10.1111/coa.13322
4. Butler DP, Morales DR, Johnson K, Nduka C. Facial palsy: when and why to refer for specialist care. *Br J Gen Pract.* (2019) 69:579–80. doi: 10.3399/bjgp19X706541
5. Lapidus JB, Lu JC, Santosa KB, Yaeger LH, Stoll C, Colditz GA, et al. Too much or too little? A systematic review of postparetic synkinesis treatment. *J Plast Reconstr Aesthet Surg.* (2020) 73:443–52. doi: 10.1016/j.bjps.2019.10.006
6. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev.* (2011). CD006283. doi: 10.1002/14651858.CD006283.pub3
7. Nakamura K, Toda N, Sakamaki K, Kashima K, Takeda N. Biofeedback rehabilitation for prevention of synkinesis after facial palsy. *Otolaryngol Head Neck Surg.* (2003) 128:539–43. doi: 10.1016/S0194-5998(02)23254-4
8. Fujiwara K, Furuta Y, Yamamoto N, Katoh K, Fukuda S. Factors affecting the effect of physical rehabilitation therapy for synkinesis as a sequela to facial nerve palsy. *Auris Nasus Larynx.* (2018) 45:732–9. doi: 10.1016/j.anl.2017.10.003
9. Miltner WHR, Weiss T, Miltner EM. Feedback training and other training programs. In: Guntinas-Lichius O, Schaitkin B, editors. *Facial Nerve Disorders and Diseases: Diagnosis and Management.* Stuttgart: Thieme (2016). p. 342–54.
10. Hammerschlag PE, Brudny J, Cusumano R, Cohen NL. Hypoglossal-facial nerve anastomosis and electromyographic feedback rehabilitation. *Laryngoscope.* (1987) 97:705–9. doi: 10.1288/00005537-198706000-00011
11. Ross B, Nedzelski JM, Mclean JA. Efficacy of feedback training in long-standing facial nerve paresis. *Laryngoscope.* (1991) 101:744–50. doi: 10.1288/00005537-199107000-00009
12. Brach JS, Vanswearingen JM, Lenert J, Johnson PC. Facial neuromuscular retraining for oral synkinesis. *Plast Reconstr Surg.* (1997) 99:1922–31; discussion: 1932–23. doi: 10.1097/00006534-199706000-00017
13. Cronin GW, Steenerson RL. The effectiveness of neuromuscular facial retraining combined with electromyography in facial paralysis rehabilitation. *OtolaryngolHead Neck Surg.* (2003) 128:534–8. doi: 10.1016/S0194-5998(03)00005-6
14. Dalla TE, Bossi D, Buonocore M, Montomoli C, Petrucci L, Alfonsi E. Usefulness of BFB/EMG in facial palsy rehabilitation. *Disabil Rehabil.* (2005) 27:809–15. doi: 10.1080/09638280400018650
15. Klingner CM, Volk GF, Brodoehl S, Witte O, Guntinas-Lichius O. The effects of deefferentation without deafferentation on functional connectivity in patients with facial palsy. *Neuroimage Clin.* (2014) 6:26–31. doi: 10.1016/j.nicl.2014.08.011
16. Taub E, Miller NE, Novack TA, Cook EW III, Fleming WC, Nepomuceno CS, et al. Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil.* (1993) 74:347–54.
17. Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke: a replication. *Stroke.* (1999) 30:586–92. doi: 10.1161/01.STR.30.3.586
18. Taub E. Constraint-induced movement therapy and massed practice. *Stroke.* (2000) 31:986–8. doi: 10.1161/01.STR.31.4.983-c
19. Neubauer J. *Ein Biofeedback-basiertes Gesichtsmuskel-Training zur Therapie peripherer Fazialisparesen evaluiert durch geschulte Beurteiler*. M. Sc., Friedrich-Schiller-Universität Jena, Jena, Germany (2016).
20. Guntinas-Lichius O, Volk GF, Olsen KD, Makitie AA, Silver CE, Zafereo ME, et al. Facial nerve electrodiagnostics for patients with facial palsy: a clinical practice guideline. *Eur Arch Otorhinolaryngol.* (2020) 277:1855–74. doi: 10.1007/s00405-020-05949-1
21. Hartwig M. *Fazialisprogramm*. Bad Honnef: Hippocampus Verlag. (2010).

22. Mothes O, Modersohn L, Volk GF, Klingner C, Witte OW, Schlattmann P, et al. Automated objective and marker-free facial grading using photographs of patients with facial palsy. *Eur Arch Otorhinolaryngol.* (2019) 276:3335–43. doi: 10.1007/s00405-019-05647-7
23. House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg.* (1985) 93:146–7. doi: 10.1177/019459988509300202
24. Stennert E. Facial nerve paralysis scoring system. In: Fisch U, editor. *Facial Nerve Surgery*. Zurich: Aesculapius Publishing (1977). p. 543–7.
25. Vrabec JT, Backous DD, Djalilian HR, Gidley PW, Leonetti JP, Marzo SJ, et al. Facial Nerve Grading System 2.0. *Otolaryngol Head Neck Surg.* (2009) 140:445–50. doi: 10.1016/j.otohns.2008.12.031
26. Ross BG, Fradet G, Nedzelski JM. Development of a sensitive clinical facial grading system. *Otolaryngol Head Neck Surg.* (1996) 114:380–6. doi: 10.1016/S0194-5998(96)70206-1
27. Flasar J, Volk GF, Granitzka T, Geissler K, Irintchev A, Lehmann T, et al. Quantitative facial electromyography monitoring after hypoglossal-facial jump nerve suture. *Laryngoscope Investig Otolaryngol.* (2017) 2:325–30. doi: 10.1002/lio2.95
28. Pereira L, Obara K, Dias J, Menacho M, Lavado E, Cardoso J. Facial exercise therapy for facial palsy: systematic review and meta-analysis. *Clin Rehabil.* (2011) 25:649–58. doi: 10.1177/0269215510395634
29. Baricich A, Cabrio C, Paggio R, Cisari C, Aluffi P. Peripheral facial nerve palsy: how effective is rehabilitation? *Otol Neurotol.* (2012) 33:1118–26. doi: 10.1097/MAO.0b013e318264270e
30. Pourmomeny AA, Asadi S. Management of synkinesis and asymmetry in facial nerve palsy: a review article. *Iran J Otorhinolaryngol.* (2014) 26:251–6. doi: 10.22038/IJORL.2014.3216
31. Beurskens CH, Heymans PG, Oostendorp RA. Stability of benefits of mime therapy in sequelae of facial nerve paresis during a 1-year period. *Otol Neurotol.* (2006) 27:1037–42. doi: 10.1097/01.mao.0000217350.09796.07
32. Fitts PM, Posner MI. *Human Performance*. Belmont: Brooks/Cole Publishing Company (1967).
33. Roemmich RT, Bastian AJ. Closing the loop: from motor neuroscience to neurorehabilitation. *Annu Rev Neurosci.* (2018) 41:415–29. doi: 10.1146/annurev-neuro-080317-062245
34. Kleynen M, Beurskens A, Olijve H, Kamphuis J, Braun S. Application of motor learning in neurorehabilitation: a framework for health-care professionals. *Physiother Theory Pract.* (2020) 36:1–20. doi: 10.1080/09593985.2018.1483987
35. Cooper L, Lui M, Nduka C. Botulinum toxin treatment for facial palsy: a systematic review. *J Plast Reconstr Aesthet Surg.* (2017) 70:833–41. doi: 10.1016/j.bjps.2017.01.009
36. Mandrini S, Comelli M, Dall'angelo A, Togni R, Cecini M, Pavese C, et al. Long-term facial improvement after repeated BoNT-A injections and mirror biofeedback exercises for chronic facial synkinesis: a case-series study. *Eur J Phys Rehabil Med.* (2016) 52:810–8.
37. Fattah A, Gurusinghe A, Gavilan J, Hadlock T, Marcus J, Marres H, et al. Facial nerve grading instruments: systematic review of the literature and suggestion for uniformity. *Plast Reconstr Surg.* (2015) 135:569–79. doi: 10.1097/PRS.0000000000000905
38. Miller MQ, Hadlock TA, Fortier E, Guarin DL. The auto-eFACE: machine learning-enhanced program yields automated facial palsy assessment tool. *Plast Reconstr Surg.* (2021) 147:467–74. doi: 10.1097/PRS.0000000000007572
39. Watts P, Breedon P, Nduka C, Neville C, Venables V, Clarke S. Cloud computing mobile application for remote monitoring of Bell's Palsy. *J Med Syst.* (2020) 44:149. doi: 10.1007/s10916-020-01605-7
40. Taeger J, Bischoff S, Hagen R, Rak K. Utilization of smartphone depth mapping cameras for app-based grading of facial movement disorders: development and feasibility study. *JMIR Mhealth Uhealth.* (2021) 9:e19346. doi: 10.2196/19346

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 22 October 2021
doi: 10.3389/fresc.2021.754118

Relating Global Cognition With Upper-Extremity Motor Skill Retention in Individuals With Mild-to-Moderate Parkinson's Disease

*Jennapher Lingo VanGilder[1], Cielita Lopez-Lennon[2], Serene S. Paul[2,3], Leland E. Dibble[2], Kevin Duff[4,5] and Sydney Y. Schaefer[1,2]**

[1] School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, United States, [2] Department of Physical Therapy and Athletic Training, University of Utah, Salt Lake City, UT, United States, [3] Discipline of Physiotherapy, Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [4] Center for Alzheimer's Care, Imaging and Research, University of Utah Health Sciences Center, Salt Lake City, UT, United States, [5] Department of Neurology, University of Utah Hospital, Salt Lake City, UT, United States

OPEN ACCESS

Edited by:
Elizabeth Skidmore, University of Pittsburgh, United States

Reviewed by:
Rachel Hawe, University of Minnesota Twin Cities, United States
Mohammad Sami Al-Wardat, Aqaba University of Technology, Jordan

***Correspondence:**
Sydney Y. Schaefer
Sydney.schaefer@asu.edu

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: 06 August 2021
Accepted: 27 September 2021
Published: 22 October 2021

Citation:
Lingo VanGilder J, Lopez-Lennon C, Paul SS, Dibble LE, Duff K and Schaefer SY (2021) Relating Global Cognition With Upper-Extremity Motor Skill Retention in Individuals With Mild-to-Moderate Parkinson's Disease. Front. Rehabilit. Sci. 2:754118. doi: 10.3389/fresc.2021.754118

Background and Purpose: Cognition has been linked to rehabilitation outcomes in stroke populations, but this remains unexplored in individuals with Parkinson's disease (PD). The purpose of this secondary data analysis from a recent clinical trial (NCT02600858) was to determine if global cognition was related to skill performance after motor training in individuals with PD.

Methods: Twenty-three participants with idiopathic PD completed 3 days of training on an upper-extremity task. For the purposes of the original clinical trial, participants trained either "on" or "off" their dopamine replacement medication. Baseline, training, and 48-h retention data have been previously published. Global cognition was evaluated using the Montreal Cognitive Assessment (MoCA). Linear regression examined whether MoCA score predicted longer-term retention at nine-day follow-up; baseline motor task performance, age, PD severity, depressive symptoms, and group (medication "on"/"off") were included as covariates. Baseline and follow-up motor task performance were assessed for all participants while "on" their medication.

Results: MoCA score was positively related to follow-up motor task performance, such that individuals with better cognition were faster than those with poorer cognition. Baseline task performance, age, PD severity, depressive symptoms, and medication status were unrelated to follow-up performance.

Discussion and Conclusions: Results of this secondary analysis align with previous work that suggest cognitive impairment may interfere with motor learning in PD and support the premise that cognitive training prior to or concurrent with motor training may enhance rehabilitative outcomes for individuals with PD. Findings also suggest that assessing cognition in individuals with PD could provide prognostic information about their responsiveness to motor rehabilitation.

Keywords: motor learning, global cognition, upper-extremity, task-specific training, Parkinson's disease

INTRODUCTION

Despite clear evidence of deficits in upper extremity motor control and dexterity in Parkinson's disease (PD) (1, 2) that meaningfully impact on one's activities of daily living (3), most rehabilitation research and clinical practice for PD focuses on gait and balance problems. When prescribed, however, motor rehabilitation can improve upper extremity movement patterns and physical function (4, 5), depending on one's ability to learn and retain novel motor skills. While individuals with PD may benefit from physical rehabilitation, they demonstrate slower learning rates (6) and learn to a lesser extent (7) than individuals without PD, yet longer-term skill retention remains unclear (8). In light of this, some people with PD show marked gains following therapeutic intervention, while others do not [e.g. (4), see also (9)]. The ability to predict therapeutic responsiveness could help therapists streamline and personalize treatments. However, most predictive tools or models of post-intervention motor outcomes are time- and cost-intensive [e.g., annual clinical measures (10), neuroimaging (11), etc.].

In contrast, cognitive assessment may be a feasible, brief, and relatively inexpensive tool for gaining insight to an individual's motor learning capacity [see (12)]. Global cognitive status has been shown to predict gains in gait speed following standard-of-care physical therapy independent of primary diagnosis (13, 14). With respect to PD specifically, physical therapy combined with cognitive training may be more efficacious in improving reactive postural adjustments (i.e., responses to perturbations) and motor symptoms than physical therapy alone (15). Furthermore, lower-extremity physical therapy (i.e., aerobic exercises, treadmill training) has been shown to improve global cognition as well in people with PD (16), although combined physical and cognitive therapy may be more beneficial (17). However, the relationship between global cognitive measures and upper-extremity improvements in PD has not been explored. Empirically, visuospatial function has been linked with upper limb motor learning in both younger (18–21) and older adults (22–26) without PD, and since visuospatial deficits can occur with PD (27–29), this may help explain why people with PD tend to learn motor skills slower and to a lesser extent than those without PD. However, the extent to which cognitive impairment (global or specific) interferes with upper extremity motor learning in individuals with PD remains unknown.

In a recent randomized clinical trial in individuals with mild-to-moderate PD (clinicaltrial.gov registration number NCT02600858) (30), motor practice while "on" dopamine replacement medication (i.e., levodopa) improved 48-h retention of a functional upper extremity motor task compared to practice "off" dopamine replacement medication. The purpose of the present study was to perform secondary analyses of these data to evaluate whether cognition was related to skill learning in the upper extremity. Based on previous findings, it was hypothesized that cognitive functioning would be related to longer-term retention of an upper extremity motor task, where better cognition would be associated with more skill retention.

METHODS

Participants

Twenty-three adults aged ≥50 years old with a confirmed diagnosis of PD were included in this secondary analysis of data from a previously published randomized clinical trial (clinicaltrials.gov registration number NCT02600858) (30). Inclusion criteria included idiopathic PD diagnosed by a neurologist, age 50–80 years, in Hoehn and Yahr stages 1–3, and had been on a stable antiparkinsonian medication regime for 1 month prior to pretest assessment as well as throughout the study. Exclusion criteria included prior surgical treatment of PD (e.g., deep brain stimulation), dementia [Montreal Cognitive Assessment (31) (MoCA) < 18] (32), and the presence of concomitant neurological conditions. Included participants must have been taking dopamine replacement medications. The clinical trial protocol required half the participants ($n = 12$) to complete upper extremity motor training while continuing to take their prescribed dose of levodopa medication; the other half ($n = 11$) skipped their first dose of medication each day of motor training such that they were "off" medication following overnight withdrawal. These participants took their remaining daily doses after they completed the motor training each morning. Details regarding dopamine medication and other participant characteristics have been previously reported (30).

Global cognition was measured using the MoCA, a brief cognitive screening tool in which scores range from zero to 30; a score of 26 (or higher) is considered to be normal cognitive functioning, as defined by the publisher (31). To evaluate upper extremity dexterity, participants completed the Nine-hole peg test (33) (a timed clinical measure of dexterity) and another timed experimental upper extremity dexterity task that simulates buttoning a shirt unimanually (24, 34, 35); for both these tasks faster trial times indicate better performance. Participants were also tested by a trained examiner with the motor subsection of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (total range of scores = 0–152) (36). To evaluate depressive symptoms, participants completed the Geriatric Depression Scale (GDS) Short Form (37), a self-report rating tool consisting of 15 items and a score of four or lower is considered normal. Participants self-reported hand dominance. All participant characteristic data, including MoCA score, were collected in an initial visit while the participants were "on" their prescribed dose of dopamine replacement medication, regardless of which group they were randomized to ("on" vs. "off" medication).

Upper-Extremity Motor Training

As described previously (30), the motor training protocol required participants to complete a familiarization trial, then 50 training trials each day for three consecutive days. More details regarding the motor task are provided below. Participants were then re-tested 2 and 9 days later. Two-day follow-up was the stated primary outcome of this clinical trial and was therefore reported previously; thus, only the longer-term nine-day follow-up was included in this analysis.

FIGURE 1 | Participants used their non-dominant hand to complete a reaching task that simulates feeding oneself; participants use a spoon to select only two beans from the center "home" cup and deposit them into target cups. One trial consisted of 15 repetitions (i.e., five arcs to each of the three target cups). This figure was adapted from "Dexterity and Reaching Motor Tasks" by MRL Laboratory is licensed under CC BY 2.0.

The motor task used in this study was designed to mimic an activity of daily living [i.e., feeding (38)]. This task has been validated against subjective and objective measures of daily functioning in a cognitively impaired sample (39). The experimental apparatus was comprised of three "target" cups placed 16 cm from a center "home" cup at 45, 90, and 135 degrees (**Figure 1**). Participants were asked to use a plastic spoon held in their non-dominant hand to collect two raw kidney beans from the home cup and transport them to one of the three target cups. The non-dominant hand was used to ensure the task was not overlearned and to avoid potential confounds of a ceiling effect (40). Participants were instructed to move first to the target cup ipsilateral to the non-dominant hand, then to the middle cup, then to the contralateral cup, repeating this pattern four more times. Thus, each trial consisted of 15 reaches. The primary measure of performance was *trial time*, which began when the participant picked up the spoon and ended when they completed all reaching movements and placed the spoon back onto the table; thus, lower trial times indicated better performance. Dropping beans, transporting an incorrect amount, or moving to the wrong target were counted as errors, and the participant could not continue until the error was corrected, therefore errors contributed to longer trial times. Participants were not provided with performance feedback but could explore different movement strategies to optimize performance [i.e., discovery learning (41)]. As noted previously, each training session consisted of 50 trials (i.e., 750 reaches per session), and participants completed three training sessions over 3 days (1/day), totaling 2,250 reaches. This dose of training was selected based on previous feasibility and efficacy studies in other clinical and healthy populations (42, 43).

Statistical Analysis

JMP Pro 14.0 (SAS Institute Inc., Cary NC) was used for all statistical analyses. To examine whether global cognition was related to the amount of learned motor skill, MoCA scores were included in a multiple linear regression model as a predictor of nine-day follow-up performance ($\alpha = 0.05$), along with baseline motor performance, age, MDS-UPDRS Motor subsection score, and GDS as covariates. The MDS-UPDRS Motor subsection score and GDS were included to control for severity of PD motor signs and depressive symptoms, respectively. All continuous variables (age, MoCA, baseline motor performance, and 9-day follow-up) were normally distributed, as determined by Shapiro-Wilk tests. Furthermore, a partial correlation matrix indicated minimal collinearity between predictors, with only a moderate correlation between age and MoCA ($r = -0.21$). In addition, quantile range analysis indicated no outliers for any of the continuous variables. Thus, assumptions for linear regression were tested and met.

Baseline motor performance was measured as the first trial of the first motor training session. Similarly, follow-up was measured as a single trial performed 9 days after the last training session. Although we did not have a specific hypothesis regarding the effect of dopamine replacement medication on learning, we also included the variable of group ("on" vs. "off" medication) as a covariate to control for any confounds of dopamine replacement medication status on the primary outcome. We note that baseline motor performance was not different between the medication groups ($p = 0.28$), consistent with results from the primary analysis of this clinical trial (30). We also note that based on results from the primary analysis of this clinical trial [see Table 2 in original publication (30)], we were sufficiently powered to detect significant differences between the two timepoints (Cohen's $d = 0.58$; effect-size $r = 0.27$).

RESULTS

Individual characteristics are provided in **Table 1**. Participants demonstrated mild PD symptoms and disease severity (median Hoehn and Yahr stage = 2, not shown in table). Using their non-dominant hand, participants completed the Nine-hole peg test and experimental dexterity task in 25.38 ± 4.31 and 102.81 ± 54.37 s (mean ± SD), respectively. Results for the Nine-hole peg test were consistent with previously reported values in PD (33). In addition, participants were bradykinetic, taking twice as long to complete the dexterity task as healthy older adults from previously reported data (35). MoCA scores ranged between 23 and 30, indicating that some participants were within the normal range of cognition while others fell below [based on (31)].

TABLE 1 | Individual participant characteristics ($n = 23$).

Age (years)	Education (years)	GDS[a]	MDS-UPDRS-3[b]	Gender	9HPT (s)[c]	UE dexterity (s)[d]	MoCA[e]
66.5	18	10	36	M	30.38	193.66	24
71.2	18	0	34	F	22.5	109.36	30
75.8	12	1	25	F	20.75	42.83	25
68.8	14	3	33	M	22.37	103.11	28
66.5	16	1	32	F	22.85	47.02	27
67.7	17	1	40	M	23.03	70.42	30
50.5	16	1	21	F	19.31	45.86	30
74.4	16	1	39	F	24.19	69.24	25
79.2	18	1	28	M	26.91	103.99	26
71.7	16	0	34	M	28.88	80.89	27
70	18	1	35	M	24.85	107.29	24
62.4	12	1	32	M	25.66	93.27	26
79.6	16	0	22	M	27.31	121.90	25
78.7	16	9	24	F	23.35	63.21	28
77.9	16	0	27	F	25.93	117.21	27
70	16	0	39	F	24.59	100.00	27
80.3	20	10	20	M	27.88	92.90	27
76.2	12	1	37	F	22.52	100.33	24
66.2	20	9	13	F	19.44	61.37	27
73.9	20	0	24	M	28.53	96.05	29
70.8	14	2	27	F	24.44	153.98	28
63.4	20	5	25	F	27.63	94.89	23
72.9	14	3	55	M	39.69	296.02	25

[a] *GDS, Geriatric Depression Scale.*
[b] *MDS-UPDRS-3, Movement Disorder Society—Unified Parkinson's Disease Rating Scale Motor Portion (assessed "on" medication).*
[c] *9 HPT, Nine Hole Peg Test, tested on the non-dominant hand (prior to motor training); higher scores indicate worse performance, measured in seconds.*
[d] *UE Dexterity Task, Upper Extremity Dexterity task (non-dominant hand); higher scores indicate worse performance, measured in s.*
[e] *MoCA, Montreal Cognitive Assessment; lower scores indicate worse performance.*

Overall, nine-day follow-up performance on the motor task was significantly faster (better) than that of baseline [one-sample $t_{(43)} = -3.13$; $p = 0.0016$], as shown in **Figure 2A**. This indicates an overall effect of motor learning in this sample. Linear regression model results indicated that only MoCA score predicted 9-day follow-up performance ($\beta = -2.76$; 95% CI [−5.11, −0.39], $p = 0.0248$), such that higher MoCA scores were associated with faster (better) trial times 9 days post-training. This is further illustrated in **Figure 2B**, which shows baseline and follow-up data for each participant. Line colors indicate each participant's MoCA score (warmer colors = lower MoCA scores), such that warmer colors tended to cluster at slower trial times for 9-day follow-up, while cooler colors tended to cluster at faster trial times. Participant age ($\beta = -0.18$; 95% CI [−0.89, 0.52], $p = 0.59$), severity of PD motor signs ($\beta = 0.26$; 95% CI [−0.34, 0.86], $p = 0.37$), GDS ($\beta = 0.71$; 95% CI [−0.73, 2.15], $p = 0.31$) and medication status group ($\beta = 2.83$; 95% CI [−2.02, 7.68], $p = 0.23$) were not significantly related to follow-up motor performance. Since only MoCA score was a significant predictor of follow-up performance, results from a bivariate regression are provided in **Figure 3** to further illustrate the negative relationship between the two variables (color gradient consistent with that of **Figure 2B**).

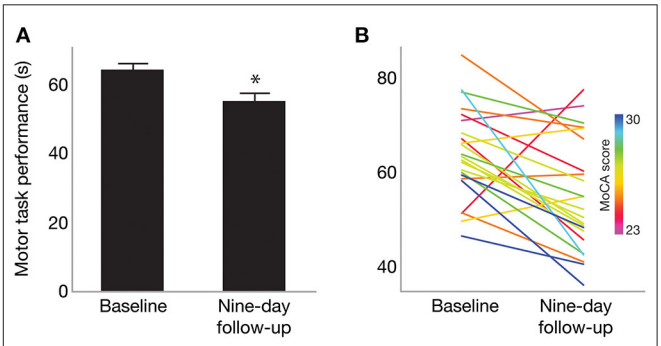


FIGURE 2 | (A) Mean motor task performance at baseline and 9-day follow-up. On average, trial time (in seconds) was significantly faster at nine-day follow-up compared to baseline. *Indicates $p = 0.0016$. **(B)** Motor performance for each participant at baseline and 9-day follow-up. Line color indicates each participant's MoCA score, with warmer colors indicating lower MoCA scores and cooler colors indicating higher MoCA scores (range 23–30).

DISCUSSION

The purpose of this secondary analysis was to determine whether cognition was related to upper extremity motor skill learning

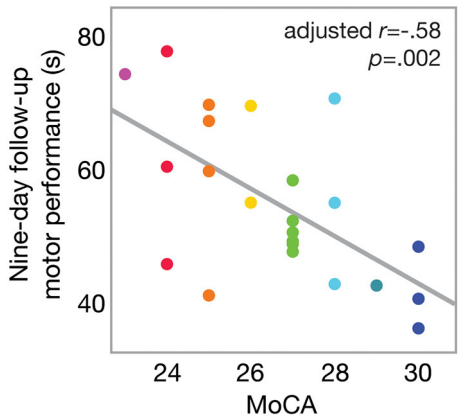


FIGURE 3 | Scatterplot of motor performance at 9-day follow-up as a function of MoCA score. Bivariate linear correlation results are shown in figure. Color gradient corresponds to that in **Figure 2**.

in individuals with PD. Results indicated that MoCA score predicted follow-up performance of a functional upper extremity motor task 9 days after the last practice session, more so than baseline performance and age (regardless of "on"/"off" medication groups). These findings align with previous work that suggest cognitive testing can be used to predict rehabilitative outcomes (44, 45) and support that global cognition may be a useful tool to predict motor learning in clinical populations (46–48). Although the MoCA was used to evaluate global cognition in this study, there is existing evidence that supports the value of assessing specific cognitive domains as predictors of motor learning (24, 44, 49).

Given the high prevalence of cognitive impairment among people with PD (50, 51), global and specific cognitive measures should be considered to identify which and to what extent various cognitive impairments interfere with learning different skills. In terms of global cognitive measures, the MoCA may be particularly sensitive to screening cognitive deficits associated with PD compared to other global cognitive measures of cognition (i.e., the Mini Mental State Examination) (32). We acknowledge, however, that the MoCA is a rapid cognitive screen that does not thoroughly assess the function of each cognitive domain nor is it validated to measure the function of individual cognitive domains, which may be a limitation to this study. Thus, a more comprehensive battery of cognitive assessments would determine whether specific cognitive domains (or specific cognitive deficits) more closely predict motor skill retention in this population. For example, visuospatial deficits may interfere with upper-extremity learning (23–25, 52, 53), while fluid cognitive skills or executive function may interfere with lower-extremity learning (54). While these previous studies have not focused on motor learning in PD specifically, the effects of particular cognitive deficits may not be PD-specific but instead generalize to a number of older patient populations who may be receiving motor rehabilitation for a number of reasons (e.g., stroke, joint replacement). As such, the effect of cognitive impairment on motor rehabilitation is gaining interest, within and beyond PD (12, 55). Future studies in motor learning should consider a more comprehensive battery of cognitive tests, especially those that evaluate visuospatial and executive abilities, in order to identify evidence-based targets for adjuvant cognitive or non-invasive brain stimulation therapies [e.g. (15, 17, 56–58)] that can be administered prior to or during upper- and lower-extremity motor therapy for people with PD.

In addition to providing empirical evidence as the groundwork for developing effective adjuvant therapies for motor rehabilitation in PD, this study offers clinicians a low-cost, easy-to-implement way to predict how responsive a person with PD might be to motor therapy. It is well-established that responsiveness to motor rehabilitation is often highly variable between PD patients [see 95% CIs in Robinson et al. (9)]. As such, the findings from the current study suggest that the MoCA may be a quick (∼5–10 min) and simple way to predict how responsive a patient might be to upper-extremity training. This would inform therapists in how to streamline and tailor their treatments, and better allocate their time to activities that they know their patients will benefit from. Predictors of therapeutic responsiveness are already being explored outside PD using neuroimaging (59–61), neurophysiology (61–63), or genotyping (64–66), but these investigational methods are time- and cost-intensive, making them unfeasible for an allied health setting and out-of-pocket therapy.

In the published clinical trial (30), there was a modest effect of medication status during training (i.e., "on"/"off" medication while practicing the task) between baseline and 48-h follow-up task performance, such that the "on" medication group performed significantly better at this short-term retention period than did the "off" medication group. These results were interpreted to indicate that being "on" dopamine replacement medications may facilitate short term retention of motor skill. However, this secondary analysis indicates that the group difference was no longer present by the ninth day of retention, likely due to the modest effect of medication status on training previously observed. Instead, global cognition (which was not originally considered in the parent clinical trial) was a significant predictor of motor task performance well after training had been completed (9 days later), regardless of whether training had occurred "on" or "off" dopamine replacement medication. Indeed, dopamine replacement may be insufficient to offset the breadth of cognitive deficits associated with PD (67), and the short duration in which participants in the "off" group were withdrawn from their medication for training (relative to the 9-day duration of retention) may explain the lack of effect of group in this secondary analysis.

There are several limitations to this study. First, there was a limited range of MoCA scores in this sample, and more participants were in the normal range than below. Even though the MoCA is not a diagnostic tool (and is instead a cognitive screening tool), scores suggest that the majority of participants were cognitively intact, and more extensive neuropsychological testing would be necessary to determine whether participants with scores below the "normal" cut-off were in fact cognitively-impaired. This does not, however,

take away from the findings and implications of this study, whereby rehabilitation-focused clinicians could still use the MoCA as a quick screening tool to better predict how patients might respond to upper-extremity skill training. Future studies will investigate a larger cohort of more cognitively-impaired individuals [such as people with PD who experience "freezing" (68–71)] to further test the generalizability of these findings. Second, a limitation of this study is that the participants in the "off" medication group resumed their regularly prescribed dopamine replacement therapy after training each day and throughout the 9-day retention period; thus, we are unable to discern potential effects of medication adherence or withdrawal on motor skill consolidation and retention. It is well-established that consolidation and retention are critical periods for motor learning, as well as acquisition (72). Third, we acknowledge that this study was not designed to directly test if global cognition would be predictive of clinical rehabilitation motor outcomes in individuals with PD, since it only evaluated the amount of skill retained over a period of 9 days. Performance of the functional upper extremity task used in this study has, however, been associated with subjective and objective measures of daily functioning in individuals diagnosed with Mild Cognitive Impairment (39), suggesting that the benefits of training may generalize to activities of daily living.

CONCLUSIONS

Our study supports the premise that cognitive impairments interfere with motor skill learning in PD, and provides the proof-of-principle that (1) cognitive screening may be a viable solution for personalizing motor rehabilitation for people with PD and (2) cognitive therapy and/or brain stimulation prior to, or concurrent with, motor training could enhance functional outcomes. Future mechanistic work should systematically test which specific cognitive domains are most relevant for different types of motor learning in PD to help inform targeted adjuvant cognitive or neurostimulation therapies that can enhance motor rehabilitation. For example, fluid cognition training may enhance gait adaptation, or non-invasive stimulation of parietal cortex could enhance functional upper-extremity training via visuospatial processes.

DATA AVAILABILITY STATEMENT

Meta-data are available upon reasonable request. Requests to access these datasets should be directed to lee.dibble@hsc.utah.edu.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

LD and SP organized the database. JLV and SS performed the statistical analysis. JLV wrote the first draft with assistance from CL-L. All authors contributed to conception and design of the study and contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was supported in part by the National Institute on Aging at the National Institutes of Health (K01 AG047926 to SS and F31 AG062057 to JLV); University of Utah Office of Research (2015-16 grant), USA; the American Parkinson's Disease Association (2015-16 postdoctoral fellowship grant).

REFERENCES

1. Nowak DA, Hermsdörfer J. Objective evaluation of manual performance deficits in neurological movement disorders. *Brain Res Rev*. (2006) 51:108–24. doi: 10.1016/j.brainresrev.2005.10.003
2. Ingvarsson PE, Gordon AM, Forssberg H. Coordination of manipulative forces in Parkinson's disease. *Exp Neurol*. (1997) 145:489–501. doi: 10.1006/exnr.1997.6480
3. Raggi A, Leonardi M, Ajovalasit D, Carella F, Soliveri P, Albanese A, et al. Disability and profiles of functioning of patients with Parkinson's disease described with ICF classification. *Int J Rehabil Res*. (2011) 34:141–50. doi: 10.1097/MRR.0b013e328344ae09
4. Vanbellingen T, Nyffeler T, Nigg J, Janssens J, Hoppe J, Nef T, et al. Home based training for dexterity in Parkinson's disease: a randomized controlled trial. *Parkinsonism Relat Disord*. (2017) 41:92–8. doi: 10.1016/j.parkreldis.2017.05.021
5. Nackaerts E, Vervoort G, Heremans E, Smits-Engelsman BCM, Swinnen SP, Nieuwboer A. Relearning of writing skills in Parkinson's disease: a literature review on influential factors and optimal strategies. *Neurosci Biobehav Rev*. (2013) 37:349–57. doi: 10.1016/j.neubiorev.2013.01.015
6. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism Relat Disord*. (2009) 15:S53–8. doi: 10.1016/S1353-8020(09)70781-3
7. Felix K, Gain K, Paiva E, Whitney K, Jenkins ME, Spaulding SJ. Upper extremity motor learning among individuals with Parkinson's disease: a meta-analysis evaluating movement time in simple tasks. *Parkinsons Dis*. (2012) 2012:589152. doi: 10.1155/2012/589152
8. Mak MK, Wong-Yu IS, Shen X, Chung CL. Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nat Rev Neurol*. (2017) 13:689–703. doi: 10.1038/nrneurol.2017.128
9. Robinson AG, Dennett AM, Snowdon DA. Treadmill training may be an effective form of task-specific training for improving mobility in people with Parkinson's disease and multiple sclerosis: a systematic review and meta-analysis. *Physiotherapy*. (2019) 105:174–86. doi: 10.1016/j.physio.2018.11.007
10. Salmanpour MR, Shamsaei M, Saberi A, Klyuzhin IS, Tang J, Sossi V, et al. Machine learning methods for optimal prediction of motor outcome in Parkinson's disease. *Phys Med*. (2020) 69:233–40. doi: 10.1016/j.ejmp.2019.12.022
11. Leung KH, Salmanpour MR, Saberi A, Klyuzhin IS, Sossi V, Jha AK, et al. Using deep-learning to predict outcome of patients with Parkinson's disease. In: *IEEE Nuclear Science Symposium and Medical Imaging Conference Proceedings (NSS/MIC)*. (2018). p. 1–4. doi: 10.1109/NSSMIC.2018.8824432

12. Van Gilder JL, Hooyman A, Peterson DS, Schaefer SY. Post-stroke cognitive impairments and responsiveness to motor rehabilitation: a review. *Curr Phys Med Rehabil Rep*. (2020) 8:461–8. doi: 10.1007/s40141-020-00283-3
13. Schaefer SY, Sullivan JM, Peterson DS, Fauth EB. Cognitive function at admission predicts amount of gait speed change in geriatric physical rehabilitation. *Ann Phys Rehabil Med*. (2020) 63:359–61. doi: 10.1016/j.rehab.2019.08.004
14. Friedman PJ, Baskett JJ, Richmond DE. Cognitive impairment and its relationship to gait rehabilitation in the elderly. *N Z Med J*. (1989) 102:603–6.
15. Jung SH, Hasegawa N, Mancini M, King LA, Carlson-Kuhta P, Smulders K, et al. Effects of the agility boot camp with cognitive challenge (ABC-C) exercise program for Parkinson's disease. *NPJ Parkinsons Dis*. (2020) 6:31. doi: 10.1038/s41531-020-00132-z
16. Avenali M, Picascia M, Tassorelli C, Sinforiani E, Bernini S. Evaluation of the efficacy of physical therapy on cognitive decline at 6-month follow-up in Parkinson disease patients with mild cognitive impairment: a randomized controlled trial. *Aging Clin Exp Res*. (2021). doi: 10.1007/s40520-021-01865-4. [Epub ahead of print].
17. Bernini S, Alloni A, Panzarasa S, Picascia M, Quaglini S, Tassorelli C, et al. A computer-based cognitive training in mild cognitive impairment in Parkinson's disease. *NeuroRehabilitation*. (2019) 44:555–67. doi: 10.3233/NRE-192714
18. Bo J, Seidler RD. Visuospatial working memory capacity predicts the organization of acquired explicit motor sequences. *J Neurophysiol*. (2009) 101:3116–25. doi: 10.1152/jn.00006.2009
19. Langan J, Seidler RD. Age differences in spatial working memory contributions to visuomotor adaptation and transfer. *Behav Brain Res*. (2011) 225:160–8. doi: 10.1016/j.bbr.2011.07.014
20. Jeunet C, Jahanpour E, Lotte F. Why standard brain-computer interface (BCI) training protocols should be changed: an experimental study. *J Neural Eng*. (2016) 13:36024. doi: 10.1088/1741-2560/13/3/036024
21. Jeunet C, Kaoua B, Subramanian S, Hachet M, Lotte F. Predicting mental imagery-based BCI performance from personality, cognitive profile and neurophysiological patterns. *PLoS ONE*. (2015) 10:e0143962. doi: 10.1371/journal.pone.0143962
22. Bo J, Borza V, Seidler RD. Age-related declines in visuospatial working memory correlate with deficits in explicit motor sequence learning. *J Neurophysiol*. (2009) 102:2744–54. doi: 10.1152/jn.00393.2009
23. Van Gilder JL, Hengge CR, Duff K, Schaefer SY. Visuospatial function predicts one-week motor skill retention in cognitively intact older adults. *Neurosci Lett*. (2018) 664:139–43. doi: 10.1016/j.neulet.2017.11.032
24. Van Gilder JL, Walter CS, Hengge CR, Schaefer SY. Exploring the relationship between visuospatial function and age-related deficits in motor skill transfer. *Aging Clin Exp Res*. (2020) 32:1451–8. doi: 10.1007/s40520-019-01345-w
25. Van Gilder JL, Lohse KR, Duff K, Wang P, Schaefer SY. Evidence for associations between Rey-Osterrieth Complex Figure test and motor skill learning in older adults. *Acta Psychol (Amst)*. (2021) 214:103261. doi: 10.1016/j.actpsy.2021.103261
26. Chan JSY, Wu Q, Liang D, Yan JH. Visuospatial working memory training facilitates visually-aided explicit sequence learning. *Acta Psychol*. (2015) 161:145–53. doi: 10.1016/j.actpsy.2015.09.008
27. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, et al. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. *Mov Disord*. (2016) 31:95–102. doi: 10.1002/mds.26359
28. Cummings JL. The dementias of Parkinson's disease: prevalence, characteristics, neurobiology, and comparison with dementia of the Alzheimer type. *Eur Neurol*. (1988) 28:15–23.
29. Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, et al. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain*. (1988) 111:695–718. doi: 10.1093/brain/111.3.695
30. Paul SS, Dibble LE, Olivier GN, Walter C, Duff K, Schaefer SY. Dopamine replacement improves motor learning of an upper extremity task in people with Parkinson disease. *Behav Brain Res*. (2020) 377:112213. doi: 10.1016/j.bbr.2019.112213
31. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
32. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology*. (2009) 73:1738–45. doi: 10.1212/WNL.0b013e3181c34b47
33. Earhart GM, Cavanaugh JT, Ellis T, Ford MP, Foreman KB, Dibble L. The 9-hole PEG test of upper extremity function: average values, test-retest reliability, and factors contributing to performance in people with Parkinson disease. *J Neurol Phys Ther*. (2011) 35:157–63. doi: 10.1097/NPT.0b013e318235da08
34. Schaefer SY. Preserved motor asymmetry in late adulthood: is measuring chronological age enough? *Neuroscience*. (2015) 294:51–9. doi: 10.1016/j.neuroscience.2015.03.013
35. Walter CS, Hengge CR, Lindauer BE, Schaefer SY. Declines in motor transfer following upper extremity task-specific training in older adults. *Exp Gerontol*. (2019) 116:14–9. doi: 10.1016/j.exger.2018.12.012
36. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. (2008) 23:2129–70. doi: 10.1002/mds.22340
37. Yesavage JA, Sheikh JI. 9/Geriatric Depression Scale (GDS). *Clin Gerontol*. (1986) 5:165–73. doi: 10.1300/J018v05n01_09
38. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the Index of ADL1. *Gerontologist*. (1970) 10:20–30. doi: 10.1093/geront/10.1_Part_1.20
39. Schaefer SY, Hooyman A, Duff K. Using a timed motor task to predict one-year functional decline in amnestic mild cognitive impairment. *J Alzheimers Dis*. (2020) 77:53–8. doi: 10.3233/JAD-200518
40. Suchy Y, Kraybill ML, Franchow E. Practice effect and beyond: reaction to novelty as an independent predictor of cognitive decline among older adults. *J Int Neuropsychol Soc*. (2011) 17:101–11. doi: 10.1017/S135561771000130X
41. Orrell AJ, Eves FF, Masters RSW. Implicit motor learning of a balancing task. *Gait Posture*. (2006) 23:9–16. doi: 10.1016/j.gaitpost.2004.11.010
42. Schaefer SY, Dibble LE, Duff K. Efficacy and feasibility of functional upper extremity task-specific training for older adults with and without cognitive impairment. *Neurorehabil Neural Repair*. (2015) 29:636–44. doi: 10.1177/1545968314558604
43. Schaefer SY, Patterson CB, Lang CE. Transfer of training between distinct motor tasks after stroke. *Neurorehabil Neural Repair*. (2013) 27:602–12. doi: 10.1177/1545968313481279
44. Toglia J, Fitzgerald KA, O'Dell MW, Mastrogiovanni AR, Lin CD. The mini-mental state examination and montreal cognitive assessment in persons with mild subacute stroke: relationship to functional outcome. *Arch Phys Med Rehabil*. (2011) 92:792–8. doi: 10.1016/j.apmr.2010.12.034
45. Saverino A, Waller D, Rantell K, Parry R, Moriarty A, Playford ED. The role of cognitive factors in predicting balance and fall risk in a neuro-rehabilitation setting. *PLoS ONE*. (2016) 11:e0153469. doi: 10.1371/journal.pone.0153469
46. Zietemann V, Georgakis MK, Dondaine T, Müller C, Mendyk A-M, Kopczak A, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. *Neurology*. (2018) 91:e1838 LP-e1850. doi: 10.1212/WNL.0000000000006506
47. Lim K-B, Kim J, Lee H-J, Yoo J, You E-C, Kang J. Correlation between montreal cognitive assessment and functional outcome in subacute stroke patients with cognitive dysfunction. *Ann Rehabil Med*. (2018) 42:26–34. doi: 10.5535/arm.2018.42.1.26
48. Abzhandadze T, Rafsten L, Lundgren Nilsson Å, Palstam A, Sunnerhagen KS. Very early MoCA can predict functional dependence at 3 months after stroke: a longitudinal, cohort study. *Front Neurol*. (2019) 10:1051. doi: 10.3389/fneur.2019.01051
49. Wang P, Infurna FJ, Schaefer SY. Predicting motor skill learning in older adults using visuospatial performance. *J Mot Learn Dev*. (2019) 8:38–51. doi: 10.1123/jmld.2018-0017
50. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. (2008) 23:837–44. doi: 10.1002/mds.21956
51. Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*. (2009) 72:1121–6. doi: 10.1212/01.wnl.0000338632.00552.cb

52. Van Gilder JL, Hooyman A, Bosch PR, Schaefer SY. Generalizing the predictive relationship between 1-month motor skill retention and Rey-Osterrieth Delayed Recall scores from nondemented older adults to individuals with chronic stroke: a short report. *J Neuroeng Rehabil*. (2021) 18:94. doi: 10.1186/s12984-021-00886-4
53. Mullick AA, Subramanian SK, Levin MF. Emerging evidence of the association between cognitive deficits and arm motor recovery after stroke: a meta-analysis. *Restor Neurol Neurosci*. (2015) 33:389–403. doi: 10.3233/RNN-150510
54. French MA, Cohen ML, Pohlig RT, Reisman DS. Fluid cognitive abilities are important for learning and retention of a new, explicitly learned walking pattern in individuals after stroke. *Neurorehabil Neural Repair*. (2021) 35:419–30. doi: 10.1177/15459683211001025
55. McDonald MW, Black SE, Copland DA, Corbett D, Dijkhuizen RM, Farr TD, et al. Cognition in stroke rehabilitation and recovery research: consensus-based core recommendations from the second stroke recovery and rehabilitation roundtable. *Neurorehabil Neural Repair*. (2019) 33:943–50. doi: 10.1177/1545968319886444
56. Begemann MJ, Brand BA, Curčić-Blake B, Aleman A, Sommer IE. Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. *Psychol Med*. (2020) 50:2465–86. doi: 10.1017/S0033291720003670
57. King LA, Mancini M, Smulders K, Harker G, Lapidus JA, Ramsey K, et al. Cognitively challenging agility boot camp program for freezing of gait in Parkinson Disease. *Neurorehabil Neural Repair*. (2020) 34:417–27. doi: 10.1177/1545968320909331
58. Jiang Y, Guo Z, McClure MA, He L, Mu Q. Effect of rTMS on Parkinson's cognitive function: a systematic review and meta-analysis. *BMC Neurol*. (2020) 20:377. doi: 10.1186/s12883-020-01953-4
59. Cirstea CM, Lee P, Craciunas SC, Choi I-Y, Burris JE, Nudo RJ. Pre-therapy neural state of bilateral motor and premotor cortices predicts therapy gain after subcortical stroke: a pilot study. *Am J Phys Med Rehabil*. (2018) 97:23–33. doi: 10.1097/PHM.0000000000000791
60. Tozlu C, Edwards D, Boes A, Labar D, Tsagaris KZ, Silverstein J, et al. Machine learning methods predict individual upper-limb motor impairment following therapy in chronic stroke. *Neurorehabil Neural Repair*. (2020) 34:428–39. doi: 10.1177/1545968320909796
61. Burke Quinlan E, Dodakian L, See J, McKenzie A, Le V, Wojnowicz M, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. *Ann Neurol*. (2015) 77:132–45. doi: 10.1002/ana.24309
62. Stinear CM, Byblow WD, Ackerley SJ, Smith M-C, Borges VM, Barber PA. Proportional motor recovery after stroke: implications for trial design. *Stroke*. (2017) 48:795–8. doi: 10.1161/STROKEAHA.116.016020
63. Smith M-C, Byblow WD, Barber PA, Stinear CM. Proportional recovery from lower limb motor impairment after stroke. *Stroke*. (2017) 48:1400–3. doi: 10.1161/STROKEAHA.116.016478
64. Qin L, Jing D, Parauda S, Carmel J, Ratan RR, Lee FS, et al. An adaptive role for BDNF Val66Met polymorphism in motor recovery in chronic stroke. *J Neurosci*. (2014) 34:2493–502. doi: 10.1523/JNEUROSCI.4140-13.2014
65. Pham M Van, Miyaguchi S, Watanabe H, Saito K, Otsuru N, Onishi H. Effect of repetitive passive movement before motor skill training on corticospinal excitability and motor learning depend on BDNF polymorphisms. *Front Hum Neurosci*. (2021) 15:621358. doi: 10.3389/fnhum.2021.621358
66. Kim E-J, Park C-H, Chang WH, Lee A, Kim ST, Shin Y-I, et al. The brain-derived neurotrophic factor Val66Met polymorphism and degeneration of the corticospinal tract after stroke: a diffusion tensor imaging study. *Eur J Neurol*. (2016) 23:76–84. doi: 10.1111/ene.12791
67. Kulisevsky J, García-Sánchez C, Berthier ML, Barbanoj M, Pascual-Sedano B, Gironell A, et al. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. *Mov Disord*. (2000) 15:613–26. doi: 10.1002/1531-8257(200007)15:4<613::aid-mds1005>3.0.co;2-f
68. Ginis P, Heremans E, Ferrari A, Bekkers EMJ, Canning CG, Nieuwboer A. External input for gait in people with Parkinson's disease with and without freezing of gait: one size does not fit all. *J Neurol*. (2017) 264:1488–96. doi: 10.1007/s00415-017-8552-6
69. Hall JM, Shine JM, Walton CC, Gilat M, Kamsma YPT, Naismith SL, et al. Early phenotypic differences between Parkinson's disease patients with and without freezing of gait. *Parkinsonism Relat Disord*. (2014) 20:604–7. doi: 10.1016/j.parkreldis.2014.02.028
70. Peterson DS, Fling BW, Mancini M, Cohen RG, Nutt JG, Horak FB. Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze. *J Neurol Neurosurg Psychiatry*. (2015) 86:786–92. doi: 10.1136/jnnp-2014-308840
71. Cancela JM, Nascimento CM, Varela S, Seijo-Martinez M, Lorenzo-Lopez L, Millan-Calenti JC, et al. Influence of cognitive impairment on the freezing of gait in non-demented people with Parkinson's disease. *Rev Neurol*. (2018) 66:289–96. doi: 10.33588/rn.6609.2017289
72. Kantak SS, Winstein CJ. Learning-performance distinction and memory processes for motor skills: a focused review and perspective. *Behav Brain Res*. (2012) 228:219–31. doi: 10.1016/j.bbr.2011.11.028

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Rehabilitation Sciences

METHODS
published: 23 November 2021
doi: 10.3389/fresc.2021.777981

Combining Repetitive Transcranial Magnetic Stimulation and Video Game-Based Training to Improve Dexterity in Parkinson's Disease: Study Protocol of a Randomized Controlled Trial

Manuela Pastore-Wapp[1,2], *Dirk Lehnick*[3,4], *Tobias Nef*[2], *Stephan Bohlhalter*[1,5] *and Tim Vanbellingen*[1,2]*

[1] Neurocenter, Luzerner Kantonsspital, Lucerne, Switzerland, [2] ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation Group, University of Bern, Bern, Switzerland, [3] Biostatistics and Methodology, Clinical Trials Unit Central Switzerland, Lucerne, Switzerland, [4] Department of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland, [5] University of Zurich, Zurich, Switzerland

OPEN ACCESS

Edited by:
Elizabeth Skidmore,
University of Pittsburgh, United States

Reviewed by:
Rachel M. Proffitt,
University of Missouri, United States
Mohammad Sami Al-Wardat,
Aqaba University of Technology, Jordan

***Correspondence:**
Tim Vanbellingen
tim.vanbellingen@luks.ch;
tim.vanbellingen@artorg.unibe.ch

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: 16 September 2021
Accepted: 08 October 2021
Published: 23 November 2021

Citation:
Pastore-Wapp M, Lehnick D, Nef T, Bohlhalter S and Vanbellingen T (2021) Combining Repetitive Transcranial Magnetic Stimulation and Video Game-Based Training to Improve Dexterity in Parkinson's Disease: Study Protocol of a Randomized Controlled Trial. Front. Rehabilit. Sci. 2:777981. doi: 10.3389/fresc.2021.777981

Introduction: Patients with Parkinson's disease (PD) often exhibit difficulties with dexterity during the performance of activities of daily living (ADL) due to dysfunctional supplementary motor area (SMA). The aim of this clinical trial protocol work is to describe how the effectiveness of a combined repetitive transcranial magnetic stimulation (rTMS) over SMA and video-game-based skill training (VBT) in PD will be evaluated. The short and long-term benefits are assessed.

Methods and analysis: A single-blind (patients) stratified (based on Hoehn & Yahr) parallel randomized sham-controlled rTMS-VBT study with a baseline and two follow-up measurements (3 and 12 weeks) is being conducted. These measurements include the dexterity questionnaire 24 (DextQ-24) as a primary outcome, and nine hole peg test and coin rotation task as main secondary dexterity outcomes. Further secondary outcomes will be the subscale II of the movement disorders society unified PD rating scale (MDS-UPDRS) to assess improvements on overall ADL and the Parkinson's Disease Questionnaire-39 to assess quality of life. Thirty-six outpatients (from one neurorehabilitation center) with PD (diagnosis based on brain bank criteria) will be recruited who report difficulties with dexterity in performing ADL. All PD patients will receive a 45-min VBT three times a week for 3 weeks. The PD patients randomized in the experimental group will receive VBT preceded by real rTMS, being intermittent theta burst (iTBS) stimulation sessions. The PD patients randomized to the control group receive a VBT with sham rTMS.

Discussion: The study will provide evidence to determine whether a combined iTBS and VBT skill intervention is more effective than a VBT intervention alone to improve dexterity in PD.

Ethics and dissemination: The study was approved by the Ethics Committee for Northwest and Central Switzerland (EKNZ), Switzerland 2019–00433. The study will be conducted in accordance with the Helsinki Declaration and the Guidelines of Good Clinical Practice. Informed consent will be signed prior to subject enrolment. Dissemination will include submission to international peer-reviewed professional journals and presentation at international congresses.

The study protocol has been registered in the clinicaltrials.gov registry with the identification code: NCT04699149.

Keywords: Parkinson's disease, transcranial magnetic stimulation, dexterity, video game-based training, RCT - randomized controlled trial

INTRODUCTION

Patients with Parkinson's disease (PD) often face dexterity-related difficulties, both in performing basic (grooming, buttoning a shirt) and instrumental activities of daily living (ADL), such as cooking a meal, organizing pills in pill holders, and writing (1–4). These difficulties may be present even in early stages of the disease. They further increase the burden of disease and reduce quality of life (QoL) (2). Dopaminergic therapy only slightly improves impaired dexterity (5). Therefore, complementary treatments are needed to reduce its impact on ADL. Previous studies have shown short-term effects (immediately after training) of a particular hand training, either supervised (6) or unsupervised (7). However, no sustainable long-term effects were shown so far. A reason may be that important aspects for an optimized motor learning (8) were not sufficiently targeted, such as the variability of the load, the feedback of the performance over a longer period of time or the level of difficulty.

Video-game-based training (VBT) has been rapidly developing in PD neurorehabilitation (9). VBT is attractive and challenging, and therefore potentially suitable to motivate PD patients over time (10). Other benefits of VBT include the ability to adjust the difficulty of the exercise and to provide online visual and/or verbal feedback during the training. In terms of dexterity, several studies have now shown that VBT was feasible and improved dexterity in PD patients in the short term (immediately after the intervention) (11–14). However, long-term effects of VBT have not yet been assessed.

To further improve training effects in PD, a combination of behavioral interventions with neuromodulation techniques such as non-invasive repetitive transcranial magnetic stimulation (rTMS) has been proposed (15–18). The rationale behind a combined rTMS and behavioral training is that by applying rTMS before training, the brain may reach an optimal state of learning thereby facilitating subsequent training effects (19). The principle of activity dependent neuroplasticity (20) also suggests that combinations of behavioral training with rTMS might have promise in facilitating long term effects (21). We use herein an intermittent theta-burst protocol (iTBS), a type of rTMS, which is expected to produce behavioral effects not only outlasting the single administration (short term), but also retained after multiple applications (long term) (22–24). iTBS has been shown to be facilitatory in nature by increasing cortical excitability (25–27). When applied over primary motor cortex iTBS may enhance either sensorimotor integration (28) or mood (29) in PD patients. Similarly, if supplementary motor area (SMA) was the target region, beneficial effects on overall motor symptoms were shown by using rTMS (24, 30). The SMA also plays a key role in the generation of self-initiated, multisegmental, complex, voluntary finger movements (31, 32). In PD however, SMA activity can be reduced due to decreased positive efferent feedback arising from the basal ganglia–thalamocortical motor loop (33). Consequently, PD patients may show altered activation patterns in the SMA and less cortico–cortical excitability. Indeed, it was shown that a diminished resting state perfusion in the left SMA in PD explained poor dexterous performance, which was measured by a coin rotation (CR) task (34). These findings further attributed to the role of the SMA controlling for fine finger movements. Interestingly, one previous pilot rTMS study in PD already demonstrated a short-term improvement on handwriting, which requires good dexterous function, when patients received one session of facilitatory rTMS over the left SMA (35).

The aim of the present clinical trial protocol paper is to describe how the effectiveness of a combined iTBS-VBT skill 3-week intervention in PD will be evaluated. The short and long-term benefits of this training program will be evaluated. We predict that the use of iTBS before VBT can further strengthen the training effects and possibly also achieve sustainable long-term effects. Therefore, we expect significantly improved dexterity in both the short and long-term, which leads to improved ADL and QoL in patients with PD.

METHODS AND ANALYSIS

Trial Design

A single-blind (patients) parallel RCT with a stratified random intervention distribution is carried out. The random sequence generation using a computer software program is stratified, according to the Hoehn & Yahr (H&Y) scale, Level 1 = H&Y I to Level 4 = H&Y 4, (36) at T0. After stratification, a simple randomization (1–1) occurs within each stratum level (Level 1 to 4). Randomization and treatment allocation is concealed within SecuTrial, which is a GCP-compliant electronic data base system (https://www.secutrial.com/en/), managed externally by

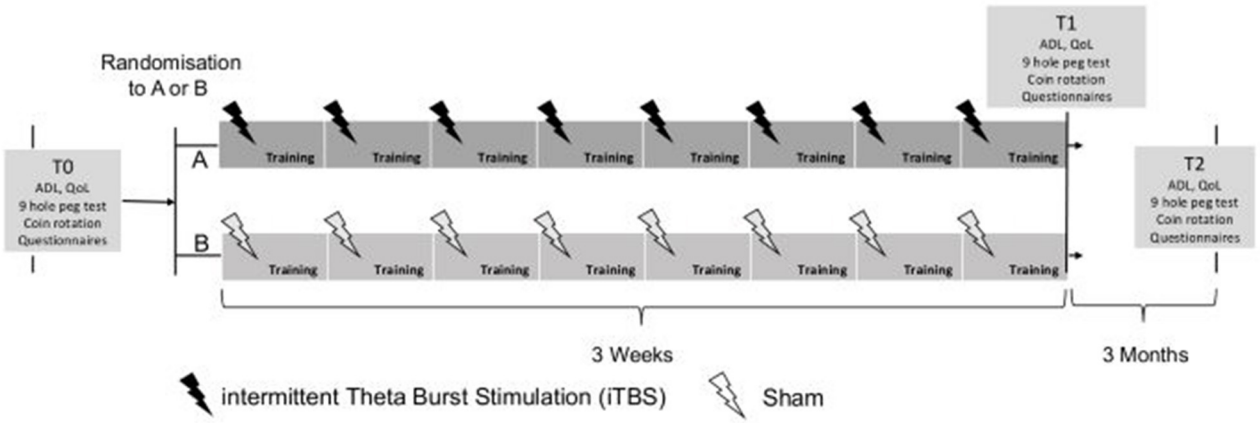


FIGURE 1 | Design of study: T0 baseline assessment, T1 end of training, T2 follow-up after 3 months. ADL, activities of daily living; QoL, quality of life.

the Clinical Trial Unit (CTU) Schweizer Paraplegiker Zentrum (SPZ) Nottwil. After the baseline assessment (hereinafter referred to as T0), all PD patients receive 45-min manual dexterity intervention three times a week for a period of 3 weeks. The PD patients randomized in the experimental group will receive VBT each time, preceded by true iTBS stimulation. The PD patients randomized to the control group receive a VBT with a preceding sham TMS each time (see **Figure 1**). Patients will be blinded to the rTMS protocol (sham vs. real). This means that patients will not be informed throughout the whole trial whether they received real or sham rTMS stimulation. Follow-up measurements (T1 and T2) are carried out after a period of 3 weeks and 3 months. All data is collected within SecuTrial. The study will be performed according to the CONSORT (Consolidated Standards of Reporting Trials) statement, http://www.consort-statement.org/.

Participants

The patients are recruited by two investigators (TV, SB), not involved in the assessment and treatment procedures, at the Neurocenter, Lucerne Cantonal Hospital, Switzerland. Inclusion criteria are confirmed PD according to the brain back criteria (37); H&Y I to IV (36); age 50–90 years old; written and signed informed consent and experiencing dexterous difficulties in performing ADL. Exclusion criteria are significant medical, psychiatric comorbidity including dementia as defined by Montreal Cognitive Assessment (MOCA $<$ 21) (38); inability to understand the scope of the study and to follow the study procedures according to the protocol, e.g., filling out questionnaires and participating in another intervention study. Exclusion criteria for TMS use are current pregnancy, personal history of epilepsy or seizures, and any psychiatric, neurological, or medical history other than PD. All data related to the study will be collected at the outpatient neurorehabilitation center, Lucerne Cantonal Hospital.

Sample Size Calculation

The significance level alpha is defined as 0.05 (two-tailed) for detecting a mean difference between groups on the primary outcome being the Dexterity Questionnaire 24 (DextQ-24) (4) in favor of the real iTBS-VBT dexterity group. Based on previously observed data one may assume a within-group standard deviation of up to 10 points. The study is designed to detect a mean difference of 10 or more points, which exceeds the MDC95 of 8 points found in our validation study (4). A total sample size of 30 evaluable subjects, 15 per group, is required to detect a mean difference of an at least 1.1-fold within-group standard deviation with a target power of at least 80%. Considering a maximal drop-out rate of 15%, we aim to recruit 36 patients in total.

In any case, patients who do not complete the training sessions and/or even decide to drop out of the study for whatever reason will be encouraged to continue to participate in the scheduled assessments for at least T1 (and/or a time point prior to the individual end of the study) and ideally to provide a postbaseline assessment for at least the primary endpoint.

Material

At T0 handedness (39), disease duration, medication dosage intake per day, the Montreal Cognitive Assessment test [MoCA, (40)] are assessed. The MoCA is divided into visuo-spatial abilities, short-term memory, executive function, attention and working memory, language and phonemic fluency, and orientation.

Parkinsonian motor symptoms are assessed by the Movement Disorders Society unified Parkinson's Disease Rating Scale (MDS-UPDRS) subscale III (41) at T0, T1, and T2. Severity of the upper limb motor deficits is measured with the items 3.3 to 3.6 and 3.15 to 3.18 of the MDS-UPDRS subscale III.

Primary Endpoint

The DextQ-24 is assessed at T0, T1, and T2, which is a standardized patient self-rated outcome measure for evaluating dexterity related ADL in PD (4). This questionnaire

contains 24 questions, which are divided into five subgroups ("washing/grooming;" "dressing;" "meals and kitchen;" "everyday tasks;" "TV/CD/DVD"). For each question, patients must state whether they have no problems (1 point), minor problems (2 points), major problems (3 points), or need aid (4 points) to perform the task. Points are added in each subgroup and summed to a total score. Score ranges from a minimum of 24 to a maximum of 96 points.

Secondary Endpoints

The Nine Hole Peg test (9-HPT) and the coin rotation (CR) task are used to explore hand and finger function at T0, T1, and T2. The 9-HPT is a standardized, well established, and reliable measure of hand performance in patients with PD (42, 43). The patients have to take nine pegs one by one into the holes on a board and then move them back to the container. The CR task (44) measures fine coordinated finger movements and has proven to be a suitable and valid dexterity test in patients with PD (5, 45). The CR task requires the patient to rotate a 20 swiss cent through consecutive 180° half turns, as rapidly as possible for 10 rotations. Time to complete the 9-HPT and the CR tasks are recorded, by an experienced non-blinded outcome assessor (MP-W), twice for each hand separately.

The subscale II of the MDS-UPDRS (41), containing 13 items, and each of them scored on a 0–4 rating scale (0 = normal; 1 = slight problem, 2 = mild problem, 3 = moderate problem, 4 = severe problem), is used to assess improvements on overall ADL. The scale is designed to be a self-administered questionnaire, but can be reviewed by the outcome assessor to ensure completeness and clarity.

To assess QoL (at T0, T1, and T2), we used the Parkinson's disease questionnaire-39 (PDQ-39) (46). This patient self-rated questionnaire consists of 39 questions, which are divided into eight subscales (mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort). The total score is given by the sum of all items and is then transformed in a range from 0 to 100. A lower value corresponds to a better perception of subject's QoL.

Stimulation Protocol

iTBS is applied using a MagPro R30 stimulator (Medtronic Functional Diagnostics, Skovlunde, Denmark), connected to a figure-of-eight coil (Magnetic Coil Transducer MC-B70, Medtronic) with an outer radius of 50 mm or to a similar looking sham coil (Magnetic Coil Transducer MC-P-B70, Medtronic). An iTBS protocol is used as done in our previous rTMS study (4). For the iTBS protocol a theta burst of three pulses with a 20-ms interval repeated as a train of 10 bursts with a repetition rate of 5 Hz is used. Trains are repeated 20 times with an interval of 8-s. During stimulation, the examiner places the figure-eight coil over the left or right SMA, depending on the side of the more severe dexterity problems. The position for SMA stimulation is determined in each patient as follows. First, the optimal position for activation of the right abductor hallucis muscle will be determined by moving the coil in 1 cm steps along the sagittal midline around scalp vertex (Cz) with the handle pointing to the right. The active motor threshold (AMT) for this muscle is then determined. Next, stimuli at 120% AMT are given, moving the coil anteriorly along the sagittal mid-line in 1 cm steps. The SMA is defined as being 1 cm anterior to the last site from which motor evoked potentials (MEPs) can be evoked during contraction (47). Following these criteria, the position for SMA stimulation is expected to be 3 cm anterior from the optimal position for activation of the abductor hallucis muscle in most patients. Sham stimulation is applied by the same iTBS protocol, however a sham coil is used. The patients are asked to keep their eyes closed during stimulation. Immediately after stimulation the PD patients start with the VBT.

VBT Intervention

The VBT intervention takes place at the neurorehabilitation outpatient center, Lucerne Cantonal Hospital. The interactive training program contains the use of two different devices. Each device is used for about 15 min. The first interactive device is the GripAble (https://gripable.co/) (**Figure 2A**), which is a new wireless device allowing the training of upper-arm and hand movements during wrist extension and flexion, pronation and supination, wrist radial and ulnar deviation, and also hand and pinch grip-force (48). To be able to manipulate objects well-one needs good hand/finger pinch grip and release (49, 50). The device is able to capture fine hand/finger movements. It can be connected (by bluetooth) with a tablet on which a GripAble app including different therapy games is installed. So far, nine games are available, of which five were chosen to be used for the present trial, since each of these five games focus on different hand/finger movements. Finger movements (pinch grip) can be done by adding a pinch pin.

Plume

In this activity, the user is controlling the bird as it flies along a course using wrist flexion to move downward and wrist extension to move upward. The patient has to collect as many feathers as possible and to avoid different obstacles. If the bird flies in an obstacle the patients lose points. High level of visual perception and concentration is required. The time taken increases as the user works through the levels (**Figure 2B** top middle).

Windowsill

This activity requires wrist pronation, supination, and grip release. This activity presents pots in different places on a windowsill. A bag of soil is then moved left to right (using pronation/supination) until it is placed directly above one of the pots. When still, the soil can be released to fill the pot by gripping. Once the pot is full, a seed can be placed into the pot using the same control. This is followed by a watering can which needs to be poured until the flower appears. As the levels progress, more pots appear and are at a wider spacing (**Figure 2C** top right).

Balloon Buddies

The focus is on controlled grip (requiring hand/finger strength and endurance) and release. The patient controls an owl which is suspended from the balloon. The owl needs to collect all the stars to gain points. Squeezing GripAble inflates the balloon to make the owl go up the screen. Releasing GripAble brings the owl

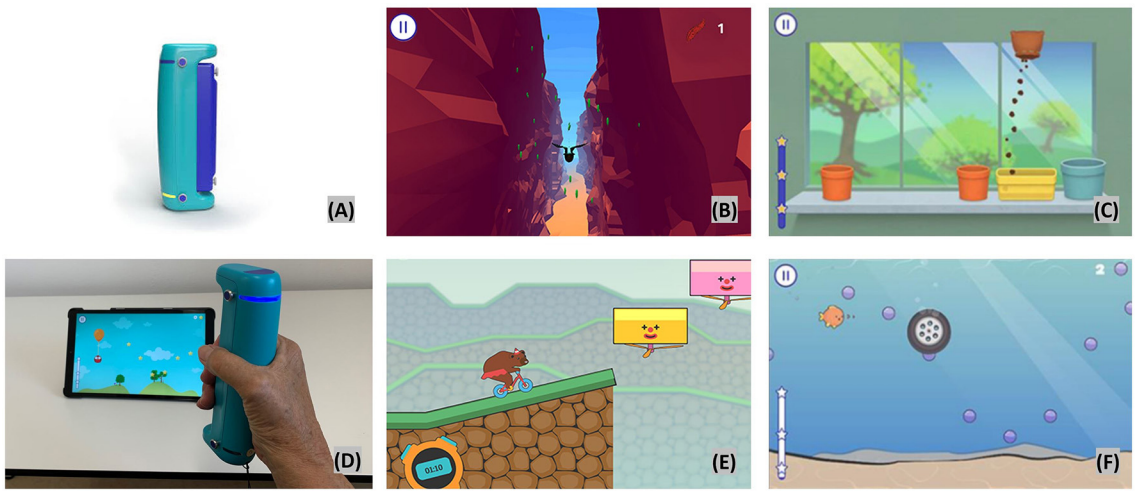


FIGURE 2 | Video based training with GripAble. Top left **(A)** GripAble device; top middle **(B)** Plume; top right **(C)** Windowsill; bottom left **(D)** patient playing Balloon Buddies; bottom middle **(E)** Circus Escape; bottom right **(F)** Pufferfish.

down the screen. The levels give increased time and complexity of the required control. The emphasis is on smooth transition between grip and release. The placement and the smoothness of the curve of stars alters through the levels to give gradual increase in demand (see **Figure 2D** bottom left).

Circus Escape

This activity targets controlled and fast reaction in grip and release. The goal is for the patients to power the bear on the cycle along the course without falling off the cliff. The patient will need to squeeze with more intensity and harder as the cycle moves up hills. The levels increase in complexity and length as they progress. There is a natural break within each level as the user waits for the hazards to reach the point of safe movement (**Figure 2E** bottom middle).

Pufferfish

This activity requires wrist ulnar and radial hand deviation, optional grip and release. The patient is controlling the fish to move up and down the screen by moving GripAble through wrist radial and ulnar deviation. The fish needs to catch the bubbles. In Level 3 onwards, hazards appear which need to be avoided or can be blown away by squeezing. The fish will not be affected by swimming over the sandy area at the base of the screen (**Figure 2F** bottom right).

The second device is the Leap Motion™ Controller, LMC™ (https://www.leapmotion.com/) which is an optoelectronic commercially available device suitable for hand gesture-controlled user interfaces allowing human–computer interaction. It tracks hand and finger movements by modelling all physiological hand and finger joints within a virtual reality (VR) environment (51, 52). The patients see their hand in real time on the screen (**Figure 3**).

Four games were downloaded from the manufacturer's Web site (Leap Motion Gallery: Blocks, Flowers, Tilt Your Ball and Fragmental 3D (see also https://gallery.leapmotion.com/), which were partly evaluated in our previous pilot study (14). In short, in the first game, *Tilt Your Ball* (**Figure 3A** top left), the screen shows a room filled with four colored blocks. There are also four bodies. The aim is to use the fingers to connect the colored blocks to the body (pinch grip). The second game shows a flower (**Figure 3B** top right) made of steel with seven pedals. The aim is to remove the pedals one by one with the fingers. In *Tilt Your Ball* (**Figure 3C** bottom left), the patient has to navigate a small metal ball through different levels by tilting his hand. The successive levels become more and more difficult. *Fragmented 3D* (**Figure 3D** bottom right) is played by moving, rotating, and dropping blocks to form rows across a 3D grid. The goal is to build rows across the grid to erase lines, make combos and thus score points. The games Blocks, Flower, Fragmented

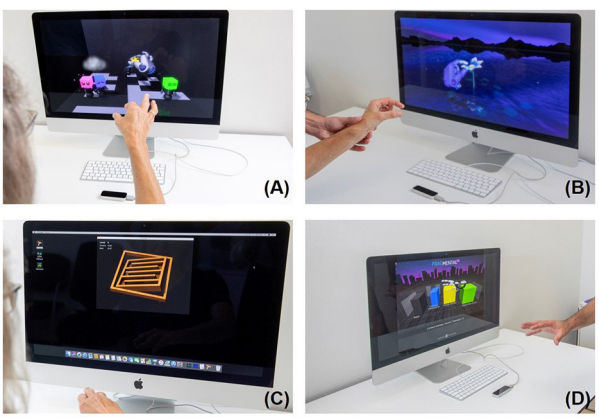


FIGURE 3 | Leap Motion training, Top left **(A)** Blocks; top right **(B)** flower; bottom left **(C)** Tilt Your Ball; bottom right **(D)** Fragmented 3D.

3D specifically requires fine coordinated movements. Tilt Your Ball requires fine combined wrist flexion extension, forearm prosupination movements, which are all needed for optimal object manipulation.

Statistical Analysis

Descriptive statistics are used to present baseline characteristics and results of outcome measurements. In order to investigate the treatment effect for the primary endpoint, a hierarchical testing strategy is applied. For DextQ-24 at T1, an ANCOVA model is used with a fixed effect for treatment and the baseline (T0) value of DextQ-24 as a covariate. If a treatment effect at T1 could have been shown (null hypothesis rejected), the same approach will be performed for DextQ-24 at T2 in order to see whether the treatment effect is sustainable. An estimate for the treatment effect will be derived from the model together with a corresponding 95% confidence interval. As a postestimation procedure effect size measures such as (partial) eta square with corresponding 95% intervals will be provided. In an exploratory manner, the secondary endpoints are tested utilizing the same methodology. As a sensitivity analysis, e.g., to explore the robustness of the results in case of missing values, the primary and secondary endpoints are analyzed using linear mixed effects models with fixed effects for treatment, time point, interaction of treatment and time point, baseline value as a covariate and with subject as a random effect. Estimates for the treatment effects at T1 and T2 with corresponding 95% confidence intervals can be obtained as contrasts derived from these models. Further supportive analyses to check the robustness of the treatment effect estimators can be performed by adjusting the model from the primary analysis for the stratifying variable, namely the H&Y scale.

According to the treatment policy strategy (Intention to treat (ITT) principle) every randomized PD patient, including the drop-outs, is included for final evaluation. For all analyses the level of significance is set to alpha = 0.05 (two-tailed). Statistical analyses are performed using Stata (Version 16.1 or later, StataCorp, College Station, Texas, USA).

DISCUSSION

Dexterity related difficulties during the performance of several ADL are frequently reported in PD, leading to reduced QoL (1–3, 7). Specific dexterity trainings have shown short, (6, 12, 14) but no long-term effects (7). The present study choses an innovative multimodal therapeutical approach, not done before, by using a VBT intervention using two types of devices (GripAble and LMC™), each having its own focus. The GripAble games chosen herein, focus on training train hand/finger pinch grip and release, and different hand movements, which are all key elements for good manipulation of objects. The LMC™ training focus more on independent finger movements. To further boost the effects on dexterity the VBT training is combined with an facilitatory iTBS over SMA, a cortical region being involved in fine motor control (34, 35).

The present proof-of-concept RCT aims at combining, for the first time, VBT and iTBS targeting SMA. The VBT used herein is an attractive new way to train dexterity in PD (9). The games, delivered by using GripAble and LMC™ in this RCT, provide direct feedback, are fun, motivating, and incorporate several levels of difficulty, all aspects which are important to trigger motor learning in PD (8). By combining this attractive training with iTBS we expect to achieve sustainable long-term benefits in dexterity-related ADL also leading to improved QoL in patients with PD. The reason for choosing iTBS is its shorter application time, therefore clinically being more applicable, and lower stimulation intensities compared with conventional rTMS paradigms, inducing more longer-lasting neural effects (23). Currently, TBS seems to be one of the most powerful neuromodulatory stimulation protocols currently available (23).

The total dosage of the present study is 405 min of combined iTBS-VBT training (45 min, three times a week, 3 weeks), representing a short but intensive training. Previous studies using a similar amount of rTMS sessions, already suggested longer lasting behavorial effects, even up to 3 months (53, 54). We assume that a 3-week combined iTBS-VBT training will be enough to achieve both short as well as long-term effects. Furthermore, due to the short training period, it has the potential to be easily implemented in the daily routine of a neurorehabilitation center and at home.

Some limitations have to be mentioned which might occur during the trial. These could be related to the technical devices used in the VBT. The developers of GripAble (see for acknowledgments) are continuously doing efforts to upgrade their system, also by developing new games, potentially interesting for the present trial. However, to avoid contamination of training effects, we will not implement these new games. The long-term follow-up (12 weeks after training) might be a challenge for some PD patients, and may lead to some drop-outs. However, we expect no drop-out rate exceeding 10%, as shown in our previous RCT with a similar design (7).

In summary, the present project aims to investigate, for the first time, the effectiveness of a combined iTBS-VBT 3-week intervention in PD. Its short and long-term benefits will be evaluated. By using iTBS before VBT we expect to further strengthen the VBT effects, also to achieve sustainable long-term effects. The improved dexterity in both the short and long term, will lead to improved ADL and QoL in patients with PD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee for Northwest and Central Switzerland (EKNZ), Switzerland 2019-00433. The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP-W responsible for patient recruitment, provides data collection, and manuscript writing. DL gave critical review of concept, design of the study, and critically revised the manuscript. TN gave critical review of concept, design of the study, and critically revised the manuscript. SB provided concept and design of the study and critically revised the manuscript conceptualization. TV obtained funding, conceived the idea for the present study, overall project coordination, and manuscript writing. All authors contributed to the design of the interventions and outcome measures. All authors assisted in editing and reviewing the submitted manuscript. They all read and approved the final form.

FUNDING

The study is funded by the Jacques and Gloria Gossweiler Foundation.

ACKNOWLEDGMENTS

The authors are very grateful to Simona Wapp and Brigitte C. Kaufmann, who assisted with the experiments, and Nicola Goldsmith, clinical director of GripAble, who provided detailed information about the device, and checked for English grammar and style.

REFERENCES

1. Foki T, Vanbellingen T, Lungu C, Pirker W, Bohlhalter S, Nyffeler T, et al. Limb-kinetic apraxia affects activities of daily living in Parkinson's disease: a multi-center study. *Eur J Neurol.* (2016) 23:1–10. doi: 10.1111/ene.13021
2. Vanbellingen T, Hofmänner D, Kübel S, Bohlhalter S. Limb kinetic apraxia is an independent predictor for quality of life in Parkinson's disease. *Mov Disord Clin Pract.* (2018) 5:156–9. doi: 10.1002/mdc3.12572
3. Vanbellingen T, Kersten B, Bellion M, Temperli P, Baronti F, Müri R, et al. Impaired finger dexterity in Parkinson's disease is associated with praxis function. *Brain Cogn.* (2011) 77:48–52. doi: 10.1016/j.bandc.06.003
4. Vanbellingen T, Nyffeler T, Nef T, Kwakkel G, Bohlhalter S, van Wegen EE. Reliability and validity of a new dexterity questionnaire (DextQ-24) in Parkinson's disease. *Parkinsonism Relat Disord*. (2016) 33:78–83. doi: 10.1016/j.parkreldis.09.015
5. Gebhardt A, Vanbellingen T, Baronti F, Kersten B, Bohlhalter S. Poor dopaminergic response of impaired dexterity in Parkinson's disease: Bradykinesia or limb kinetic apraxia? *Mov Disord.* (2008) 23:1701–6. doi: 10.1002/mds.22199
6. Mateos-Toset S, Cabrera-Martos I, Torres-Sánchez I, Ortiz-Rubio A, González-Jiménez E, Valenza M. Effects of a single hand-exercise session on manual dexterity and strength in persons with Parkinson disease: a randomized controlled trial. *PM R.* (2016) 8:115–22. doi: 10.1016/j.pmrj.06.004
7. Vanbellingen T, Nyffeler T, Nigg J, Janssens J, Hoppe J, Nef T, et al. Home based training for dexterity in Parkinson's disease: a randomized controlled trial. *Parkinsonism Relat Disord*. 41:92–98. doi: 10.1016/j.parkreldis.05.021
8. Nieuwboer A, Rochester L, Müncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism Relat Disord.* (2009) 15:S53–8. doi: 10.1016/S1353-8020(09)70781-3
9. Garcia-Agundez A, Folkerts AK, Konrad R, Caserman P, Tregel T, Goosses M, et al. Recent advances in rehabilitation for parkinson's disease with exergames: a systematic review. *J Neuroeng Rehabil.* (2019) 16:1–17. doi: 10.1186/s12984-019-0492-1
10. Harris DM, Rantalainen T, Muthalib M, Johnson L, Teo WP. Exergaming as a viable therapeutic tool to improve static and dynamic balance among older adults and people with idiopathic Parkinson's disease: a systematic review and meta-analysis. *Front Aging Neurosci.* (2015) 7:167. doi: 10.3389/fnagi.2015.00167
11. Fernández-González P, Carratalá-Tejada M, Monge-Pereira E, Collado-Vázquez S, Sánchez-Herrera Baeza P, Cuesta-Gómez A, et al. Leap motion controlled video game-based therapy for upper limb rehabilitation in patients with Parkinson's disease: a feasibility study. *J Neuroeng Rehabil.* (2019) 16:1–10. doi: 10.1186/s12984-019-0593-x
12. Oña ED, Balaguer C, Cano-de la Cuerda R, Collado-Vázquez S, Jardón A. Effectiveness of serious games for leap motion on the functionality of the upper limb in parkinson's disease: a feasibility study. *Comput Intell Neurosci.* (2018) 2018:7148427. doi: 10.1155./2018/7148427
13. Sánchez-Herrera-Baeza P, Cano-de-la-Cuerda R, Oña-Simbaña ED, Palacios-Ceña D, Pérez-Corrales J, Cuenca-Zaldivar JN, et al. The impact of a novel immersive virtual reality technology associated with serious games in Parkinson's disease patients on upper limb rehabilitation: a mixed methods intervention study. *Sensors*. (2020) 20:2168. doi: 10.3390/s20082168
14. van Beek J, van Wegen E, Bohlhalter S, Vanbellingen T. Exergaming-Based Dexterity training in persons with Parkinson disease: a pilot feasibility study. *J Neurol Phys Ther.* (2019) 43:168–74. doi: 10.1097/NPT.0000000000000278
15. El Tamawy MS, Darwish MH, El Gohary AM, Khalifa HA. S187 Influence of repetitive transcranial magnetic stimulation on cognitive and motor performance in Parkinson's disease patients. *Clin Neurophysiol*. (2017) 128:e238. doi: 10.1016/j.clinph.07.197
16. Nardone R, Versace V, Brigo F, Golaszewski S, Carnicelli L, Saltuari L, et al. Transcranial magnetic stimulation and gait disturbances in Parkinson's disease: a systematic review. *Clin Neurophysiol*. (2020) 50:213–25. doi: 10.1016/j.neucli.05.002
17. Yang C, Guo Z, Peng H, Xing G, Chen H, McClure M, et al. Repetitive transcranial magnetic stimulation therapy for motor recovery in Parkinson's disease: a meta-analysis. *Brain Behav*. (2018) 8:e01132. doi: 10.1002/brb3.1132
18. Yang YR, Tseng CY, Chiou SY, Liao KK, Cheng SJ, Lai KL, et al. Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in parkinson disease: a randomized trial. *Neurorehabil Neural Repair.* (2013) 27:79–86. doi: 10.1177/1545968312451915
19. Butler AJ, Wolf SL. Putting the brain on the map: use of transcranial magnetic stimulation to assess and induce cortical plasticity of upper-extremity movement. *Phys Ther.* (2007) 87:719–36. doi: 10.2522/ptj.20060274
20. Petzinger GM, Fisher BE, Van Leeuwen JE, Vukovic M, Akopian G, Meshul CK, et al. Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Mov Disord.* (2010) 25:S141–5. doi: 10.1002/mds.22782
21. Dimyan MA, Cohen LG. Contribution of transcranial magnetic stimulation to the understanding of functional recovery mechanisms after stroke. *Neurorehabil Neural Repair.* (2010) 24:125–35. doi: 10.1177/1545968309345270
22. Chen YJ, Huang YZ, Chen CY, Chen CL, Chen HC, Wu CY, et al. Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol.* (2019) 19:1–10. doi: 10.1186/s12883-019-1302-x
23. Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. (2016) 63:43–64. doi: 10.1016/j.neubiorev.01.008
24. Ji GJ, Liu T, Li Y, Liu P, Sun J, Chen X, et al. Structural correlates underlying accelerated magnetic stimulation in Parkinson's disease. *Hum Brain Mapp.* (2021) 42:1670–81. doi: 10.1002/hbm.25319

25. Di Lazzaro V, Pilato F, Dileone M, Profice P, Oliviero A, Mazzone P, et al. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *J Physiol.* (2008) 586:3871–9. doi: 10.1113/jphysiol.2008.152736
26. Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. *Eur J Neurosci.* (2012) 35:125–34. doi: 10.1111/j.1460-9568.2011.07924.x
27. Huang YZ, Rothwell JC, Chen RS, Lu CS, Chuang WL. The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clin Neurophysiol.* (2011) 122:1011–8. doi: 10.1016/j.clinph.08.016
28. Degardin A, Devos D, Defebvre L, Destée A, Plomhause L, Derambure P, et al. Effect of intermittent theta-burst stimulation on akinesia and sensorimotor integration in patients with Parkinson's disease. *Eur J Neurosci.* (2012) 36:2669–78. doi: 10.1111/j.1460-9568.2012.08158.x
29. Benninger DH, Berman BD, Houdayer E, Pal N, Luckenbaugh DA, Schneider L, et al. Intermittent theta-burst transcranial magnetic stimulation for treatment of Parkinson disease. *Neurology.* (2011) 76:601–9. doi: 10.1212/WNL.0b013e31820ce6bb
30. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. *Neurology.* (2013) 80:1400–5. doi: 10.1212/WNL.0b013e31828c2f66
31. Johns P. Parkinson's disease. In: *Clinical Neuroscience.*, Churchill Livingstone (2014). p. 163–79. doi: 10.1016./B978-0-443-10321-6.00013-8
32. Nachev P, Kennard C, Husain M. Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci.* (2008) 9:856–69. doi: 10.1038/nrn2478
33. Jenkins IH, Fernandez W, Playford ED, Lees AJ, Frackowiak RSJ, Passingham RE, et al. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. *Ann Neurol.* (1992) 32:749–57. doi: 10.1002/ana.410320608
34. Kübel S, Stegmayer K, Vanbellingen T, Walther S, Bohlhalter S. Deficient supplementary motor area at rest: Neural basis of limb kinetic deficits in Parkinson's disease. *Hum Brain Mapp.* (2018) 39:3691–700. doi: 10.1002/hbm.24204
35. Randhawa BK, Farley BG, Boyd LA. Repetitive transcranial magnetic stimulation improves handwriting in parkinson's disease. *Parkinson's Dis.* (2013) 2013:751925. doi: 10.1155./2013/751925
36. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement disorder society task force report on the hoehn and yahr staging scale: status and recommendations. *Mov Disord.* (2004) 19:1020–8. doi: 10.1002/mds.20213
37. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* (1992) 55:181. doi: 10.1136/jnnp.55.3.181
38. Gill DJ, Freshman A, Blender JA, Ravina B. The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease. *Movement Disorders.* (2008) 23:1043–6. doi: 10.1002/mds.22017
39. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia.* (1971) 9:97–113.doi: 10.1016/0028-3932(71)90067-4
40. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
41. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* (2008) 23:41–7. doi: 10.1002/mds.22340
42. Earhart GM, Cavanaugh JT, Ellis T, Ford MP, Foreman KB, Dibble L. The 9-hole peg test of upper extremity function: average values, test-retest reliability, and factors contributing to performance in people with parkinson disease. *J Neurol Phys Ther.* (2011) 35:157–63. doi: 10.1097/NPT.0b013e318235da08
43. Proud E, Morris ME, Bilney B, Miller KJ, Nijkrake MJ, Munneke M, et al. Hand dexterity assessment in Parkinson's disease: construct validity of the 9-hole peg test for the more affected hand. *Disabil Rehabil.* (2020) 1–5. doi: 10.1080./09638288.2020.1754474
44. Mendoza JE, Apostolos GT, Humphreys JD, Hanna-Pladdy B, O'Bryant SE. Coin rotation task (CRT): a new test of motor dexterity. *Arch Clin Neuropsychol.* (2009) 24:287–92. doi: 10.1093/arclin/acp030
45. Ineichen-Furrer K, Vanbellingen T. Screening für die fingergeschicklichkeit – coin rotation test. *Physiopraxis.* (2016) 14:48–9. doi: 10.1055/s-0042-102406
46. Peto V, Jenkinson C, Fitzpatrick RAY. Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. *Age Ageing.* (2001) 30:299–302. doi: 10.1093/ageing/30.4.299
47. Matsunaga K, Maruyama A, Fujiwara T, Nakanishi R, Tsuji S, Rothwell JC. Increased corticospinal excitability after 5 Hz rTMS over the human supplementary motor area. *J Physiol.* (2005) 562:295–306. doi: 10.1113/jphysiol.2004.070755
48. Mace M, Rinne P, Liardon JL, Bentley P, Burdet E. Comparison of flexible and rigid hand-grip control during a feed-forward visual tracking task. In: *IEEE International Conference on Rehabilitation Robotics.* IEEE (2015) p. 792–7. doi: 10.1109./ICORR.2015.7281299
49. Johansson RS, Westling G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res.* (1984) 56:550–64. doi: 10.1007/BF00237997
50. Thonnard JL, Opsomer L, Lefèvre P, Pletser V, McIntyre J. GRIP: dexterous manipulation of objects in weightlessness. In: *Preparation of Space Experiments*. (2020). doi: 10.5772./intechopen.93462
51. Smeragliuolo AH, Hill NJ, Disla L, Putrino D. Validation of the leap motion controller using markered motion capture technology. *J Biomech.* (2016) 49:1742–50. doi: 10.1016/j.jbiomech.04.006
52. Weichert F, Bachmann D, Rudak B, Fisseler D. Analysis of the accuracy and robustness of the leap motion controller. *Sensors.* (2013) 13:6380–93. doi: 10.3390/s130506380
53. Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol.* (2012) 259:83–92. doi: 10.1007/s00415-011-6128-4
54. Chang WH, Kim YH, Bang OY, Kim ST, Park YH, Lee PKW. Long-term effects of RTMS on motor recovery in patients after subacute stroke. *J Rehabil Med.* (2010) 42:758–64. doi: 10.2340/16501977-0590

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.

frontiers in Rehabilitation Sciences

BRIEF RESEARCH REPORT
published: 03 January 2022
doi: 10.3389/fresc.2021.793451

Does Right-Hemispheric Anodal tDCS Enhance the Impact of Script Training in Chronic Aphasia? A Single-Subject Experimental Study

Mathieu Figeys[1], *Esther Sung Kim*[1,2]* *and Tammy Hopper*[1,2]

[1] *Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada,* [2] *Department of Communication Sciences and Disorders, University of Alberta, Edmonton, AB, Canada*

Background: Script training is an aphasia treatment approach that has been demonstrated to have a positive effect on communication of individuals with aphasia; however, it is time intensive as a therapeutic modality. To augment therapy-induced neuroplasticity, transcranial direct current stimulation (tDCS) may be implemented. tDCS has been paired with other speech-language treatments, however, has not been investigated with script training.

Aims: The purpose of this study was to determine if tDCS improves communication proficiency when paired with script training, compared to script training alone.

Methods and Procedures: A single-subject experimental design was implemented with a participant with non-fluent aphasia, using two scripts across treatment conditions: script training with sham-tDCS, and script training with anodal-tDCS. Treatment sessions were 75 min long, administered three times weekly. Anodal tDCS was implemented for 20 min with a current of 1.5 mA over the right inferior frontal gyrus.

Results: Large effect sizes were obtained on script mastery for both stimulation conditions (anodal $d_2 = 9.94$; sham $d_2 = 11.93$). tDCS did not improve script accuracy, however, there was a significant improvement in the rate of change of script pace relative to baseline (3.99 seconds/day, $p < 0.001$) in the anodal tDCS condition.

Conclusion: Despite a null tDCS result on accuracy, the script training protocol increased script performance to a near-fluent level of communication. There is preliminary evidence to suggest that tDCS may alter the rate of script acquisition, however, further research to corroborate this finding is required. Implications for future studies are discussed.

Keywords: aphasia, script training, transcranial direct current stimulation, right-hemispheric anodal stimulation, automaticity, tDCS, stroke rehabilitation

OPEN ACCESS

Edited by:
Gail A. Eskes,
Dalhousie University, Canada

Reviewed by:
Jed A. Meltzer,
Baycrest Hospital, Canada
Julia Schuchard,
Children's Hospital of Philadelphia, United States

***Correspondence:**
Esther Sung Kim
esther.kim@ualberta.ca

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *12 October 2021*
Accepted: *02 December 2021*
Published: *03 January 2022*

Citation:
Figeys M, Kim ES and Hopper T (2022) Does Right-Hemispheric Anodal tDCS Enhance the Impact of Script Training in Chronic Aphasia? A Single-Subject Experimental Study. Front. Rehabilit. Sci. 2:793451. doi: 10.3389/fresc.2021.793451

INTRODUCTION

Aphasia is an acquired language impairment primarily caused by cerebrovascular accidents involving the left middle cerebral artery. Aphasia can cause significant communication deficits; even mild aphasia can have significant deleterious effects on a person's ability to participate in everyday life activities and fulfill social roles (1). Approximately one-third of people who survive

a cerebrovascular accident will experience some degree of aphasia (2). To date, there is no cure for aphasia, however, several behavioral treatments exist that help improve language and communication specific to aphasia (2). One functional speech-language rehabilitative approach is script training, which has emerged as a potentially promising treatment option for aphasia.

Script training in aphasia typically involves the repeated practice of words, phrases, and sentences embedded within a monolog or dialogue that is individualized to the person with aphasia (3). People with aphasia (PWA) engage in repeated script practice using a fading of cues protocol until they can speak the script automatically and use it in everyday communication situations (4, 5). Script training is based on the Instance Theory of Automatization (6), which posits that automaticity of skills is achieved by retrieving intact, context-dependent information (in this case, scripts of language) from long-term memory. Scripts are encoded through repetition, and typically the clinician uses a fading cues protocol until the PWA can recall and speak the script automatically (5, 6). Since the development of script training protocols, there has been an increasing literature base exploring the effectiveness of script training in PWA. Most have been single-subject experimental designs or case series of individuals with chronic aphasia of mild-moderate severity (5, 7). However, studies employing larger samples also demonstrate positive treatment outcomes related to spoken and written language and communication (8–10).

One caveat for the use of script training is that it requires extensive practice and time. For example, 22–44 in-person formal training sessions have been reported to master three scripts, excluding individual time practicing at home (4, 5). Some attempts have been made to use technology to increase the efficiency of training [i.e., virtual therapist (8)], but PWA may still need to devote significant time and cognitive effort in the learning process. One potential method to assist in increasing efficiency of the script training approach is through neuromodulation using transcranial direct current stimulation (tDCS).

tDCS and Aphasia Treatment

Transcranial direct current stimulation (tDCS) involves the application of a low-dose electrical current across the brain to alter neuronal transmembrane polarities (11). This subthreshold current is not strong enough to invoke an action potential, however, it is proposed to hypopolarize or hyperpolarize the neuronal resting state to achieve heightened sensitivity or dampening in cortical regions of interest (11).

tDCS applications should include the consideration of factors such as the selection of an appropriate region of stimulation, current strength, duration, and frequency. Another consideration specific to stroke-acquired aphasia is the size and location of the lesion, as the distribution of the current can be altered by this lesioned tissue (12). Most tDCS studies for aphasia have utilized anodal stimulation over the perilesional structures in the left-hemisphere, and/or cathodal stimulation over the right-hemisphere (13).

In addition to targeting perilesional tissue with anodal tDCS, there is increasing evidence to suggest other electrode montages are beneficial for PWA. For instance, left-cathodal, as well as right-anodal stimulation may promote secondary language processing within the right-hemisphere (14–21). Anodal-tDCS over the right-hemisphere paired with speech-language treatment has been utilized in previous aphasia studies with reports of increased verbal fluency (17) and naming ability (18). When left-hemisphere damage is extensive, the right-hemisphere may become the dominant language promoter (22). Therefore, right-hemispheric anodal-stimulation may increase language performance if the right-hemisphere has become the primary neural-area for language processing [i.e., after a large left-hemisphere lesion (23)].

Indeed, previous studies have demonstrated that tDCS stimulation over the right inferior frontal gyrus can improve language functioning (17, 18). The right inferior frontal gyrus is suggested to be involved in homologous speech-language processing, such as singing and intonation, by incorporating the right arcuate fasciculus and communicating structures; these neural pathways are implicated in melodic intonation therapy for aphasia (17, 24, 25). By inducing tDCS-neuromodulation to these areas, language abilities may be improved, particularly when paired with speech-language therapies (including script training), to enhance and/or expedite treatment effects.

Script training has been demonstrated to be an effective treatment option in improving functional communication in PWA. Whereas, tDCS may improve the efficiency and efficacy of script training, it has not been examined together with script training. Therefore, the purpose of this study was to determine if outcomes from script training could be enhanced when combined with tDCS in an individual with post-stroke aphasia. An anodal right-hemispheric montage was selected, as the presence of a large left-hemisphere lesion precluded left-hemisphere placement. The specific research questions were as follows:

1. *What are the effects of script training for an individual with post-stroke aphasia with an extensive left-hemispheric lesion?*
2. *What are the effects of combining anodal right-hemispheric tDCS over the inferior frontal gyrus with script training for an individual with chronic post-stroke aphasia with an extensive left-hemispheric lesion?*

MATERIALS AND METHODS

Design

A *n*-of-1, single-blinded A - B - B+C - A design was implemented where "A" indicates conventional baseline measures, "B" indicates script training paired with sham-tDCS, and "B+C" represents script training with active anodal-tDCS.

Participant

The participant (JB) was recruited based on convenience sampling. JB, was a 45-year-old English-speaking male, 3 years, 11 months post-onset of a large left-hemispheric stroke resulting in chronic aphasia, apraxia of speech and right-sided hemiplegia. His lesion encompassed the left parietal, temporal, and frontal lobes seen on neuroimaging (**Figure 1**). JB had 4 years of post-secondary education and worked as a project manager prior to the stroke.

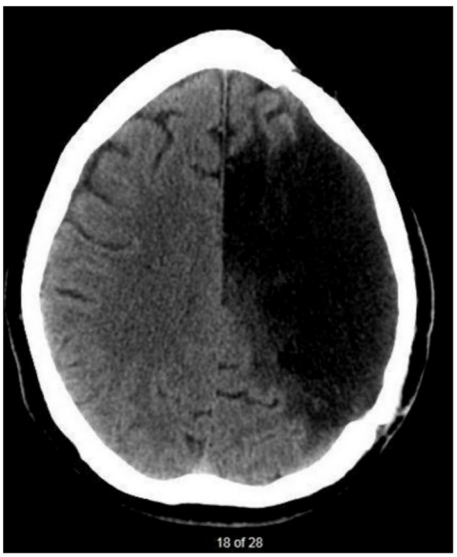


FIGURE 1 | CT scan taken 3 years after JB's stroke. There is evidence of a large, chronic post-stroke lesion within the left-hemisphere. Regions affected are associated with branches of the left middle cerebral artery.

Prior to commencing the study, JB completed screenings of vision: (Rosenbaum pocket vision screener; 20/20 bilaterally uncorrected at 14″ distance), hearing [minimal-pairs discrimination task using words/non-words adapted from *PALPA* 1 and 2 (26); 98% correct] and non-verbal fluid intelligence [Raven's Coloured Progressive Matrices (27); 34/37 correct]. The severity and profile of aphasia were characterized by the *WAB-Revised* [WAB-R (28)]. JB presented with non-fluent (Broca's) aphasia with a WAB-R Aphasia Quotient of 51.7. Auditory comprehension was a relative strength. Verbal expression consisted of mainly single words spoken in a slow, halting manner. JB used frequent gestures as well as a tablet-based augmentative and alternative communication program with pictographic and synthesized voice support to supplement his limited spoken language.

Ethics

This project was approved by the University of Alberta Research Ethics Board (Pro00054921). Study procedures were explained to JB and his spouse in written and verbal form using supported communication strategies, and JB provided signed informed consent. The participant received a fifty-dollar gift card as compensation for participating in the study.

Intervention

Script Training

In collaboration with JB, two dialogue-based scripts were developed using standardized templates adapted from Kaye and Cherney (3). As our participant had a limited timeframe to participate in this study, six participant-phrases per script were selected from the standardized templates and personalized. After script personalization, Script 1 had a Flesch-Kincaid reading level of 1.4, and Script 2 had a reading level of 1.2.

TABLE 1 | Script Training Procedures Implemented.

Step	Description
1	Phrase modeling by the researcher
2	Reading of the phrase between the client and researcher in unison
3	Reading of the phrase in unison, with the researcher slowly fading their voice out
4	Independent phrase production by the client (with cueing)
5	Independent phrase production by the client (without cueing)
6	After 20 successful independent productions of the phrase, the next phrase is added on to the mastered phrases

[Adapted from Youmans et al. (4)].

Five baseline probes (Phase A) were administered for Script 1 prior to initiating treatment. During Phase B, while Script 1 was being trained, probes were conducted for Script 2. During each probe, the participant had access to the printed script and attempted to read it aloud. No training or feedback was given during probes.

During the treatment phases (B, B+C), a fading cue-hierarchy protocol (4) was used during the script training. Scripts were taught one phrase at a time, using a dialogue-turn format (**Table 1**). Throughout the script training procedure, JB had access to the whole printed script in addition to cue cards with one script line written on each. Independent spoken production of the script was defined as the participant correctly saying the phrase aloud, without cueing. The participant was required to independently say the phrase aloud 20 times before the next phase in the script was added to the previously mastered phrase(s). The researcher immediately corrected errors (defined as any distortion of a word or deviation in syntactic structure), and the individual repeated the word or phrase aloud. Two scripts were taught sequentially; JB chose the order. Script 1 (ordering a pizza) was first during treatment phase B; Script 2 (grocery shopping) was second in phase B+C. A minimum of three sessions in each phase was required, however, no limit on treatment sessions was set for either script. Rather, a script was considered mastered after JB demonstrated two consecutive sessions with over 90% percent of script correct (4, 5).

During B and B+C, probing continued at the beginning of each session prior to script training. When mastery was achieved for Script 1, Script 2 training was initiated. Training on Script 1 was discontinued, although the participant continued to practice Script 1 at home. After demonstrating mastery of Script 2, script training was discontinued. Four maintenance data points were collected at one, five, seven, and fourteen weeks after completing treatment phase B+C. Maintenance data probes were conducted the same way as baseline data probes, with the participant having the printed script and attempting to read it aloud. No feedback or cueing was provided.

The protocol was conducted in person three times per week, in 75-min sessions at a university research lab. Homework was assigned in the form of 15-min of script practice per day. Audio files using the fading-of-cue protocol were recorded for both scripts on JB's tablet at the start of each training phase to facilitate

script training at home. The participant kept a homework log to record daily practice.

tDCS Stimulation

In the anodal-tDCS condition, a 1.5 mA current for 20-min was applied through 5 cm × 7 cm electrode sponges, saturated in 10 mL of 0.9% NaCl solution, using a Magstim HDCStim device. The anodal-electrode was placed over the right inferior frontal gyrus, determined to be at the intersection of T4-Fz and F8-Cz (29), and secured with a hairnet. The cathodal electrode was placed on the left deltoid muscle (30).

For a blinding procedure during phase B, a 1.5 mA current was applied for 1 min with a 15-second ramp-up and ramp-down period, to create the sensation of electrical stimulation (31). tDCS was implemented for the first 20 min of the script training period, and the electrodes were taken off at the end of the session.

Dependent Measures

Three outcome measures were used to examine treatment effects: (1) script mastery (defined as 90% of script spoken correctly over two consecutive sessions); (2) total time to complete script turns; and (3) the number of sessions required to demonstrate script mastery.

Script mastery was measured using both binary scoring (Correct/Incorrect) and the Naming and Oral Reading for Language in Aphasia 6-Point Scale [NORLA-6 (32)]. Using this scale, each word in the script is scored from 0 to 5, where 0 indicates no communicative output, and 5 indicates a perfect response. NORLA-6 scoring provided a more fine-grained analysis of script production, accounting for speech/language errors (such as delays in production, distortions of words, tenses, morphemes, and phonemes). Total time to complete script turns was calculated based on the sum of time JB required to complete his turns in the scripted dialogue. A turn was defined by the end of the researcher's probe until the end of JB's turn.

Analyses

In line with single-subject research designs, traditional visual analysis methods [outlined in Kratochwill et al. (33)] and effect sizes [using the modified Cohen's d_2 as described in Beeson and Robey (34)] using baseline and post-treatment scores for each script are reported. The magnitude of effect sizes will be interpreted as 2.6, 3.9, and 5.8 for small, moderate, and large effect sizes respectively (34, 35). In addition, a modeling technique to account for change across time—an Interrupted Time Series Analysis [ITSA (36)] was also used.

ITSA can determine if significant differences exist between the slopes (trends) and levels (corresponding y-values) in time-series designs. ITSA is advantageous as it can be utilized for between group comparisons, and with multiple treatment phases across time (36). ITSA accounts for autocorrelation and utilizes an ordinary least squares regression process to create a regression-based model of the dataset while calculating pre- and post-intervention levels and trends after an intervention is started or withdrawn. An ITSA package (37) available for Stata (38) from the Statistical Software Archive was used to run the ITSA models.

RESULTS

Interrater Reliability

A second coder independently scored each word (using binary and NORLA-6 scoring) for both scripts across conditions, for nine sessions chosen at random. The individual was trained on the NORLA-6 scale by the primary author. A Krippendorff's alpha was calculated in SPSS (IBM Corp., Version 24, Armonk, NY). An $\alpha = 0.99$ was obtained, suggesting strong interrater reliability between both raters across scoring methods.

Script Mastery

Binary Scoring

Scores were transformed to percent script correct based on the sum of words correct and the total number of words in the script. Upon visual analysis, a stable pattern is noted during the initial baseline period across both study conditions (**Figure 2A**). Using ITSA, a non-significant difference between both scripts during the baseline period was calculated, indicating similar performance between both scripts during the baseline period.

Applying ITSA across study phase B, there was an increase in the slope and change in level for Script 1. This change in daily trend was determined to be 1.54%/day ($p = 0.034$, 95% CI [0.12, 2.96]). That is, JB was improving at a rate of 1.54% /day compared to baseline on the trained script. Script 2, which remained untrained, remained comparable to the baseline period (−0.40%/day; $p = 0.685$, 95% CI [−2.44, 1.63]). Applying ITSA across phase B+C, there appears to be an increase in performance for Script 2. Indeed, the change in daily trend within treatment phase B+C for Script 2 was significant, increasing 1.71%/day relative to baseline ($p = 0.021$, 95% CI [0.39, 3.02]). When comparing the slopes before and after anodal tDCS was administered, no significant differences in the interaction of group and intervention phase was observed.

A post-trend analysis within ITSA using a linear combination of estimators (*lincom*) revealed no significant difference between script training with anodal-tDCS compared to script training with sham-tDCS in the maintenance period. This suggests no significant difference between retention of the scripts across sham and anodal conditions during the maintenance phase.

Large effect sizes were seen for both treatment conditions; the effect size for script training with sham-tDCS was $d_2 = 9.94$, compared to script training with anodal-tDCS $d_2 = 11.93$. Despite the large effect sizes, there remained a lack of statistical significance from ITSA when comparing between both conditions (slopes of 1.54%/day for Script 1, compared to 1.71%/day for Script 2).

NORLA-6 Scoring

NORLA-6 scores were transformed to a percentage, based on the maximum NORLA-6 score achievable. Visual analysis of the NORLA-6 model complements the results of the binary scoring method. In the baseline period, both scripts appear to be stable without any significant fluctuations in performance (**Figure 2B**). Within treatment phase B, NORLA-6 scores for Script 1 improved significantly, evident by the rise in trend, and change in level. Script 2 mastery continued to demonstrate a

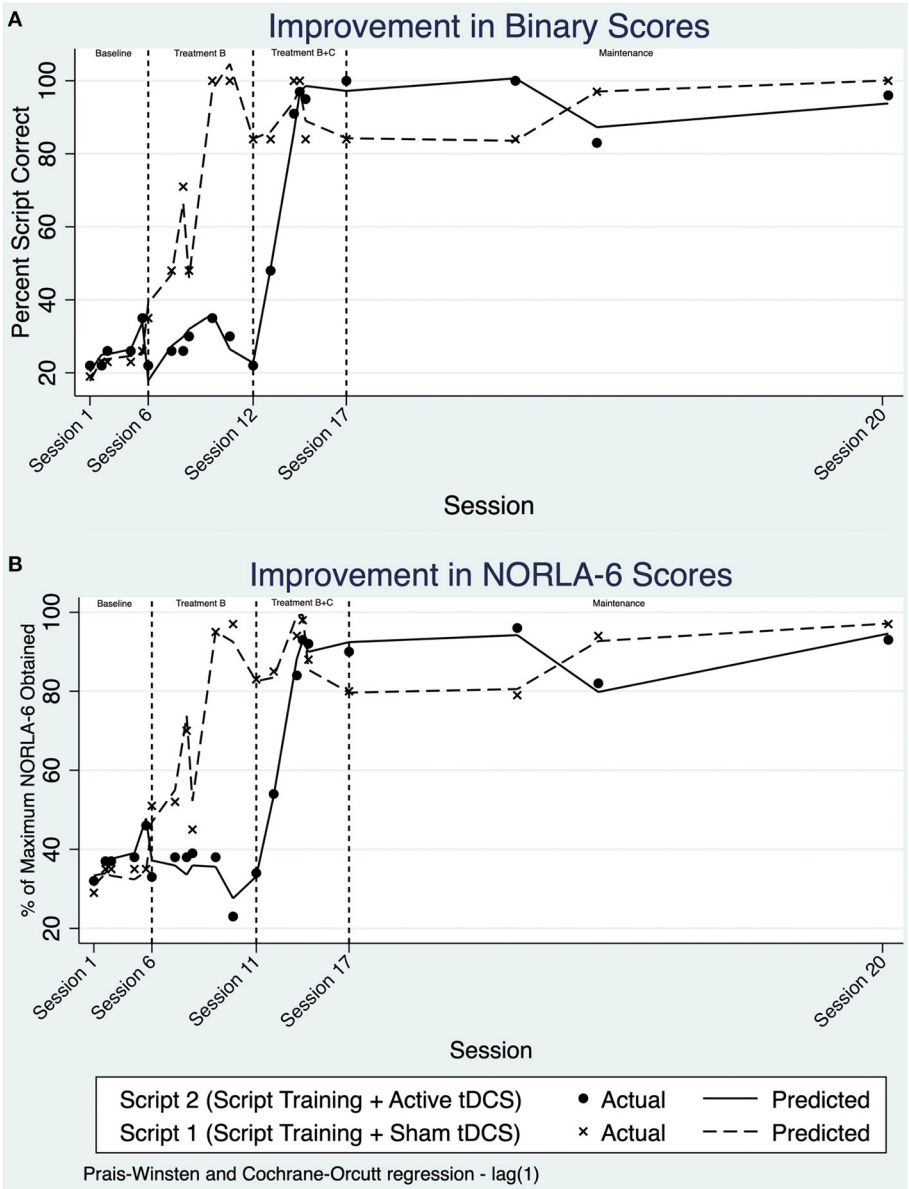


FIGURE 2 | (A) Line chart of percent script correct using binary scoring over treatment sessions and maintenance. **(B)** Line chart of percent script correct using NORLA-6 scoring over treatment sessions and maintenance.

baseline-like pattern, without any significant changes, until the initiation of B+C. Script 2 also had a rise in trend and overall level in phase B+C, with script 1 remaining relatively stable. This stability was further extended into the maintenance period.

With ITSA, there were no significant differences between treatment conditions with NORLA-6 scoring. Further, no significant differences in the interaction of group and intervention phase were observed. Within the maintenance period, there was no significant difference between the anodal-tDCS and sham-tDCS phases using *lincom* post-trend analysis. Like binary scoring, a large effect size was obtained for script training with sham-tDCS ($d_2 = 8.88$), and a moderate effect size was seen in script training paired with anodal-tDCS ($d_2 = 12.23$). tDCS did not impact script retention, evidenced by similar performance across scripts during the maintenance period.

Time to Complete Scripts

Visual analysis of **Figure 3** suggests that the time needed to complete script turns decreased across both scripts starting within the baseline phase, suggesting a potential learning effect prior to implementing script training.

Once intervention phase B was implemented, the trend for script 1 decreased at a faster rate than seen during baseline. Script 2 also appears to become faster over this phase. The daily rate

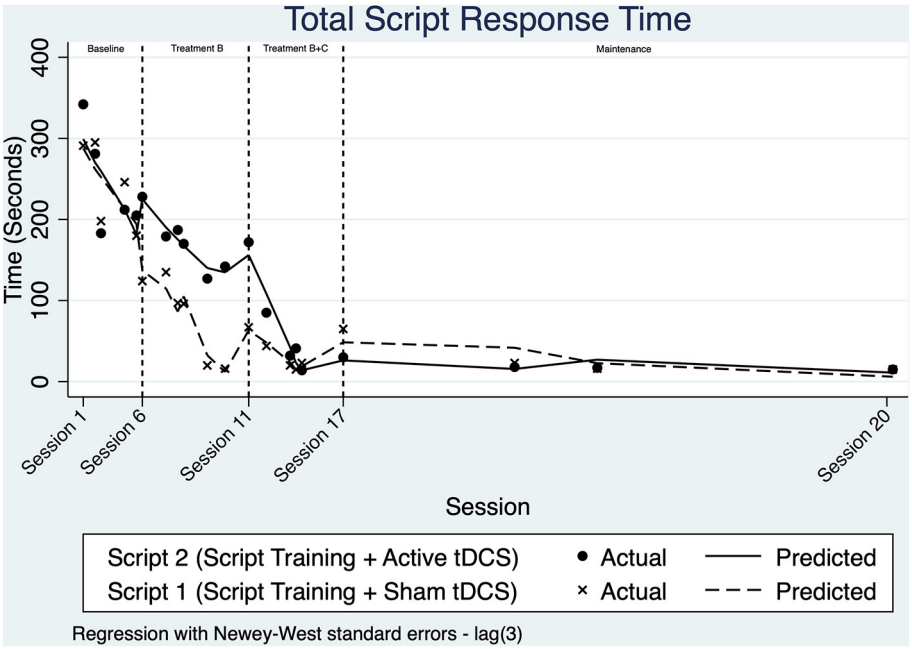


FIGURE 3 | Line chart of the change in total time (in seconds) required to complete script phrases.

of change across phase B for Script 1 was modeled with ITSA to improve by an additional 3.68 seconds/day relative to the baseline ($p = 0.303$, 95% CI [−3.56, 10.93]).

Upon visual analysis across treatment phase B+C, there is a change in level after a marked decrease in trend for script 2. A non-significant change in daily trend and level is evident within treatment B+C for script 1. ITSA modeled the change in slope for Script 2 time relative to baseline to be 3.99 s/day ($p < 0.001$, 95% CI [2.44, 5.56]). When examining the interaction of group and intervention phase (non-relative to baseline), no significant differences were noted.

Time to complete script turns remained stable during the maintenance period for both scripts. ITSA modeling revealed that there were no statistical differences between the time taken to speak the two scripts during the maintenance period. Effect size measures for both conditions were similar, with a $d_2 = -5.31$ for script training with sham-tDCS, and a $d_2 = -3.42$ for script training paired with anodal-tDCS.

Number of Sessions to Achieve Mastery

JB achieved script mastery, defined as speaking 90% of the script correctly and independently over two consecutive sessions, after six sessions for Script 1 (paired with sham-tDCS) and five sessions for Script 2 (paired with anodal-tDCS).

DISCUSSION

The study participant demonstrated positive outcomes related to script mastery, total time to complete script turns, and the number of sessions to mastery in both treatment conditions in this study. There was no difference in script mastery or total script time between the two treatment conditions. There is preliminary evidence from the ITSA analysis that the use of tDCS may have facilitated faster learning of the second script, however, the generalizability of this result is limited due to the single-subject design. The findings of this study are important from both a methodological perspective and may inform future research designs.

The results of this study are consistent with the existing literature regarding the variable effects of tDCS in aphasia protocols [see (39–41)]. These conflicting results may be explained by differences in the tDCS treatment parameters used across studies, heterogeneity among participants, variable treatment paradigms, and methodological differences (39). Several factors may have contributed to the obtained results of tDCS paired with script training. First, tDCS placement may have mitigated the potential benefits of neuromodulation. Anodal-tDCS over the right IFG was selected based on the model proposed by Anglade et al. (23). In the absence of neuroimaging-guided tDCS placement (42), it is unknown whether the right IFG was the optimal stimulation site for our participant. Stimulation in more posterior brain structures, such as the superior temporal gyrus, could potentially engage a greater homologous related ventral stream response [refer to Hickok and Poeppel (43) for a discussion on dorsal and ventral streams]. Further research is necessary to determine optimal montage, target structures of interest, as well as hemispheric effects and the individualization of tDCS protocols.

Second, the design of the study may have resulted in sub-optimal effects of the tDCS. In the current study, sessions were not consecutive. Thus, the effects of tDCS may have diminished between sessions. In previous studies, the frequency

of tDCS stimulation, as well as stimulation parameters have varied (12, 22), and it remains unclear if the frequency of tDCS stimulation is correlated to an improvement in learning and language performance. For instance, Monti et al. (14) report increased naming accuracy in individuals after a single session of left-hemispheric cathodal stimulation (2 mA for 10 min). In contrast, Spielmann et al. (40) reported no significant changes in individuals who received left-hemisphere anodal tDCS for 5 consecutively administered sessions per week, over 2 weeks (1 mA for 20 min).

Third, floor and ceiling effects are present in the dataset; once JB mastered the scripts, he consistently achieved near-perfect performance. Although the scripts were challenging at first, they may have been too easy such that any potential differential effect of the use of tDCS on learning accuracy was masked. We noted that time to complete both scripts decreased during the baseline probes and treatment phase B, suggesting learning/practice effects for the untreated script. Upon closer review, there were no corresponding improvements in accuracy for the untreated script, and the reduced time reflected reductions in speech breaks/pauses. ITSA revealed only the trained scripts showed significant changes relative to baseline (**Figure 2**) during the treatment phases. Thus, it seems explicit training of the scripts was necessary to increase script accuracy, however, mass exposure without training may reduce script time due to potential learning and habituation effects.

Other design considerations may impact future study results, for example, adding additional treatment phases and washout periods (44). Future studies should examine the effects of an untrained script and include other speech-language tasks. Due to participant time constraints, it was decided to provide sham tDCS first to remove the need for a washout period. Thus, the research team was not blinded. Double-blinding is recommended in future studies. Further research pairing script training with the use of neuroimaging-based approaches is recommended to examine larger neuronal networks utilized in script training acquisition and in long-term maintenance. In addition, structural imaging can be utilized to model tDCS electrical fields on each participant to optimize electrode placement. Furthermore, brain-derived neurotrophic factor genotyping would be of benefit to optimize tDCS for PWA (45). Finally, other factors including neuropharmacological agents were not controlled for and may have physiologically impacted the effects of tDCS (46).

Despite the null tDCS results on script accuracy, our participant demonstrated significant gains on the two practiced scripts due to the script training protocol. These successful script training results are consistent with previously reported studies of patients with similar aphasia profiles (4, 7) and add to the existing literature in this area. Further, we extend the literature on the topic of the personalization of scripts. Personalization of scripts may increase communicative gains to a greater extent than non-personalized scripts (47). In this study, scripts were personalized regarding names, places, and favorite foods in JB's environment. Participant reports and detailed logs from our participant demonstrated significant interest in both scripts. JB was very motivated and continues to individually practice the scripts after completion of the study. This demonstrates an individualized functional benefit of the implemented script training protocol for our participant.

In conclusion, script training had a positive effect on communication for an individual with post-stroke aphasia with a large left-hemispheric lesion. The addition of tDCS did not increase functional communication, including the time required to complete the script or script accuracy. Script training, as well as tDCS applications, may be a promising rehabilitation approach to assist in communicative compensation for individuals with post-stroke aphasia, however, due to limitations in this study, future research is necessary, with a focus on larger sample sizes.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Alberta. 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

MF, EK, and TH contributed to the conception, design of the study, and wrote sections of the manuscript. MF was involved in data collection, intervention administration, and data analysis. EK and TH provided guidance and supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank Dr. Carol Boliek, Dr. Torrey Loucks, and Roujan Khaledan for their contributions and support throughout the project. We would also like to thank JB and his family for participating in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fresc.2021.793451/full#supplementary-material

REFERENCES

1. Wray F, Clarke D, Forster A. How do stroke survivors with communication difficulties manage life after stroke in the first year? A qualitative study. *Int J Lang Commun Disord.* (2019) 54:814–27. doi: 10.1111/1460-6984.12487
2. Brady MC, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev.* (2016) 2016:CD000425. doi: 10.1002/14651858.CD000425.pub4
3. Kaye R, Cherney L. Script templates: a practical approach to script training in aphasia. *Top Lang Disord.* (2016) 36:136–53. doi: 10.1097/TLD.0000000000000086
4. Youmans G, Holland A, Muñoz ML, Bourgeois M, Mun ML, Bourgeois M. Script training and automaticity in two individuals with aphasia. *Aphasiology.* (2005) 19:435–50. doi: 10.1080/02687030444000877
5. Youmans G, Youmans SR, Hancock AB. Script training treatment for adults with apraxia of speech. *Am J Speech Lang Pathol.* (2011) 20:23–37. doi: 10.1044/1058-0360(2010/09-0085)
6. Logan GD. Toward an instance theory of automatization. *Psychol Rev.* (1988) 95:492–527. doi: 10.1037/0033-295X.95.4.492
7. Goldberg S, Haley KL, Jacks A. Script training and generalization for people with aphasia. *Am J Speech Lang Pathol.* (2012) 21:222–38. doi: 10.1044/1058-0360(2012/11-0056)
8. Cherney LR, Halper AS, Holland AL, Cole R. Computerized script training for aphasia: preliminary results. *Am J Speech Lang Pathol.* (2008) 17:19–34. doi: 10.1044/1058-0360(2008/003)
9. Manheim L, Halper A, Cherney L. Patient-reported changes in communication after computer-based script training for aphasia. *Arch Phys Med Rehabil.* (2009) 90:623–7. doi: 10.1016/j.apmr.2008.10.022
10. Cherney L, Halper A, Kaye R. Computer-based script training for aphasia: emerging themes from post-treatment interviews. *J Commun Disord.* (2011) 44:493–501. doi: 10.1016/j.jcomdis.2011.04.002
11. Thair H, Holloway AL, Newport R, Smith AD. Transcranial direct current stimulation (tDCS): a Beginner's guide for design and implementation. *Front Neurosci.* (2017) 11:641. doi: 10.3389/fnins.2017.00641
12. Biou E, Cassoudesalle H, Cogné M, Sibon I, De Gabory I, Dehail P, et al. Transcranial direct current stimulation in post-stroke aphasia rehabilitation: a systematic review. *Ann Phys Rehabil Med.* (2019) 62:104–21. doi: 10.1016/j.rehab.2019.01.003
13. Sandars M, Cloutman L, Woollams A. Taking sides: an integrative review of the impact of laterality and polarity on efficacy of therapeutic transcranial direct current stimulation for anomia in chronic poststroke aphasia. *Neural Plast.* (2016) 2016:1–21. doi: 10.1155/2016/8428256
14. Monti A, Cogiamanian F, Marceglia S, Ferrucci R, Mameli F, Mrakic-Sposta S, et al. Improved naming after transcranial direct current stimulation in aphasia. *J Neurol Neurosurg Psychiatry.* (2008) 79:451–3. doi: 10.1136/jnnp.2007.135277
15. Kang E, Kim Y, Sohn H, Cohen L, Paik N. Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. *Restor Neurol Neurosci.* (2011) 29:141–52. doi: 10.3233/RNN-2011-0587
16. You D, Kim D, Chun M, Jung S, Park S. Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. *Brain Lang.* (2011) 119:1–5. doi: 10.1016/j.bandl.2011.05.002
17. Vines BW, Norton AC, Schlaug G. Non-invasive brain stimulation enhances the effects of melodic intonation therapy. *Front Psychol.* (2011) 2:230. doi: 10.3389/fpsyg.2011.00230
18. Flöel A, Meinzer M, Kirstein R, Nijhof S, Deppe M, Knecht S, et al. Short-term anomia training and electrical brain stimulation. *Stroke.* (2011) 42:2065–7. doi: 10.1161/STROKEAHA.110.609032
19. Jung I, Lim J, Kang E, Sohn H, Paik N. The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. *Ann Rehabil Med.* (2011) 35:460. doi: 10.5535/arm.2011.35.4.460
20. Shah-Basak PP, Norise C, Garcia G, Torres J, Faseyitan O, Hamilton RH. Individualized treatment with transcranial direct current stimulation in patients with chronic non-fluent aphasia due to stroke. *Front Hum Neurosci.* (2015) 9:201. doi: 10.3389/fnhum.2015.00201
21. Nicolo P, Fargier R, Laganaro M, Guggisberg AG. Neurobiological correlates of inhibition of the right Broca homolog during new-word learning. *Front Hum Neurosci.* (2016) 10:371. doi: 10.3389/fnhum.2016.00371
22. Cherney L, Babbitt E, Hurwitz R, Rogers L, Stinear J, Wang X, et al. Transcranial direct current stimulation and aphasia: the case of mr. C. *Top Stroke Rehabil.* (2013) 20:5–21. doi: 10.1310/tsr2001-5
23. Anglade C, Thiel A, Ansaldo A. The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. *Brain Inj.* (2014) 28:138–45. doi: 10.3109/02699052.2013.859734
24. Schlaug G, Maechina S, Norton A. From singing to speaking: why singing may lead to recovery of expresive language function in patients with broca's aphasia. *Music Percept.* (2008) 25:315–23. doi: 10.1525/mp.2008.25.4.315
25. Schlaug G, Norton A, Marchina S, Zipse L, Wan CY. From singing to speaking: facilitating recovery from nonfluent aphasia. *Future Neurol.* (2010) 5:657–65. doi: 10.2217/fnl.10.44
26. Kay J, Lesser R, Coltheart M. *Psycholinguistic Assessment of Language Processing in Aphasia (PALPA)*. 1st ed. London: Lawrence Erlbaum Associates (1992). p. 686.
27. Raven J, Raven J, Court J. *Raven's Progressive Matrices and Vocabulary Scales*. San Antonio TX: Pearson (1998).
28. Kertesz A. *WAB-R: Western Aphasia Battery-Revised* San Antonio: Psych Corp (2007).
29. Lifshitz Ben Basat A, Gvion A, Vatine JJ, Mashal N. Transcranial direct current stimulation to improve naming abilities of persons with chronic aphasia: a preliminary study using individualized based protocol. *J Neurolinguistics.* (2016) 38:1–13. doi: 10.1016/j.jneuroling.2015.09.004
30. Marangolo P. The potential effects of transcranial direct current stimulation (tDCS) on language functioning: combining neuromodulation and behavioral intervention in aphasia. *Neurosci Lett.* (2017) 719:133329. doi: 10.1016/j.neulet.2017.12.057
31. Ambrus G, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in - short stimulation - fade out approach to sham tDCS - reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimul.* (2012) 5:499–504. doi: 10.1016/j.brs.2011.12.001
32. Pitts LL, Hurwitz R, Lee JB, Carpenter J, Leora R, Pitts LL, et al. Validity, reliability and sensitivity of the NORLA-6 : naming and oral reading for language in aphasia 6-point scale. *Int J Speech Lang Pathol.* (2018) 20:274–83. doi: 10.1080/17549507.2016.1276962
33. Kratochwill TR, Hitchcock JH, Horner RH, Levin JR, Odom SL, Rindskopf DM, et al. Single-case intervention research design standards. *Remedial Spec Educ.* (2013) 34:26–38. doi: 10.1177/0741932512452794
34. Beeson PM, Robey RR. Evaluating single-subject treatment research: lessons learned from the aphasia literature. *Neuropsychol Rev.* (2006) 16:161. doi: 10.1007/s11065-006-9013-7
35. Robey RR, Schultz MC, Crawford AB, Sinner CA. Single-subject clinical-outcome research: designs, data, effect sizes, and analyses. *Aphasiology.* (1999) 13:445–73. doi: 10.1080/026870399402028
36. Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J.* (2015) 15:480–500. doi: 10.1177/1536867X1501500208
37. Linden A. *ITSA: Stata Module to Perform Interrupted Time Series Analysis for Single Andmultiple Groups*. Boston: Stat Softw Components (S457793) (2014).
38. StataCorp. College Station, TX, USA.
39. ALHarbi M, Armijo-Olivo S, Kim E. Transcranial direct current stimulation (tDCS) to improve naming ability in post-stroke aphasia: a critical review. *Behav Brain Res.* (2017) 332:7–15. doi: 10.1016/j.bbr.2017.05.050
40. Spielmann K, van de Sandt-Koenderman W, Heijenbrok-Kal M, Ribbers G. Transcranial direct current stimulation does not improve language outcome in subacute poststroke aphasia. *Stroke.* (2018) 49:1018–20. doi: 10.1161/STROKEAHA.117.020197
41. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *Cochrane database Syst Rev.* (2019) 5:1–110. doi: 10.1002/14651858.CD009760.pub4
42. Datta A, Truong D, Minhas P, Parra L, Bikson M. Inter-Individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Front psychiatry.* (2012) 3:91. doi: 10.3389/fpsyt.2012.00091

43. Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition.* (2004) 92:67–99. doi: 10.1016/j.cognition.2003.10.011
44. Kazdin A. *Single-Case Research Designs: Methods for Clinical and Applied Settings. 2nd ed.* Oxford University Press (2010).
45. Fridriksson J, Elm J, Stark B, Basilakos A, Rorden C, Sen S, et al. BDNF genotype and tDCS interaction in aphasia treatment. *Brain Stimul.* (2018) 11:1276–81. doi: 10.1016/j.brs.2018.08.009
46. McLaren M, Nissim N, Woods A. The effects of medication use in transcranial direct current stimulation: a brief review. *Brain Stimul.* (2018) 11:52–8. doi: 10.1016/j.brs.2017.10.006
47. Cherney L, Kaye R, Lee J, van Vuuren S. Impact of personal relevance on acquisition and generalization of script training for aphasia: a preliminary analysis. *Am J Speech Lang Pathol.* (2015) 24:S913–22. doi: 10.1044/2015_AJSLP-14-0162

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.

frontiers in Rehabilitation Sciences

BRIEF RESEARCH REPORT
published: 11 January 2022
doi: 10.3389/fresc.2021.795306

Dalfampridine for Mobility Limitations in People With Multiple Sclerosis May Be Augmented by Physical Therapy: A Non-randomized Two-Group Proof-of-Concept Pilot Study

Prudence Plummer[1], Silva Markovic-Plese[2] and Barbara Giesser[3]*

[1] Department of Physical Therapy, MGH Institute of Health Professions, Boston, MA, United States, [2] Department of Neurology, Thomas Jefferson University, Philadelphia, PA, United States, [3] Multiple Sclerosis Neurology, Brain Health Center, Pacific Neuroscience Institute, Santa Monica, CA, United States

OPEN ACCESS

Edited by:
Carolee Winstein,
University of Southern California,
United States

Reviewed by:
Ljubica Konstantinovic,
Faculty of Medicine, University of Belgrade, Serbia
Sandra R. Hundza,
University of Victoria, Canada
Kathy Zackowski,
National Multiple Sclerosis Society, United States

***Correspondence:**
Prudence Plummer
pplummer@mghihp.edu

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: 14 October 2021
Accepted: 15 December 2021
Published: 11 January 2022

Citation:
Plummer P, Markovic-Plese S and Giesser B (2022) Dalfampridine for Mobility Limitations in People With Multiple Sclerosis May Be Augmented by Physical Therapy: A Non-randomized Two-Group Proof-of-Concept Pilot Study. Front. Rehabilit. Sci. 2:795306. doi: 10.3389/fresc.2021.795306

Purpose: To demonstrate proof-of-concept for a combined physical therapy and pharmacological intervention and obtain preliminary estimates of the therapeutic efficacy of a motor-relearning physical therapy intervention with and without concurrent dalfampridine treatment on gait speed in people with mobility limitations due to multiple sclerosis (MS).

Methods: Using a non-randomized, two-group design, 4 individuals with MS newly prescribed dalfampridine as part of their routine medical care, and 4 individuals with MS not taking dalfampridine completed a 3-week drug run-in or no-treatment baseline, respectively. After 3 weeks, all participants commenced physical therapy twice weekly for 6 weeks. Participants taking dalfampridine took the medication for the study duration. The physical therapy program comprised functional strengthening, gait training, balance training, and dual-task training. The primary outcome was Timed 25-foot Walk (T25FW) at the end of the 6-week physical therapy program.

Results: For the 4 participants taking dalfampridine, average improvement in T25FW on drug only was 12.8% (95% CI 1.2 to 24.4%). During the 6-week physical therapy phase, both groups significantly improved T25FW, but the effect tended to favor the group taking dalfampridine (mean difference = −0.93 s, 95% CI −1.9 to 0.07 s, $p = 0.064$, $d = 1.6$). Whereas the physical therapy group had average T25FW improvement of 10.8% (95% CI 1.0 to 20.5%), the physical therapy plus dalfampridine group demonstrated average improvement of 20.7% (95% CI 3.8 to 37.6%).

Conclusions: Further research is warranted to examine whether dalfampridine for mobility impairment may be augmented by physical therapy in people with MS.

Keywords: physical therapy, rehabilitation, dalfampridine, gait, walking, multiple sclerosis

INTRODUCTION

Clinical efficacy of oral dalfampridine extended-release for improving gait speed in people with multiple sclerosis (MS) has been demonstrated in two Phase 3 clinical trials (1, 2); however, only 38% of patients taking dalfampridine were "responders" to the medication (3). Responders were defined as patients whose Timed 25-Foot Walk (T25FW) gait speed was faster for at least 3 of the 4 on-drug assessments compared to their fastest off-drug assessment. While the average T25FW improvement of 25% observed in responders is impressive (3), equivalent to 0.16 m/s (4), there are a large number of patients who do not achieve a meaningful response to the medication and for whom adjunct or alternate interventions for gait impairment are necessary.

Task-specific gait training (5–8) such as that provided in physical therapy can also produce positive effects on gait speed in people with MS (4). Although the precision of effect size estimates for gait training are currently limited by very small rehabilitation studies (4), interventions with promising effect sizes have included conventional gait training (6) as well as robot-assisted and treadmill-based gait training (5, 9, 10). Further, it is possible that combining physical therapy with dalfampridine may increase the effect size of dalfampridine on gait speed and the proportion of patients who experience a clinically meaningful treatment effect (11).

The purpose of this pilot study was to demonstrate proof-of-concept and obtain preliminary effect size estimates of dalfampridine combined with physical therapy (D+PT) after an initial drug-only run-in phase to determine responsiveness to dalfampridine alone, and to compare the effects to physical therapy without dalfampridine (PT) in people with MS, on gait speed assessed under fastest comfortable (i.e., T25FW).

METHODS

This pilot study was a non-randomized two-group design with pre-post assessment and 1-month follow up. To be included, participants had to have a diagnosis of MS (any phenotype) and either have been prescribed dalfampridine by their neurologist as part of their usual care or not taking dalfampridine (and not have previously taken it). Participants in both groups had self-reported issues with mobility and/or falls, were 18–70 years old, could complete the T25FW in 6–45 s without physical assistance, and were able to follow a 3-step verbal command in English. Individuals were not eligible if they had experienced an exacerbation in the last 60 days, recent myocardial infarction or illness requiring hospitalization, reported a history of any other neurological disease, lower extremity amputation, or uncorrected hearing impairment that would prevent ability to perform the dual-task assessment. All participants provided written informed consent. The study was approved by the local Institutional Review Board.

Twelve participants were enrolled and 8 participants completed all study related interventions and primary outcome analyses. The 4 withdrawals (non-completers) were related to inability to complete study visits according to schedule ($n = 1$), development of medical issues that prevented continuation in the study ($n = 1$), or substantial delays in obtaining approval from insurance providers for dalfampridine following prescription by the neurologist ($n = 2$). Since this was a proof-of-concept pilot study with the principal aim to explore effect sizes of combined dalfampridine and physical therapy compared to physical therapy alone, we only analyzed data for subjects who completed the full intervention protocol ($n = 4$ each cohort).

Four of the 8 completers had been prescribed dalfampridine by their physician, and 4 were not taking the medication. Only 5 of the 8 participants who completed the intervention were available to attend the 1-month follow-up; the 3 who missed their follow-up assessments were due to travel/holidays. Thus, the 1-month follow-up timepoint was omitted from the analyses reported herein.

Interventions

Participants taking dalfampridine took 10 mg doses every 12 h per physician prescription. The physical therapy intervention has been described elsewhere (11) but critical components are detailed here.

The physical therapy intervention was a progressive, mobility and balance motor-relearning (i.e., restorative-focused) intervention provided one-on-one by a licensed physical therapist that included training in functional strengthening, coordination, static and dynamic balance, dual-tasking, and gait. The intervention was standardized in terms of the philosophical approach and structure, but the specific activities were customized to the participant's individual needs (selected from a range of defined activities within the components of the program) and difficulty level. This intervention model is consistent with current clinical practice, which is characterized by a multimodal approach (12). Moreover, this intervention is based on the current best evidence demonstrating that multimodal interventions produce larger improvements in mobility outcomes in people with MS than unimodal interventions (13).

Physical therapy was provided at our research facility or clinical practice location two times per week for 6 weeks (12 sessions). Each session included 40 min of therapeutic intervention, lasting approximately one hour in total. Using theoretical frameworks for motor relearning, each session comprised three specific components: (i) part-practice (10 min), (ii) whole-practice (20 min), and (iii) contextual practice (10 min) to facilitate transfer to real world environments. Additionally, home practice was encouraged but not tracked and relevant patient education was provided.

Training activities were performed initially in closed environments (quiet room) and progressed on an individual basis to open environments (e.g., busy corridor area; background conversations). An intervention catalog in the Manual of Procedures listed the specific activities for each training component as well as five prescribed levels of difficulty for training progression. Therapists had autonomy in the selection of activities to address individual-specific impairments and customization of difficulty to ensure that a high degree of challenge was maintained throughout. Exercise programs that provide a high degree of challenge are consistently more

effective than those providing only a moderate degree of challenge (14). This personalized approach, while adhering to the structured principles and components of this motor-relearning intervention, was considered to maximize potential for individual therapeutic gain while simultaneously ensuring that the target intensity for each activity could be achieved. Treatment fidelity was ensured by having all therapists undergo a 3-h training in the intervention protocol, co-treating with the first author for at least 3 sessions, providing a detailed Manual of Procedures to guide clinical decision-making, and periodic auditing of the intervention sessions and documentation. Three therapists, including the first author, provided the intervention.

For **part-practice**, therapists selected activities that targeted static and dynamic standing balance, lower extremity coordination, functional strengthening, and single-step training (e.g., swing and stance control). Intensity of part-practice was documented as sets and repetitions of each activity, with the goal to complete 2–3 sets of 12–15 repetitions of 2 different activities in 10 min. **Whole-practice** included activities that involved continuous practice of gait. Whole-task practice was a mixture of overground gait training and treadmill gait training (no body weight support). Whole-task activities also included narrow walking, side-stepping, backward walking, and speed modulation. For treadmill walking, participants were encouraged *not* to hold onto the handrail to maximize practice with full weight bearing and to improve dynamic balance and confidence, as well as maximize degree of challenge. Therapists provided intermittent assistance at the trunk or lower limbs as needed to facilitate balance and kinematics of limb movement. Emphasis was on motor control, not aerobic training, although speed was increased when possible. Intensity of whole-practice was documented by continuous minutes and bouts of treadmill walking, and sets and repetitions of overground practice activities. If a session included overground practice only, then at least 2 activities with 2 sets of 12–15 repetitions was performed in 20 min.

Contextual transfer practice included obstacle negotiation, stair climbing, stopping and turning, terrain/surface/lighting changes, and outdoor walking. Contextual transfer practice was an extension of whole-practice that applied key motor-learning principles of task variability, progression, and challenge, and was always conducted overground in the "real world" (e.g., hallways, cafeteria, escalators, and outdoors pending weather). Two contextual transfer activities were performed in each session. Since these activities involved real-world practice of continuous ambulation in various contexts, intensity of contextual practice was measured by number and duration of rests required to obtain 10 min of practice. Dual-task training was incorporated as part of the intervention (starting in week 2 of the program, as appropriate) to increase the challenge and provide task-specific practice of ecologically-valid mobility tasks (e.g., talking while walking). During dual-task training, participants performed cognitive tasks while practicing gait and balance activities. Several different cognitive activities were used with two different activities assigned to each session to ensure all participants practiced a range of dual-tasks (11).

As is customary in outpatient physical therapy, home-based practice of the skills (part and/or whole) was asked of the participants to enhance their ability to transfer and consolidate learning to everyday mobility situations. It was assumed that contextual transfer practice was occurring during everyday mobility activity in the home and community environments. Patient education included advice on stretching, fatigue/energy management, and strategies for transitioning to ongoing home and community practice after the completion of the 6-week intervention.

Outcome Measures

The primary outcome was T25FW (timed using a handheld stopwatch) after the physical therapy/combined intervention. The T25FW was used primarily to enable direct comparison with the dalfampridine clinical trials. We also measured self-selected single-task and dual-task gait speed. For the dual-task, participants walked at their self-selected speed while performing the auditory "clock task" (15). Response time and accuracy were recorded during walking (dual-task) and during seated performance of the clock task (single-task). Gait data were acquired using a 20-foot instrumented walkway (ProtoKinetics, Havertown, PA). For both single-task and dual-task walking, participants completed 4 continuous passes across the walkway with turns performed off the walkway such that only steady state strides were used in the analysis.

Secondary outcome measures were selected to explore potential treatment effects on performance-based and patient-reported measures of balance, cognition, and fatigue. These included the Mini-BESTest, Four-Square Step Test, the Symbol-Digit Modalities Test, and self-reported outcomes for walking disability (12-Item MS Walking scale; MSWS-12), fatigue (Fatigue Severity Scale), balance self-efficacy (Activities-specific Balance Confidence scale), and quality of life (MS Impact Scale, MSIS-29).

The outcome measures were administered at (i) initial baseline, which was before dalfampridine was commenced in the medication group (Week 0), (ii) after the 3-week run period, which was the drug-only phase for the D+PT group and no-treatment phase for the PT group (Week 3), (iii) after the 6-week physical therapy intervention (Week 9), and (iv) 1-month after completion of the 6-week intervention. Since only 5 of the 8 participants were available to complete the follow-up visit at their scheduled time, these data were omitted from the statistical analyses. Outcome assessments were conducted by a trained evaluator who was naïve to dalfampridine status of each participant at each timepoint.

Data Analysis

The groups were compared at baseline using independent samples *t*-tests or non-parametric tests as appropriate. Due to the preliminary nature of this pilot study, we placed most emphasis on the effect size comparison and confidence intervals rather than statistical significance. Thus, the main analysis was a between-group comparison of absolute change scores during the physical therapy phase (i.e., change between Week 3 and Week 9 for D+PT vs. PT). Effect sizes are reported as Cohen's

TABLE 1 | Demographic and baseline characteristics of participants in each group.

Participant	Age (years)	Sex	Years since diagnosis	Type of MS	Falls in last year	EDSS	T25FW (s)	STGS (m/s)	DTGS (m/s)	MSWS-12 (transformed score)	Assistive device
Dalfampridine plus physical therapy ($n = 4$)											
D1	59	F	6	RRMS	1	3.0	6.61	0.96	0.98	91.7	None
D2	59	F	12	RRMS	7	6.5	8.36	0.60	0.74	72.9	Rollator
D3	42	F	4.3	RRMS	2	6.0	9.07	0.64	0.65	87.5	Cane
D4	38	F	2	SPMS	12	6.5	13.86	0.49	0.30	89.6	Quad cane
Mean/Median	49.5		6.1		4.5	6.3	9.47	0.67	0.67	85.4	
(SD/IQR)	(11.1)		(4.3)		(1.3–10.8)	(3.8–6.5)	(3.1)	(0.20)	(0.28)	(8.5)	
Physical therapy ($n = 4$)											
P1	63	F	15.5	SPMS	1	4.5	6.36	1.09	0.95	47.9	None
P2	65	F	5.8	RRMS	1	3.0	6.27	1.07	1.19	50.0	None
P3	53	M	0.5	PPMS	3	6.0	12.84	0.54	0.41	83.3	Cane
P4	29	F	5	RRMS	2	6.0	6.0	0.98	0.72	54.2	Cane
Mean/Median	52.5		6.9		1.5	5.3	7.9	0.92	0.82	58.9	
(SD/IQR)	(16.5)		(6.3)		(1.0–2.8)	(3.4–6.0)	(3.3)	(0.26)	(0.33)	(16.5)	

F, female; IQR, interquartile range; M, male; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS; T25FW, Timed 25-foot walk (seconds); STGS, single-task gait speed (meters per second); DTGS, dual-task gait speed (meters per second); MSWS-12, 12-Item MS Walking Scale.

TABLE 2 | Timed 25-foot walk test data by subject and group (faster times are better; negative percentages are improvement).

Participant	Week 0 T25FW (s)	Week 3 T25FW (s)	Week9 T25FW (s)	% change Week 0–3	% change Week 3–9	% change Week 0–9
Dalfampridine plus physical therapy ($n = 4$)						
D1	6.61	6.14	5.24	−7.1%	−14.7%	−20.7%
D2	8.36	6.74	4.27	−19.4%	−36.7%	−48.9%
D3	9.07	7.36	6.19	−19.0%	−15.9%	−31.8%
D4	13.86	13.05	11.02	−5.8%	−15.6%	−20.5%
Mean	9.48	8.32	6.68	−12.8%	−20.7%	−30.5%
(SD)	(3.10)	(3.19)	(3.00)	(7.3%)	(10.7%)	(13.4%)
Physical therapy ($n = 4$)						
P1	6.36	6.24	5.81	−1.9%	−6.9%	−8.7%
P2	6.27	6.08	4.88	−3.0%	−19.8%	−22.3%
P3	12.84	11.05	10.27	−13.9%	−7.1%	−20.0%
P4	6.00	4.74	4.30	−21.0%	−9.4%	−28.4%
Mean	7.87	7.03	6.31	−10.0%	−10.8%	−19.8%
(SD)	(3.32)	(2.76)	(2.71)	(9.2%)	(6.1%)	(8.3%)

d. Given the small and exploratory nature of the study, we also observed individual response patterns in the primary outcome measure, T25FW.

RESULTS

The characteristics of the participants are presented in **Table 1**. At Week 0 (study enrollment), the two groups did not differ significantly in age, disease duration, education, Symbol-Digit Modalities Test, Mini-BESTest, Four Square Step Test, T25FW, fatigue, self-selected gait speed, or dual-task gait speed. However, the D+PT group, on average, was relatively more impaired than the PT groups in most outcomes at baseline, largely driven by one outlier with EDSS 6.5 (**Table 1**). The D+PT group had significantly higher self-rated walking disability ($p = 0.029$) and lower balance self-efficacy at Week 0 ($p = 0.046$), as well as slightly higher median EDSS and a higher median number of falls in the last 12 months, but these latter differences were not statistically significant.

Timed 25-Foot Walk

The T25FW data are presented in **Table 2**. During the 3-week drug-only run-in phase (Week 0-3), the D+PT group decreased T25FW time from 9.5 s (SD 3.1 s) to 8.3 s (SD 3.2 s; $p = 0.032$, $d = 1.89$), which represented a 12.8% improvement (95% CI 1.2 to 24.4%). During the no-treatment

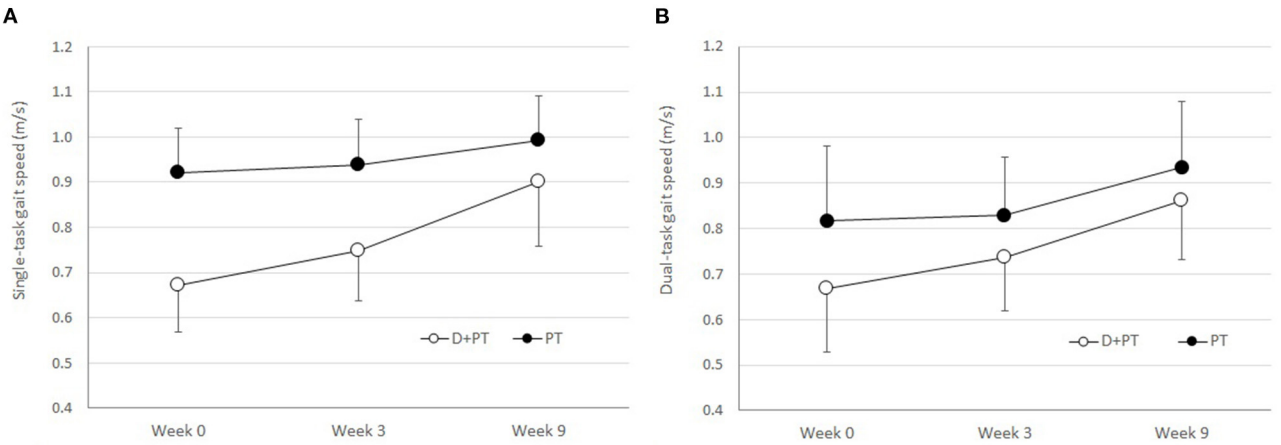


FIGURE 1 | (A) Single-task gait speed and **(B)** dual-task gait speed by group and time point. Week 0–3 represents dalfampridine only for D+PT group and no-treatment phase for PT group. Week 3–9 represents the physical therapy phase with or without dalfampridine. D+PT denotes dalfampridine plus physical therapy; PT denotes physical therapy without dalfampridine. Error bars are SEM.

phase (Week 0–3) for the PT group, T25FW also decreased from 7.9 s (SD 3.3 s) to 7.0 s (SD 2.8 s, $p = 0.133$; $d = 1.02$), which represented a 10.0% improvement (95% CI −4.6 to 24.5%); however, this appeared to be driven by one outlier (see **Table 2**, P4) who walked 1.3 s faster at the second baseline visit. With the outlier removed, the PT group change during Week 0–3 was −6.3% (95% CI to 22.8 to 10.2%).

During the 6-week physical therapy intervention phase (Week 3–9), the D+PT group further decreased T25FW time to 6.7 s (SD 3.0 s; $p = 0.021$, $d = 2.24$), which represented a further 20.7% improvement (95% CI 3.8 to 37.6%) for an overall Week 0–9 improvement of 30.5% (95% CI 9.2 to 51.8%). The PT group further decreased T25FW time to 6.3 s (SD 2.7 s, $p = 0.029$, $d = 1.96$), which represented a further 10.8% improvement (95% CI 1.0 to 20.5%) for an overall Week 0–9 improvement of 19.8% (95% CI 6.7 to 33.0%).

The between-group comparison of the absolute change in T25FW time between Week 3 and Week 9 favored the D+PT group but was not statistically significant (mean difference [MD] = −0.93s, 95% CI −1.9 to 0.07s, $p = 0.064$, $d = 1.6$). The results were similar when comparing the groups on percent change in T25FW between Week 3 and Week 9: there was a nonsignificant but large effect in favor of the D+PT group (MD = 9.9%, 95% CI −5.1 to 24.9%, $d = 1.1$).

Among the 4 participants taking dalfampridine, none of the participants achieved 25% improvement in T25FW on 3 weeks of the drug alone, which was the average improvement observed in dalfampridine clinical trial "responders" (3). After adding 6 weeks of physical therapy, all 4 participants taking dalfampridine demonstrated T25FW improvements >20% from baseline, with 2 participants exceeding 30% improvement (**Table 1**). The relative improvements in T25FW among the PT-only group in response to the physical therapy intervention were generally smaller, ranging from 6.9 to 19.8%.

Self-Selected Single and Dual-Task Gait Speed

The improvement in self-selected single-task gait speed during the physical therapy intervention phase (Week 3–9) favored the D+PT group, but it was not statistically significant (MD = 0.12 m/s, 95% CI −0.01 to 0.24 m/s, $p = 0.070$, $d = 1.56$). There were similar improvements in dual-task gait speed in both groups (MD = 0.02 m/s, 95% CI −0.11 to 0.14 m/s, $p = 0.747$, $d = 0.24$), illustrated in **Figure 1**.

There were no significant changes in dual-task effects on gait speed or clock-task performance across time or between groups. Dual-task performance was characterized by large between-subject variability in both gait speed and the clock task.

Secondary Outcome Measures

The secondary outcome measures are presented in **Table 3**. The between-group intervention effect sizes for the physical therapy phase were moderate to large and favored the D+PT group for balance (Mini-BESTest), self-rated walking disability (MSWS-12), and balance self-efficacy (ABC), but only the ABC was statistically significant. The D+PT group also had a slightly greater improvement on the MSIS-29, but the between-group effect size was small. The PT group had a significantly greater improvement on the Symbol-Digit Modalities Test than the D+PT group. The Four Square Step Test showed slight worsening (increase in time) after the intervention in both groups, but slightly more so in the D+PT group (small effect size). There was no remarkable change in fatigue for either group despite moderately severe fatigue at baseline.

DISCUSSION

The purpose of this pilot study was to demonstrate proof-of-concept of combining physical therapy with prescription

TABLE 3 | Mean (SD) for secondary outcome measures and between-group differences in change during physical therapy (PT) intervention phase (Week 3–9).

	Dalfampridine + Physical therapy ($n = 4$)						Physical therapy ($n = 4$)						Between-group difference in PT phase change (Week 9 minus Week 3) (D+PT minus PT)	
	Week 0		Week 3		Week 9		Week 0		Week 3		Week 9		MD (95% CI)	*d*
Mini-BESTest (max. 28)	13.5	(7.6)	15.8	(7.5)	19.8	(5.1)	21.8	(3.3)	22.0	(2.8)	22.5	(4.8)	3.5 (−7.2, 14.2)	0.68
Four-Square Step Test (s)	20.3	(7.9)	17.2	(7.5)	19.4	(10.9)	15.9	(8.4)	13.6	(5.1)	14.2	(9.1)	1.6 (−5.2, 8.3)	0.41
SDMT (number correct)	47.8	(9.9)	50.8	(10.4)	49.8	(8.5)	50.8	(7.9)	50.5	(8.3)	55.5	(6.6)	−6.0 (−10.1, −1.9)	2.55
MSWS-12 (0–100 transformed)	85.4	(8.5)	68.2	(18.3)	44.3	(10.0)	58.9	(16.5)	53.6	(17.9)	48.9	(23.5)	−19.3 (−42.9, 25.8)	1.41
ABC (%)	47.0	(17.5)	45.2	(13.8)	66.7	(18.4)	73.8	(12.2)	69.4	(18.0)	76.4	(15.1)	14.5 (7.1, 22.0)	3.39
Fatigue Severity Scale (max. 64)	55.0	(14.0)	45.5	(23.3)	43.3	(16.3)	40.8	(8.7)	45.8	(9.4)	43.0	(18.1)	0.5 (−14.3, 15.3)	0.06
MSIS-29 (max. 145)	91.0	(19.8)	74.8	(13.9)	67.0	(17.5)	70.8	(15.9)	69.5	(18.6)	70.5	(18.2)	−8.8 (−43.3, 25.8)	0.44

ABC, Activities-specific Balance Confidence scale; MD, mean difference; MSIS-29, 29-Item Multiple-Sclerosis Impact Scale; MSWS-12, 12-Item Multiple Sclerosis Walking Scale; PT, physical therapy; SDMT, Symbol-Digit Modalities Test.

dalfampridine to improve walking speed in people with MS. The effects of dalfampridine (alone) on walking speed have been well-established in several large clinical trials (1–3, 16, 17), but the proportion of people who experience a meaningful response to the drug is fewer than 40% (3). Physical therapy is the other mainstream treatment approach for mobility limitations in people with MS, but the effect of combining these two interventions has not yet been systematically studied. The physical therapy intervention represented an evidence-based motor relearning approach that is consistent with outpatient clinical practice. This rehabilitation approach, despite being relatively conventional, is also not well studied in people with MS and has unknown responder rates. Thus, the control group in this study (PT only) provided preliminary effect estimates of this rehabilitation approach.

While we found that both groups improved walking speed in response to this physical therapy intervention, the relative improvement was almost twice as large in the group taking dalfampridine. Further, whereas none of the individuals taking dalfampridine met Hobart's criterion of "responders" (≥20% improvement in T25FW) (18) in response to dalfampridine alone, after 6-weeks of physical therapy concurrently with dalfampridine, all participants achieved >20% improvement from initial baseline. Thus, it is reasonable to assert that combining physical therapy with dalfampridine when the medication is first prescribed could improve the responder rate well above the previously observed 38%. It is surprising that physical therapy is not routinely prescribed with dalfampridine. The LIBERATE Trial, a post-authorization investigation of dalfampridine in a routine practice setting, found that only 14% of individuals prescribed dalfampridine received concurrent physical therapy (19). However, it is not clear whether dalfampridine is a first-line treatment choice by physicians for mobility impairments, or whether it is prescribed when physical therapy has failed or is declined by the patient.

The evidence for physical therapy in MS is presently limited by small studies and highly variable treatment protocols. Furthermore, rehabilitation research in MS has been dominated by "exercise training," mostly comprising aerobic and resistance training (13, 20–23) and specialized, unimodal interventions such as robotic-assisted gait training (8, 9, 24) and body-weight supported treadmill training (5, 10, 25–27). There have been only a handful of studies that have examined a pragmatic intervention that is representative of physical therapy practice for neurological rehabilitation (28–30). This pilot study has demonstrated that the rigorous and progressive motor relearning intervention customized to individual ability can produce important improvements in patients with mild to moderate mobility limitations.

The D+PT group had significantly greater improvement in the MSWS-12, reflecting improved self-perceived walking ability, with the average improvement during the PT period alone being 23.9 points, far exceeding the minimally important change of 10.4 points (31). The finding that the PT group did not report meaningful improvement in self-rated walking disability is likely due to starting with only moderate self-perceived walking disability at baseline, compared to the very high disability rating of the D+PT group. Further, the PT group had mean T25FW under 8 s at baseline, thus creating a potential ceiling effect. Nonetheless, 2 of the 4 participants in the PT-only group had MSWS-12 improvements exceeding 10.4 points, while one of the fastest walkers at baseline reported no change, and one participant reported 8.8 point decline. Interestingly, the latter participant also reported increased fatigue at Week 9, which may have influenced her walking disability perception. It is also noteworthy that even though the D+PT group were "non-responders" to dalfampridine (alone) using Hobart's criterion of ≥20% improvement on T25FW (18), the average patient-perceived improvement on the MSWS-12 during the drug-only run in was an astonishing 17.2 points. Thus, it may be necessary to also consider patient

perception of improvement when defining responders, rather than relying solely on objective measures of (fast) gait speed. Indeed, it has been suggested that T25FW in combination with MSWS-12 may be optimal for determining response to dalfampridine (32).

It was unexpected that the PT group, on average, experienced an improvement in T25FW time during the no-treatment baseline phase. However, this change was largely driven by one individual, the fastest walker at baseline, who walked 21% faster at the second baseline visit. It is not uncommon to observe small systematic increases in gait speed between multiple baseline assessments in individuals with mobility disability (33), which could be due to greater comfort level with testing procedures and environment on repeat occasions. Importantly, this magnitude of variation during the no-treatment phase was not observed for self-selected gait speed in either single-task or dual-task conditions. Thus, we believe the observed effects on the T25FW during the no-treatment phase for the PT group are likely due to the T25FW being a test of fastest gait speed, which could be influenced by how the instructions for the test were delivered or emphasized on each occasion, as well as personal factors such as fatigue or motivation on any given day.

The fact that dual-task gait speed improved equivalently in both groups is quite encouraging. This finding suggests that our physical therapy program was able to improve gait automaticity regardless of dalfampridine treatment. We can infer improved gait automaticity from the physical therapy intervention since there was no reciprocal decline in the cognitive task performance associated with the improvement in dual-task gait speed (34). Although there was no between-group difference in change on the Mini-BESTest scores (range 0–28, higher scores indicate better balance), the D+PT group demonstrated an average improvement during the D+PT phase of 4 points (and a 6.3 point increase overall), which is considered clinically important (35). The therapy-related change in the Mini-BESTest was smaller and likely not meaningful in the PT group (<2 points on average), but this could be due to a higher initial baseline score. Perhaps more important to note is that the two most severely impaired individuals (both in the D+PT group) with initial Mini-BESTest scores of 6 and 11, respectively, each improved by only one point on the drug alone, but by 7 and 12 points, respectively, with PT. Whether gains this size among severely impaired individuals could be achieved with this PT program without concurrent dalfampridine treatment is unclear; there were no participants in the PT group with equivalent balance impairment at baseline. The Four Square Step Test showed slight worsening after the intervention in both groups, but we believe this could reflect greater caution as opposed to worse balance, especially when considered alongside the Mini-BESTest results.

There are several limitations that must be acknowledged. Inarguably, the small sample size is a limitation. However, the study achieved its purpose in demonstrating proof-of-concept and obtaining effect size estimates for PT with and without dalfampridine. Although our point estimates lack precision, the group results (many of which were statistically significant) together with visual analysis of the individual patterns and the large effect sizes point to the value of further, larger investigations. The between-group comparisons on walking speed outcomes are limited by the non-randomized design. The non-randomized design was necessary because the budget did not enable the investigators to provide the medication as part of the study. Consequently, the groups were not directly comparable on disability at baseline. The tendency for higher disability in the D+PT group is not surprising and may have contributed to the reasons these individuals were prescribed dalfampridine clinically. Future study designs wishing to examine therapeutic efficacy in patients routinely prescribed dalfampridine should endeavor to match control participants on disability level at baseline or consider a randomized design with placebo medication. Because we recruited patients who were prescribed dalfampridine as part of their routine clinical care, we relied on physician referral to the study, which posed some degree of challenge for recruitment. Volunteers for the PT-only group self-referred to the study via community advertisements. Matching PT-only participants to the D+PT group would have further delayed study enrollment. The physical therapy intervention in this study was limited to 6 weeks (12 sessions), which approximated the typical outpatient physical therapy practice for patients with MS in our hospital system at the time of the study. The study is lacking follow-up analysis. However, the objective of this study was to assess immediate effects of PT with and without dalfampridine on gait speed and related outcomes, to assess whether future investigations would be worthwhile.

CONCLUSION

The findings from this proof-of-concept pilot study provide promising new evidence that physical therapy that adheres to motor relearning principles and the challenge framework, provided concurrently with dalfampridine, may offer potential benefit to patients with MS who fail to achieve meaningful improvement after treatment with dalfampridine alone. Dalfampridine combined with physical therapy is worthy of further, controlled investigation.

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 North Carolina at Chapel Hill. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PP conceptualized and designed the study, with input from BG and SM-P. PP developed and delivered the physical therapy intervention, trained and supervised project staff, collected data, conducted the data analysis, and lead the writing of the manuscript. PP and BG acquired the funding. PP and SM-P recruited participants. All authors contributed to the revision, editing, final development of the manuscript, and presentation of data.

FUNDING

This pilot study was funded by the National Multiple Sclerosis Society (PP-1503-03495).

REFERENCES

1. Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, et al. phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol.* (2010) 68:494–502. doi: 10.1002/ana.22240
2. Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet.* (2009) 373:732–8. doi: 10.1016/S0140-6736(09)60442-6
3. Goodman AD, Brown TR, Schapiro RT, Klingler M, Cohen R. Blight AR. A pooled analysis of two phase 3 clinical trials of dalfampridine in patients with multiple sclerosis. *Int J Multiple Scler Care.* (2014) 16:153–60. doi: 10.7224/1537-2073.2013-023
4. Plummer P. Critical Appraisal of evidence for improving gait speed in people with multiple sclerosis: dalfampridine versus gait training. *Int J MS Care.* (2016) 18:105–15. doi: 10.7224/1537-2073.2014-114
5. Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. *Neurorehabil Neural Repair.* (2008) 22:661–71. doi: 10.1177/1545968308318473
6. Schwartz I, Sajin A, Moreh E, Fisher I, Neeb M, Forest A, et al. Robot-assisted gait training in multiple sclerosis patients: a randomized trial. *Multiple Scler.* (2012) 18:881–90. doi: 10.1177/1352458511431075
7. van den Berg M, Dawes H, Wade DT, Newman M, Burridge J, Izadi H, et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. *J Neurol Neurosurg Psychiatry.* (2006) 77:531–3. doi: 10.1136/jnnp.2005.064410
8. Vaney C, Gattlen B, Lugon-Moulin V, Meichtry A, Hausammann R, Foinant D, et al. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. *Neurorehabil Neural Repair.* (2012) 26:212–21. doi: 10.1177/1545968311425923
9. Beer S, Aschbacher B, Manoglou D, Gamper E, Kool J, Kesselring J. Robot-assisted gait training in multiple sclerosis: a pilot randomized trial. *Multiple Scler.* (2008) 14:231–6. doi: 10.1177/1352458507082358
10. Ruiz J, Labas MP, Triche EW, Lo AC. Combination of robot-assisted and conventional body-weight-supported treadmill training improves gait in persons with multiple sclerosis: a pilot study. *J Neurol Phys Ther.* (2013) 37:187–93. doi: 10.1097/NPT.0000000000000018
11. Plummer P, Bohling CJ, Nickles LE, Williams AA, Thomas A, Markovic-Plese S, et al. Combining dalfampridine with multicomponent exercise and gait training in a person with multiple sclerosis: case report. *Int J Multiple Scler Care.* (2018) 20:238–43. doi: 10.7224/1537-2073.2017-074
12. American Physical Therapy Association. Guide to physical therapist practice. *Phys Ther.* (2001) 81:9–744.
13. Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. *Arch Phys Med Rehabil.* (2015) 96:1339–48. doi: 10.1016/j.apmr.2015.02.011
14. Gunn H, Markevics S, Haas B, Marsden J, Freeman J. Systematic review: the effectiveness of interventions to reduce falls and improve balance in adults with multiple sclerosis. *Arch Phys Med Rehabil.* (2015) 96:1898–912. doi: 10.1016/j.apmr.2015.05.018
15. Plummer-D'Amato P, Altmann LJP, Saracino D, Fox E, Behrman AL, et al. Interactions between cognitive tasks and gait after stroke: a dual task study. *Gait Posture.* (2008) 27:683–8. doi: 10.1016/j.gaitpost.2007.09.001
16. Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology.* (2008) 71:1134–41. doi: 10.1212/01.wnl.0000326213.89576.0e
17. Goodman AD, Cohen JA, Cross A, Vollmer T, Rizzo M, Cohen R, et al. Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. *Multiple Scler.* (2007) 13:357–68. doi: 10.1177/1352458506069538
18. Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology.* (2013) 80:1509–17. doi: 10.1212/WNL.0b013e31828cf7f3
19. Castelnovo G, Gerlach O, Freedman MS, Bergmann A, Sinay V, Castillo-Triviño T, et al. Safety, Patient-Reported Well-Being, and Physician-Reported Assessment of Walking Ability in Patients with Multiple Sclerosis for Prolonged-Release Fampridine Treatment in Routine Clinical Practice: Results of the LIBERATE Study. *CNS Drugs.* (2021) 35:1009–22. doi: 10.1007/s40263-021-00840-x
20. Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology.* (2004) 63:2034–8. doi: 10.1212/01.WNL.0000145761.38400.65
21. Sabapathy NM, Minahan CL, Turner GT, Broadley SA. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. *Clin Rehabil.* (2011) 25:14–24. doi: 10.1177/0269215510375908
22. Snook EM, Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabil Neural Repair.* (2009) 23:108–16. doi: 10.1177/1545968308320641
23. Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G. Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev.* (2005) 2005:CD003980. doi: 10.1002/14651858.CD003980.pub2
24. Straudi S, Benedetti MG, Venturini E, Manca M, Foti C, Basaglia N. Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. *NeuroRehabilitation.* (2013) 33:555–63. doi: 10.3233/NRE-130990
25. Pilutti LA, Lelli DA, Paulseth JE, Crome M, Jiang S, Rathbone MP, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. *Arch Phys Med Rehabil.* (2011) 92:31–6. doi: 10.1016/j.apmr.2010.08.027
26. Wier LM, Hatcher MS, Triche EW, Lo AC. Effect of robot-assisted versus conventional body-weight-supported treadmill training on quality of life for people with multiple sclerosis. *J Rehabil Res Dev.* (2011) 48:483–92. doi: 10.1682/JRRD.2010.03.0035
27. Swinnen E, Beckwee D, Pinte D, Meeusen R, Baeyens JP, Kerckhofs E. Treadmill training in multiple sclerosis: can body weight support or robot assistance provide added value? A systematic review. *Mul Scler Int.* (2012) 2012:240274. doi: 10.1155/2012/240274
28. Lord SE, Wade DT, Halligan PW, A. comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. *Clin Rehabil.* (1998) 12:477–86. doi: 10.1191/026921598677863454
29. Wiles CM, Newcombe RG, Fuller KJ, Shaw S, Furnival-Doran J, Pickersgill TP, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. *J Neurol Neurosurg Psychiatry.* (2001) 70:174–9. doi: 10.1136/jnnp.70.2.174
30. Solari A, Filippini G, Gasco P, Colla L, Salmaggi A, La Mantia L, et al. Physical rehabilitation has a positive effect on disability in

multiple sclerosis patients. *Neurology*. (1999) 52:57–62. doi: 10.1212/WNL.52.1.57
31. Baert I, Freeman J, Smedal T, Dalgas U, Romberg A, Kalron A, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair*. (2014) 28:621–31. doi: 10.1177/1545968314521010
32. Rodriguez-Leal FA, Haase R, Thomas K, Eisele JC, Proschmann U, Schultheiss T, et al. Fampridine response in MS patients with gait impairment in a real-world setting: need for new response criteria? *Multiple Scler*. (2018) 24:1337–46. doi: 10.1177/1352458517720043
33. Lewek MD, Sykes R. 3rd. Minimal Detectable Change for Gait Speed Depends on Baseline Speed in Individuals With Chronic Stroke. *J Neurol Phys Ther*. (2019) 43:122–7. doi: 10.1097/NPT.0000000000000257
34. Plummer P, Eskes G. Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci*. (2015) 9:225. doi: 10.3389/fnhum.2015.00225
35. Godi M, Franchignoni F, Caligari M, Giordano A, Turcato AM, Nardone A. Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Phys Ther*. (2013) 93:158–67. doi: 10.2522/ptj.20120171

Conflict of Interest: PP has served as a consultant and member of the Physical Therapy in Post Ischemic Stroke Advisory Board for Acorda Therapeutics, Inc.

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.

frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 21 January 2022
doi: 10.3389/fresc.2021.815111

Does Integrating Cognitive and Psychological Interventions Enhance Wellbeing After Acquired Brain Injury? Study Protocol for a Phase II Randomized Controlled Trial of the VaLiANT (Valued Living After Neurological Trauma) Group Program

Nick Sathananthan[1], Eric M. J. Morris[1], David Gillanders[2], Lucy Knox[1], Bleydy Dimech-Betancourt[1], Bradley J. Wright[1], Roshan das Nair[3†] and Dana Wong[1]*

[1] School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia, [2] School of Health in Social Sciences, University of Edinburgh, Edinburgh, United Kingdom, [3] Institute of Mental Health, University of Nottingham, Nottingham, United Kingdom

Background and Objectives: Cognitive and emotional changes affect the majority of individuals with acquired brain injury (ABI) and are associated with poorer outcomes. The evidence for "siloed" rehabilitation approaches targeting cognition and mood separately remains mixed. Valued living (i.e., acting consistently with personal values) is associated with better psychological functioning and participation in work and other productive activities. Rehabilitation interventions that concurrently address cognitive and emotional barriers to valued living may therefore result in improved outcomes. VaLiANT (Valued Living After Neurological Trauma) is an 8-week group intervention developed by our team, which uniquely combines cognitive rehabilitation and psychological therapy to improve wellbeing and meaningful participation (i.e., valued living) following ABI.

Method: This protocol describes the design and implementation of a Phase II parallel-group randomized controlled trial with blinded outcome assessors, to evaluate the potential efficacy of VaLiANT and the feasibility of a Phase III trial. Participants are adults with a history of ABI at least 3 months prior to study entry, who experience cognitive and/or emotional difficulties and associated reduced participation in valued activities. Random allocation to the treatment condition (8-week VaLiANT group program) or a usual care waitlist control condition occurs at a 2:1 treatment: control ratio. The primary outcome is wellbeing, measured by the Warwick-Edinburgh Mental Wellbeing Scale. Secondary outcomes include measures of valued living, mood, cognitive complaints, quality of life, community participation, post-traumatic growth, and self-efficacy. All measures are collected across three time points by blinded assessors (baseline, 8-week follow-up, 16-week follow-up). Trial feasibility will be evaluated against recruitment rates, drop-out rates, intervention acceptability, and treatment fidelity (manual adherence and therapist competence).

OPEN ACCESS

Edited by:
Carolee Winstein, University of Southern California, United States

Reviewed by:
Alessandro Giustini, Istituto di Riabilitazione Santo Stefano, Italy
Ann Van de Winckel, University of Minnesota Twin Cities, United States

***Correspondence:**
Dana Wong
d.wong@latrobe.edu.au

†ORCID:
Roshan das Nair
orcid.org/0000-0001-8143-7893

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *15 November 2021*
Accepted: *29 December 2021*
Published: *21 January 2022*

Citation:
Sathananthan N, Morris EMJ, Gillanders D, Knox L, Dimech-Betancourt B, Wright BJ, das Nair R and Wong D (2022) Does Integrating Cognitive and Psychological Interventions Enhance Wellbeing After Acquired Brain Injury? Study Protocol for a Phase II Randomized Controlled Trial of the VaLiANT (Valued Living After Neurological Trauma) Group Program. Front. Rehabilit. Sci. 2:815111. doi: 10.3389/fresc.2021.815111

Discussion: This trial will extend current knowledge on how to improve long-term outcomes following ABI by evaluating an innovative integrated, multi-domain approach to rehabilitation concurrently addressing cognitive and emotional barriers to participation in meaningful life roles.

Keywords: cognitive rehabilitation, psychological therapy, acquired brain injury, valued living, Acceptance and Commitment Therapy, holistic rehabilitation, combined interventions

INTRODUCTION

Acquired brain injuries (ABIs) such as stroke and traumatic brain injury (TBI) frequently result in cognitive and emotional changes. Estimates suggest that over half of those with a TBI or stroke experience long-term cognitive impairment, especially in the domains of attention, memory, and executive functions (1, 2). Similarly, clinically significant levels of depression and anxiety affect one-third of stroke and half of TBI survivors (3–5) and rates of suicide following ABI are notably higher (6). These cognitive and emotional difficulties are interrelated and highly comorbid after ABI (7), with higher mood symptoms predicting increased cognitive complaints (8), and increased cognitive complaints predicting higher mood disturbance (9). Cognitive and emotional sequelae are frequently highlighted as areas of long-term unmet need by people with ABI, indicating that they are not managed adequately by existing services (10, 11).

Importantly, cognitive impairment and mood disturbance are associated with poor long-term outcomes following ABI. Cognitive impairment predicts reduced independence in activities of daily living (ADLs), reduced participation in meaningful life activities, and poorer overall quality of life (12–15). Furthermore, cognitive impairment is a stronger predictor of negative outcomes and overall disability at 5–10 years post-ABI than the initial injury severity (16, 17). Mood symptoms also predict reduced independence in ADLs, participation in meaningful life activities (18–21), and poorer quality of life (22, 23). As such, cognitive impairment and mood disturbance act as significant barriers to adjustment and recovery from ABI, highlighting the need for evidence-based interventions that address these difficulties.

Current treatment approaches typically remain domain-specific and target cognitive impairment or mood symptoms in isolation, with a limited focus beyond the impairment level (24). Evidence for these approaches remains inconclusive, with studies demonstrating variable efficacy and limited generalization to broader outcomes. For example, memory interventions tend to result in moderate improvements to both subjective and objective memory performance following ABI (25) but provide mixed findings regarding improvement in long-term functional outcomes and quality of life (26–28). Interventions targeting attention deficits have resulted in limited improvement to attention immediately following interventions with no generalization to other long-term outcomes (29). Cognitive Behavioral Therapy (CBT) can improve depressive and anxiety symptoms and some functional outcomes following stroke (30) but these effects have not been consistently found after TBI (31), although adapted CBT that incorporated cognitive compensatory strategies including follow-up booster sessions has shown promise for treating anxiety and depression following TBI (32) with associated improvements in psychosocial outcomes (daily functioning, work, relationships, leisure). Therefore, existing "siloed" treatment approaches do not consistently demonstrate improvements to mood or cognition and positive intervention effects do not consistently translate into improved long-term outcomes such as quality of life or participation in meaningful activities.

It then follows that cognitive rehabilitation and psychological therapy techniques may need to be integrated to holistically improve outcomes beyond the impairment level by concurrently targeting cognitive and emotional barriers to activity and participation in meaningful life roles, wellbeing, and quality of life (33, 34). There is a growing body of evidence suggesting that integrated rehabilitation interventions that combine both psychological and cognitive elements into broader frameworks lead to improvements in psychological distress, meaningful participation, and quality of life, with stable or ongoing improvement up to 3 years following treatment (35, 36). Randomized controlled trial (RCT) level evidence has also suggested that such approaches are more effective at improving outcomes than standard neurorehabilitation and traditional neuropsychological intervention (37, 38). Patients have described experiencing holistic neurorehabilitation as empowering and beneficial for everyday functioning (39). However, several challenges continue to limit the implementation of such interventions including a lack of funding, resources, or other systemic factors (34). The aforementioned interventions were all lengthy with a high frequency of sessions [e.g., 15 h per week over 16 weeks; (37)] which may not be easily implemented or appropriate for all health-care systems. Further research is needed to determine whether the positive effects of integrated, holistic interventions can be replicated when the length of intervention is briefer, which may be more cost-effective and more readily implemented into existing services.

Valued living refers to the extent to which we engage in behaviors that are consistent with our personal values, and it has gained growing attention as an important outcome post-ABI. Higher levels of valued living have been linked with improved wellbeing, quality of life, better psychosocial functioning, and lower psychological distress in both ABI (40, 41) and other chronic health condition populations (42–44). Valued living has been directly related to the level of acceptance and adjustment toward one's ABI (45). However, valued living often remains reduced for a number of years following brain injury (40).

Rehabilitation interventions that target valued living may result in improved outcomes. Acceptance and Commitment Therapy (ACT) is an evidence-based psychological therapy that directly targets valued living, with growing evidence supporting its use to improve mood symptoms and psychological distress in TBI (46–49), stroke (50–52) and other neurological conditions (53, 54). However, none of these studies have specifically aimed to address cognitive impairment, and all have demonstrated limited impact beyond the level of mood disturbance and psychological distress.

A holistic and integrated intervention that targets both cognitive and emotional barriers to valued living may result in more consistent improvements to impairments (e.g., cognitive complaints or mood symptoms) while also leading to more global improvements in meaningful participation, wellbeing, and quality of life. Valued Living After Neurological Trauma (VaLiANT) is a new 8-week group intervention that aims to enhance adjustment to life with ABI by combining cognitive rehabilitation and psychological therapy using ACT principles. A Phase I study has been completed using a single case experimental design repeated across eight participants (55). This study demonstrated reliable improvements to a broad range of outcomes for the majority of participants, including overall wellbeing, anxiety symptoms, and subjective cognitive complaints. The delivery of the intervention was deemed feasible and participant acceptability ratings of the intervention were high. These Phase I findings suggested that VaLiANT may have utility in improving outcomes following ABI and warrants further investigation of the intervention.

Here, we report the protocol for our Phase II RCT evaluating VaLiANT, which aims to:

1. Compare the impact of VaLiANT against treatment-as-usual waitlist control on a range of adjustment-related outcomes including at the levels of impairment, activity, participation, and overall wellbeing and quality of life. This will identify signals of efficacy and determine parameter estimates for a definitive Phase III trial.
2. Investigate the feasibility of the trial design, including recruitment rate, retention rate, success of blinding the outcome assessor under RCT conditions, and exploring the fidelity of delivering the intervention.

METHOD

Ethics

This study has been approved by the La Trobe University Human Research Ethics Committee (HEC #18423) and has been registered in the Australian New Zealand Clinical Trials Registry (ACTRN12619001243101). Protocol amendments have been submitted to both bodies following methodological changes due to the impact of COVID-19. Written informed consent will be obtained from all participants.

Study Design

This Phase II pilot study is a prospectively registered single center, two-arm, assessor-blinded, parallel groups RCT, comparing outcomes of the 8-week VaLiANT group intervention with treatment-as-usual waitlist control. Outcome measures are collected at baseline (T1), at an 8-week follow-up (T2), and at a 16-week follow-up from baseline (T3). An overview of the study procedure is summarized in **Figure 1**. This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (56). Methodological modifications made due to the impact of COVID-19 have been reported in line with SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE-SPIRIT) guidelines (57) throughout the text and summarized in a separate paragraph. The methodological quality of the trial will be evaluated using the Physiotherapy Evidence Database – Psycbite (PEDro-P) scale upon completion of the trial (58).

Participants and Recruitment Process

This study is conducted at La Trobe Psychology Clinic (Melbourne, Australia); a psychology clinic at La Trobe University that also serves as a training clinic for postgraduate psychology students. Community-dwelling participants are identified either through self-referral or referral from a health professional. Recruitment methods include distribution of specific advertisement material (including flyers and weblinks) through local email listservs for clinicians/researchers who work with ABI (e.g., NPinOz, BRAINSPaN), local health services, practitioner networks, the Australian Stroke Clinical Registry (AuSCR), and relevant online portals for individuals living with ABI such as EnableMe (Stroke Foundation). Participants are required to be at least 3-months post-ABI (including stroke, TBI, brain tumor, hypoxic brain injury, and multiple sclerosis) before enrolment in the study; be 18 years of age or over; have reported cognitive and/or emotional difficulties (identified by self, close other and/or clinician in initial screening); and be able to attend the group program in person at La Trobe University Psychology Clinic or *via* telehealth during periods of COVID-19 related restriction. Exclusion criteria include pre-existing intellectual disability, severe psychiatric disorder, comorbid neurodegenerative condition, and insufficient cognitive and/or language abilities to complete outcome measures or participate in the intervention. Participant eligibility is determined *via* telephone screening conducted by the project coordinator (a trainee clinical neuropsychologist) prior to enrolment into the study.

Intervention

The VaLiANT program is a manualized group intervention that concurrently targets cognition and emotion by integrating cognitive rehabilitation and ACT techniques to improve engagement in valued activities following ABI. The program consists of eight 2-h group sessions delivered either in-person or *via* telehealth during periods of COVID-19 restrictions, with group sizes ranging from three to eight participants. The intervention was developed by the authors, drawing on their clinical and research expertise, however evidence-based ACT and cognitive rehabilitation techniques and materials were adapted from existing manualized treatments to supplement the new content (46, 59–62). Group delivery was chosen due to a number

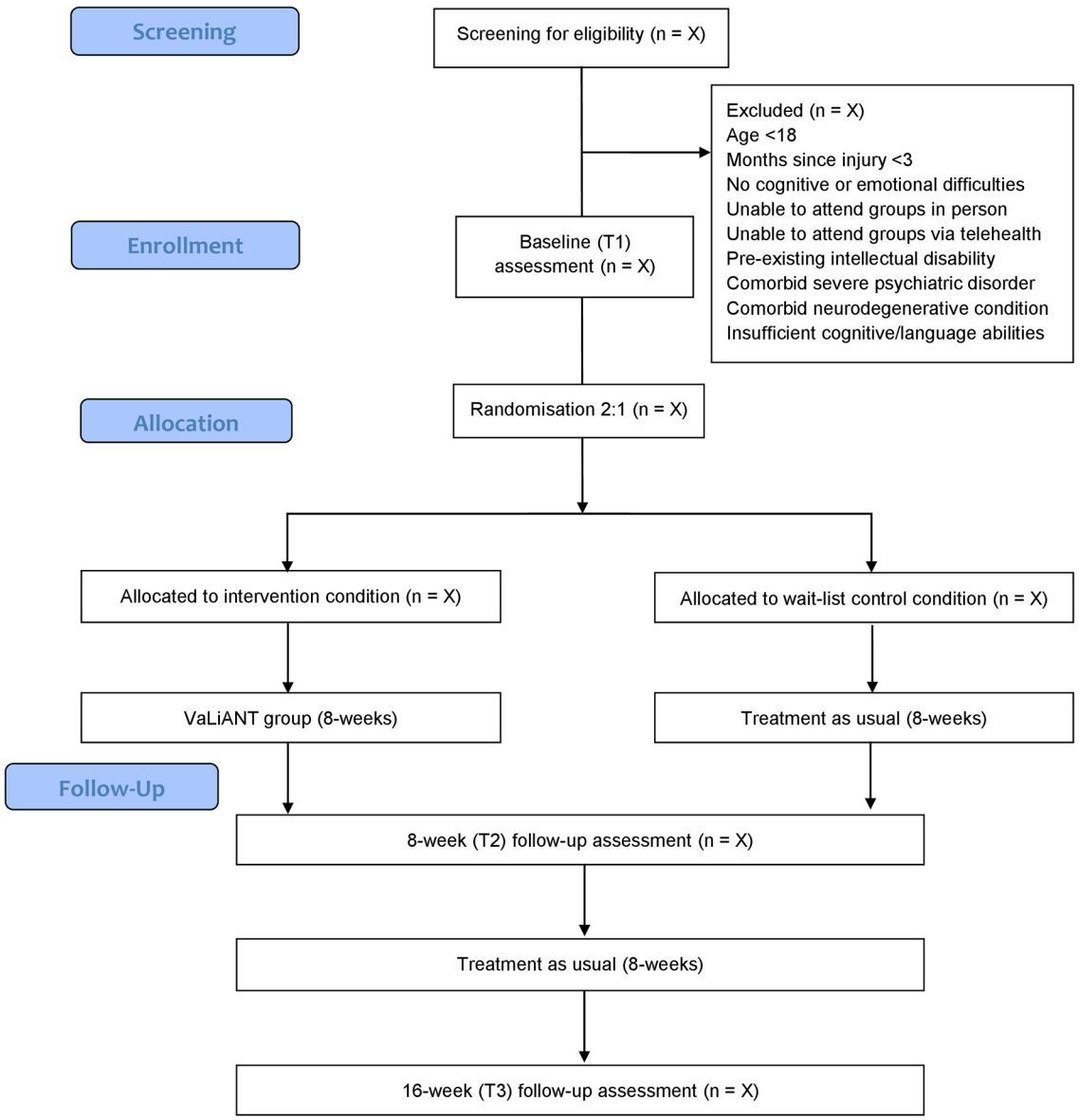


FIGURE 1 | Study flow diagram. VaLiANT, Valued Living After Neurological Trauma.

of factors: 1) the cost-effectiveness compared to individual treatment, 2) the additional benefit of group discussion and the sharing of ideas for particular topics e.g., strategies to manage particular difficulties following ABI, and 3) to address social isolation and provide access to other individuals with shared experience. A number of small revisions were made to the manual and treatment delivery following completion of the Phase I study (55): 1) additional scaffolding was added in Session 2 to assist participants with linking their values to behavior, 2) a mindfulness exercise was included in every session (previously was in most but not all sessions), and 3) email reminders for the homework activities were sent to participants at the end of each calendar week. The treatment manual and resources will be published following completion of the trial. For more information on the intervention content and additional modifications made due to COVID-19, please see **Tables 1**, **2**.

Measures

The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) was selected as the primary outcome measure as it captures the broader adjustment and quality of life outcomes that VaLiANT targets, and the majority of participants displayed reliable and clinically significant improvements on the measure during the Phase I evaluation of VaLiANT (55). The WEMWBS is a 14-item questionnaire that measures the frequency of positive mental health and wellbeing over the previous 2 weeks (64). Items such as "I've been feeling optimistic about the future" are rated

TABLE 1 | TIDieR checklist describing the Valued Living After Neurological Trauma intervention and telehealth modifications.

Item	Telehealth modification
1. Name Valued Living After Neurological Trauma (VaLiANT)	
2. Why Existing interventions that target cognition and mood separately have displayed variable effectiveness and limited generalizability to broader outcomes (e.g., participation and quality of life) which may relate to the lack of integration between cognition and emotional symptoms. Valued living has been associated with better functional and psychosocial outcomes and has been identified as a potential treatment target following brain injury. VaLiANT utilizes a combined therapeutic approach that targets both cognitive impairment and mood disturbance with an overall focus on improving valued living. This represents a novel approach to improving outcomes post brain-injury.	
3. What (materials) *Treatment manual:* Each therapist delivering the intervention has access to a treatment manual outlining the treatment objectives, content to be covered each week, participant handouts and materials, and homework activities. The manual provides detailed instructions on how to cover each treatment component or activity, including suggested wording or phrasing, and prompts for enhancing or directing discussions.	
Participant worksheets and handouts: Each week participants receive a hard-copy package of psychoeducational handouts, recordings of mindfulness activities, and worksheets that are completed during the session or between sessions.	During periods of telehealth delivery, these materials are provided electronically using either cloud-sharing or *via* email.
PowerPoint slides: Each session is supported by PowerPoint slides displayed on an electronic overhead projector. Participants receive printed copies of the PowerPoint slides with space to take written notes during sessions.	During periods of telehealth delivery these are provided electronically using either cloud-sharing or *via* email.
Values cards: Hard-copy values cards specifically designed for the intervention are provided to participants within session for values card-sorting activities.	During periods of telehealth delivery, the values cards and associated activities are accessed *via* a custom-made electronic application hosted on a cloud platform (http://www.heroku.com).
Sultanas: Sultanas are provided to participants within session for a mindful eating exercise in Session 3.	Participants are instructed to bring a dried fruit or similar substitute to the relevant session. This is included as part of their homework from the previous week and an email reminder is sent prior to the session.
Materials for passengers on the bus exercise: Post it notes and values cards are used for an *in-vivo* passengers on the bus exercise.	The materials are substituted for extra PowerPoint slides.
Whiteboard: A whiteboard is used within multiple sessions for group discussion and brainstorming activities.	The electronic whiteboard function on Zoom is used instead.
Pens: Participants are provided with pens to take written notes during sessions	Pens are not provided during telehealth delivery.
Computer/tablet and internet: Not applicable	Participants are required to have their own computer or tablet device with a webcam and stable internet connection.
4. What (procedures) Every week of the VaLiANT program focusses on a different value domain (e.g., health, work/productive activities, leisure, relationships). Each session begins with a review of the previous week's homework. Following this, participants explore and identify their important values in that week's value domain (*via* the card-sort activity) and select one value to focus on over the following week. Participants then generate SMART (specific, measurable, achievable, relevant to the value, and time-bound) goals or "committed actions" that are consistent with the chosen value and can be done over the coming week. This process is supported by the group facilitators. The remainder of each session focusses on facilitating implementation of committed actions. Psychoeducation and various activities are used to teach cognitive compensatory strategies and ACT techniques such as mindfulness, including in-session practice of those strategies. With further support from facilitators, participants identify potential cognitive or emotional barriers to their committed actions (e.g., forgetfulness or low motivation) and select appropriate strategies to enable valued living. Most activities involve group discussion to encourage reflection and exchange of ideas amongst participants. Weekly homework activities include completing the selected committed actions and other tasks that aim to increase implementation of taught strategies into everyday life. Further information on the content of each session can be found in **Table 2** and the published outline of the treatment manual [(55); supplemental material].	

(Continued)

TABLE 1 | Continued

Item	Telehealth modification
5. Who Provided The VaLiANT intervention is facilitated by a senior Clinical Neuropsychologist experienced in working with individuals with ABI and expertise in delivering group-based interventions, cognitive rehabilitation, and ACT. An additional two clinicians assist with facilitation of each group. These are primarily trainee psychologists assisting with the delivery of 1 – 2 groups as part of their postgraduate clinical neuropsychology or clinical psychology training. The assisting clinicians are provided with prior training and supervision by the senior facilitator including didactic instruction and observational learning by watching recordings of previous sessions. Quality of intervention delivery and group facilitation skills are monitored during each session by the senior facilitator, and feedback provided during supervision which occurs after every session.	
6. How The VaLiANT intervention is intended to be delivered in-person on a weekly basis in a group environment (ranging from 3 to 8 group members).	Following the onset of the COVID-19 pandemic, the intervention was redeveloped to be deliverable *via* telehealth using videoconferencing (Zoom).
7. Where In-person delivery of the intervention occurs at the La Trobe University Psychology Clinic (Melbourne, Australia).	Telehealth delivery of the intervention occurs in participants' homes, with facilitators either at the university or in their homes.
8. When and How much The intervention involves eight sessions that run weekly, for 2 h, over a period of 8–9 weeks (depending on breaks for public holidays).	
9. Tailoring The treatment manual is intended to be a flexible guide, whereby content can be tailored as long as key session objectives are met and key session components are delivered. For example, specific strategies for addressing cognitive and emotional barriers can be more strongly emphasized if several participants identify similar barriers (e.g., motivation) or only briefly covered if less relevant (e.g., word-finding strategies). There are other specific opportunities for tailoring of the intervention in particular sessions (e.g., additional "optional" activities to further explore core concepts) if the core content has been covered adequately with time remaining. This additional content is not required to cover the main concepts but allows some tailoring of the intervention depending on the abilities and preferences of group participants.	
10. Modifications	Telehealth adaptations included the development of an online program to present the values card sort task and associated weekly worksheet while also allowing facilitators to see what participants were doing in real time during these activities. This was essential to allow facilitators to support participants in generating committed actions in line with their chosen values. Due to the likelihood of technical difficulties and participants requiring additional assistance with the online tasks, the time allocated to some activities (e.g., identification of barriers) was reduced to allow more time for core components (e.g., strategies) to ensure that the key concepts were covered. Some strategies that are potentially not relevant for every participant (e.g., activity scheduling) were moved to "optional" discussions that are only covered if participants identify particular problems. Some activities were also modified slightly to allow for completion online e.g., a group experiential ACT exercise ("Passengers on the Bus") which involves participants moving around the room became more discussion based.
11. How well (planned) All VaLiANT sessions are video recorded. To measure treatment fidelity, a random selection of at least 10% of the video-recorded intervention sessions will be assessed by an independent researcher trained in cognitive rehabilitation, Acceptance and Commitment Therapy and group interventions. They will evaluate whether clinicians were able to meet the session objectives and cover the prescribed content using a checklist based on the manual for each session (i.e., treatment adherence), as well as the clinicians' competence in group facilitation (i.e., therapist competence).	

(Continued)

TABLE 1 | Continued

Item	Telehealth modification
Competency in group facilitation skills is assessed using the eNACT group facilitation competency checklist, a 4-point likert scale which measures the quality of the therapist's group facilitation across 16 skills from 0 = "skill not observed despite opportunity," to 3 = "observed – done well" (63). An additional item was added to the checklist to assess whether facilitators had delivered the intervention in an ACT-consistent manner ("Therapist demonstrates psychological flexibility in interactions with participants i.e., shows openness, flexible self-awareness and engages in their own valued actions, even when difficult topics arise in the group").	

Item 12 [how well (actual): if intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned] cannot be fully described until study completion and has been omitted.

on a 5-point Likert scale with higher scores indicating greater wellbeing (total score range 14–70). The scale demonstrates good internal consistency (0.91), test-retest reliability (0.83), and criterion validity (64) and has been used in a previous ABI RCT (51).

The Valued Living Questionnaire – Comprehension Support version (VLQ-CS[1]) was developed by members of the research team as an adaptation of the original VLQ, following evidence that multiple comprehension errors were made by people with ABI on the original measure[2]. The VLQ-CS is designed to suit to the needs of individuals with cognitive and/or communication difficulties, and includes visual communication supports, simplified instructions and examples of value-consistent behaviors to aid understanding. Ten value domains (e.g., family, work) are rated for importance on a 10-point scale (higher scores = higher importance). For domains with an importance rating ≥5, the extent to which time spent on value-consistent behaviors in that domain over the last week was "ideal" is then rated on a 10-point "consistency" scale (higher scores = more ideal). A composite score is derived by calculating the mean of the products of the importance and consistency scores. The VLQ-CS has been validated for use with ABI with greater test-retest reliability than the original measure[1].

Mood is assessed with the Hospital Anxiety and Depression Scale [HADS; (65)] and the Depression Anxiety Stress Scales [DASS-21; (66)]. The inclusion of both measures was based on previous research in brain injury which indicated that the HADS-A is more sensitive to clinically relevant symptoms of anxiety while the DASS-D is more sensitive to clinically relevant symptoms of depression (67).

All other sample characterization measures and secondary outcome measures are summarized in **Table 3**.

Feasibility and Acceptability Measures

Feasibility of the trial design will be assessed against the following criteria: 1) recruitment of the minimum number of participants required to run quarterly groups throughout the study period (minimum of 3 participants per group); 2) acceptable participant drop-out rates in intervention and control conditions (<20%); 3) adequate outcome assessment completion rates (≥80%); and 4) successful blinding of outcome assessors (≥90%). Consistent with the Phase I study (55), feasibility of the intervention will be assessed against: 1) group attendance rates (≥80% overall participant attendance); 2) and homework completion rates (≥50% completion rate for participants in attendance for each session). Acceptability of the intervention is measured by asking participants to rate their level of confidence in recommending the VaLiANT program to a friend who experiences similar problems (1 = "Not at all confident," 9 = "Very confident"). The intervention will be deemed "acceptable" if the mean rating is ≥80% (i.e., ≥7.2/9).

Randomization and Blinding

Randomization is performed by a researcher independent from the study using an online generator known as Research Randomizer (https://www.randomizer.org). Eligible participants are randomly assigned to the intervention condition or control condition with an allocation ratio of 2:1 (Intervention: Control). This allocation ratio was selected to optimize recruitment rates and maximize the number of people experiencing the intervention to allow for exploration of treatment dimensions and predictors of outcome (84, 85). Randomly permuted block sizes of 3, 6, or 9 are used to ensure a balanced allocation ratio. Group allocation is concealed, either in sequentially numbered sealed opaque envelopes (pre-COVID) or electronically *via* sequentially numbered word-documents uploaded to a protected cloud-sharing platform (post-COVID), which are opened at the end of the baseline (T1) assessment. The outcome assessors at T2 and T3 are research assistants blinded to condition allocation. Participants are reminded to not disclose their allocation during assessments, and all instances of unblinding are recorded. If unblinding occurs during a T2 assessment, then a different blinded research assistant conducts that participant's T3 assessment.

Procedure

The VaLiANT group is planned to run quarterly with an associated participant intake period prior to commencement of each group. Potential participants undergo screening

[1]Wong D, Miller H, Lawson D, Borschmann K, Sathananthan N, Kamberis N, et al. *Development and validation of the Valued Living Questionnaire - Comprehension Support Version* (in preparation).

[2]Miller H, Lawson D, Power E, das Nair R, Sathananthan N, Wong D. *How do people with acquired brain injury interpret the Valued Living Questionnaire? A cognitive interviewing study* (under review).

TABLE 2 | Overview of Valued Living after Neurological Trauma (VaLiANT).

Session	Content
1	**Introduction to the program** Overview of the program, intervention aims, and main components Establishment of group rules and group facilitator role Getting to know each other and sharing of stories Introduction to values, valued living Values card sort exercise Passengers on the bus exercise Mindfulness breathing exercise Introduction to committed actions and experiential avoidance Homework– self-monitoring form and name association task
2	**Being Healthy—Sleep and fatigue management** Introduction to "being healthy" module Values card sort exercise Discussion on four pillars of health Sleep and fatigue psychoeducation and strategies Mindfulness body scan exercise Experiential avoidance discussion (optional) Identification of committed actions and barriers Introduction to S.M.A.R.T goals Introduction to and completion of the "way to valued living worksheet" Homework—rest break scheduling and completing committed actions
3	**Being Healthy – Diet and exercise management** Review of values selected in previous session Way to valued living worksheet Diet and exercise psychoeducation Exploration of barriers Passengers on the bus exercise Mindful eating exercise Identification of committed actions Strategies for planning, memory, pacing, and motivation Activity scheduling exercise Homework—mindful eating and completing committed actions
4	**Having a Purpose—Work, study, or participation in the community** Overview to "having a purpose" module Values card sort exercise Identification of committed actions Identification of barriers Mindfulness self-compassion exercise Strategies for prospective memory and completing complex tasks Homework—prospective memory task and completing committed actions
5	**Having a Purpose—Leisure activities** Introduction to leisure exercise Psychoeducation on mood and the importance of leisure Values card sort task Exploration of leisure activities Identification of committed actions Mindfulness of the senses exercise Barriers to leisure exploration & associated strategies Homework—leisure activity schedule and completing committed actions
6	**Connecting with Others—Relationships part I** Overview of "relationships module" Values card sort task Identification of strengths in relationships Identification of committed actions Barriers exploration Mindfulness S.T.O.P exercise Strategies for cognitive communication difficulties Homework—planning a difficult conversation and completing committed actions
7	**Connecting with Others—Relationships part II (friends/family session)** *Friends/family members (1st h)* Introduction to VaLiANT Introduction to values and valued living Values card sort exercise Introduction to barriers and communication changes following brain injury Managing difficult emotions exercise *Participants (1st h)* Reflection on relationships and values they would like to bring Identification of committed actions Addressing social barriers Passengers on the bus exercise *All together (2nd h)* Mindfulness S.T.O.P exercise Strategies to support communication of abilities and needs Open communication discussion Homework – have an open conversation and completing committed actions
8	**Review and future directions—Tying it all together** Review of values, committed actions, strengths, and barriers identified in previous sessions Re-identification of helpful strategies from previous sessions Mindfulness S.T.O.P exercise Post-traumatic growth discussion (optional) Future support options Conclusion

Each session begins with a review of the previous session's content and homework tasks (excluding Session 1). In session 7 participants have the ability to bring a family member or friend who complete separate activities for the 1st h, before joining participants to practice communication strategies in the 2nd h.

to ensure eligibility before informed consent is obtained. For each intake, all eligible participants attend an initial baseline assessment (T1) which includes all baseline sample characterization measures and primary and secondary outcome measures. Randomization occurs immediately following the T1 assessment. In addition to their usual care, participants in the treatment condition then attend the 8-week VaLiANT group program at the La Trobe University Psychology Clinic, or *via* telehealth (Zoom videoconferencing) during periods of COVID-19 restrictions, while control participants undergo treatment-as-usual (i.e., their usual care). Participation in other treatment during the trial is documented, including the frequency and type of treatment. VaLiANT group sessions are facilitated by an experienced clinical neuropsychologist with assistance from two trainee psychologists. All sessions are video-recorded. Outcome assessments occur within 1–2 weeks following the intervention/waiting period (T2), and at an 8-week follow-up (T3). All assessments take roughly 90 min and are administered by assessors blinded to condition allocation. Assessments are conducted at the La Trobe University Psychology Clinic or in participants' homes if preferable. During periods where COVID-19 restrictions apply, assessments are conducted over Zoom videoconferencing.

TABLE 3 | Timing of outcome measures.

Outcome domain	Measure	T1	T2	T3
Sample characterization				
Premorbid intellectual ability	Test of Premorbid Functioning (68)	X		
Verbal memory	Rey Auditory Verbal Learning Test (69)	X		
Cognitive flexibility*	Trail Making Test—written (70) and oral (71) versions	X		
Idea generation	Controlled Oral Word Association Test (72)	X		
Treatment expectancy	The Credibility/Expectancy Questionnaire (73)	X		
Primary outcome				
Wellbeing	The Warwick-Edinburgh Mental Wellbeing Scale (64)	X	X	X
Secondary outcomes				
Mood	Hospital Anxiety and Depression Scale (65)	X	X	X
	Depression Anxiety Stress Scales – 21 (66)	X	X	X
Valued living**	Valued Living Questionnaire – original (74) and comprehension support[1] version	X	X	X
	Valuing Questionnaire (44)	X	X	X
Psychological flexibility	The Acceptance and Action Questionnaire after brain injury (75)	X	X	X
Quality of life**	World Health Organization Quality of Life scale (76)	X	X	X
Psychological adjustment**	The Head Injury Semantic Differential Scale – III (77)	X	X	X
Community participation**	The Community Integration Questionnaire – original (78) and revised (79) versions	X	X	X
Post-traumatic growth	The Changes in Outlook Questionnaire – Short form (80)	X	X	X
Cognitive strategy use	Self-report strategy use checklist (81)	X	X	X
Subjective memory functioning	The Everyday Memory Questionnaire – Revised (82)	X	X	X
Self-Efficacy	The TBI Self-Efficacy Scale (83)	X	X	X

*T1, baseline assessment; T2, 8-week follow-up assessment; T3, 16-week follow-up assessment. *Indicates measures that were adapted to be deliverable via telehealth. **Indicates measures that were included or adapted following trial commencement.*

Data Management

During the trial, hard copy information is stored at La Trobe Psychology Clinic in a locked cabinet while electronic information is stored on secure electronic databases, accessible only by the project coordinator, chief investigator, and research assistants. Prior to data analysis, all values will be checked for plausibility. Data will be retained for 7 years after completion of the project and then destroyed by securely deleting electronic records (including video and audio recordings) and shredding all paper records.

Sample Size Calculation

A power analysis was conducted using 5,000 simulations within the SimR package for R (86) to determine if the maximum possible sample size during the data collection period ($N = 64$) was sufficient for the statistical analyses. A previous evaluation of an ACT-based intervention following stroke reached a moderate group-by-time effect ($\eta 2 = 0.07$) on the Warwick and Edinburgh Mental Wellbeing Scale (51). Accordingly, a minimum sample of 52 participants is required to achieve statistical power for a linear mixed-effect model with a 2 (group) x 3 (time) design (80% power, $\alpha = 0.05$). Allowing for an attrition rate of 10%, an N of 58 is adequate to perform the primary analyses.

Statistical Analysis

Main analyses will follow an intention-to-treat approach. Little's missing completely at random (MCAR) analysis will be conducted to determine if data are MCAR (87). If <5% of data is MCAR, the appropriate data imputation technique will be employed to deal with missing values [likely Markov chain Monte Carlo method; (88)]. Univariate outliers (z +/− 1.96 SD) will be adjusted using a winsorising solution (89). Univariate checks of normality (skewness > +/− 2.58 SD) will be conducted, and variables that violate the criterion will be corrected to normal using appropriate data transformation (90). Primary and secondary outcomes will be analyzed with linear mixed models, with fixed effects of time and group, and participants modeled as random effects. The estimated marginal means from the model will be used to calculate effect sizes (Cohen's *d*) to illustrate change in both between group and timepoint contrasts. The results of the fixed effects estimates for the main effects and interaction terms will be presented as standardized *B* values and all analyses will use a two-sided alpha level of 0.05. These analyses will be conducted using JASP (91). Finally, as an adjunct to the linear mixed models, the Crawford and Howell measure of reliable change (92), which is suitable for serial testing, will be calculated for the primary outcome (93). The proportion of participants achieving reliable change in each group at both time-points will then be compared with 2 × 2 Chi square tests of independence.

Protocol Amendments Due to COVID-19

The COVID-19 pandemic has resulted in a number of essential methodological changes to the original study protocol. The trial commenced in August 2019, and then in March 2020 it was paused for 6-months after the onset of the pandemic, given that restrictions prevented in-person assessments and

intervention delivery. To allow the trial to continue, the research team redeveloped the study protocol for telehealth delivery on Zoom. To allow for outcome assessments to be conducted *via* telehealth, data collection measures have been moved from Qualtrics to REDCap, the randomization schedule has shifted from opaque envelopes to sequentially numbered word-documents uploaded to a cloud-sharing platform, and the paper-and-pencil Trail Making Test has been substituted with the oral version for telehealth baseline assessments. A telehealth version of the VaLiANT intervention was also developed (see **Table 1**). For analyses, telehealth delivery will be treated as a substitution for in-person delivery rather than as a separate treatment arm. In-person delivery remains the preferred modality and will be utilized where possible. Changes have been made to the inclusion criteria such that participants are required to be able to attend assessments and the intervention both in-person and *via* telehealth, to allow flexibility with changing restrictions.

In addition, a number of other non-essential modifications have been made following the opportunity to reflect on the trial design during the trial's pause in 2020, and further evidence accumulated during that period. In weighing up whether to introduce these changes after trial commencement, the research team considered the fact that this is a feasibility Phase II trial and therefore opted to make changes to optimize trial design and better inform a future Phase III trial. Initially, randomization occurred in randomly permuted block sizes of 6. However, it was possible for the baseline assessor to deduce the final participant's allocation in one block based on previous allocations. As such, varying block sizes (3, 6, or 9) were introduced to maximize blinding of the baseline assessor in future assessments. The Community Integration Questionnaire was updated to the revised version which includes an additional electronic social networking scale, relevant in the context of social distancing requirements. The 26-item World Health Organization Quality of Life scale (WHOQOL-BREF) and the Head Injury Semantic Differential Scale – III (HISDS-III) were included as additional outcome measures to provide more comprehensive measurement of quality of life and psychological adjustment. Finally, the Valued Living Questionnaire (VLQ) was replaced with an adapted version (VLQ-CS) following identification of validity issues with the original measures due to frequent comprehension errors made by those with ABI[2]. All modifications occurred during the pause in data collection (March – September 2020) with the exception of changes to the Valued Living Questionnaire which occurred in September 2019.

DISCUSSION

There is a recognized need for trials evaluating complex, multi-domain, person-centered interventions post-ABI that aim to improve rehabilitation outcomes beyond injury-related impairments (e.g., cognitive and mood changes) by also targeting overall adjustment to injury, meaningful participation, and quality of life (33). While a number of complex interventions have integrated cognitive rehabilitation and psychological therapy with subsequent positive long-term effects, these interventions are lengthy and require high treatment dosage which limits their implementation into routine practice. The proposed RCT aims to build on our Phase I findings (55) by evaluating the efficacy, feasibility, and acceptability of the 8-week VaLiANT group program against a treatment-as-usual waitlist control.

The study has several strengths. Many aspects of the current trial design were piloted and found to be feasible in the previous Phase I study (e.g., recruitment rates, outcome assessment completion rates). The inclusion criteria for the study are broad and include multiple forms of ABI in comparison to many intervention studies which focus on a single cohort (e.g., stroke). It is therefore anticipated that the sample will be fairly heterogeneous, supporting generalization of the study findings to the broader ABI community and implementation into ABI rehabilitation services (which are rarely devoted to a single cohort), while potentially also allowing for greater exploration of predictors of treatment outcome depending on the sample size. Additionally, the intervention was developed by a multi-disciplinary team based on current evidence (including existing manualized treatment approaches). The intervention includes specific adaptations to meet the needs of those with ABI, it can be delivered both in-person and *via* telehealth aiding flexibility, and it is group-based which may be more cost-effective than individual therapy.

Several limitations are also acknowledged. The study has been conducted during the COVID-19 pandemic in Melbourne, Australia which has been subject to multiple extended and rolling lockdowns throughout the study period. Study outcomes may be impacted during periods of restriction due to limited opportunities for intervention-related behavior change and the overall negative impact on mood and wellbeing. Additionally, there may be rapid improvements in both study conditions when lockdowns or restrictions are eased. The pandemic has also necessitated a number of changes to the study design and methodology. In particular, the variable modality of intervention delivery between participants (i.e., in-person, telehealth, or blended) may impact intervention outcome. The associated change in inclusion criteria, which requires participants to have both in-person and telehealth capacity, may also lead to a restricted sample by limiting the intervention to higher-functioning individuals. The study is also limited to English speaking individuals with sufficient cognitive and language capacity to complete the outcome assessments and participate in the group intervention, which may further limit the generalizability of findings, particularly to those with significant aphasia.

This study will extend current knowledge on the utility of complex interventions and will add to the growing body of evidence investigating the role of valued living as an important treatment target following ABI. The study findings will also add to recent evidence supporting the adaptation of ACT for those with ABI. Given that previous investigations have focused on purely ACT-based interventions without a

cognitive rehabilitation component, this study will demonstrate the utility of incorporating ACT principles within a more holistic intervention framework. Finally, study findings will help determine the feasibility and implementation of a definitive Phase III RCT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by La Trobe University Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS, EM, DG, LK, BD-B, RN, and DW were involved in the development of the intervention and the study protocol. BW was responsible for the statistical analysis plan. NS, DW, and BD-B are responsible for project coordination and administration. NS and DW were responsible for writing and revising the manuscript. All authors have read and approved the final version of the manuscript.

FUNDING

This work was supported by the La Trobe University Sport, Exercise, and Rehabilitation Research Focus Area Grant Ready Scheme. The funding body has no role in the study design, data collection, data analysis and interpretation, or write-up of the manuscript.

REFERENCES

1. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatric Clin North Am.* (2014) 37:1–11. doi: 10.1016/j.psc.2013.11.004
2. Mellon L, Brewer L, Hall P, Horgan F, Williams D, Hickey A. Cognitive impairment six months after ischaemic stroke: a profile from the ASPIRE-S study. *BMC Neurol.* (2015) 15:31. doi: 10.1186/s12883-015-0288-2
3. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke.* (2014) 9:1017–25. doi: 10.1111/ijs.12357
4. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. *Int J Stroke.* (2013) 8:545–59. doi: 10.1111/j.1747-4949.2012.00906.x
5. Anson K, Ponsford J. Coping and emotional adjustment following traumatic brain injury. *J Head Trauma Rehabilitation.* (2006) 21:248–59. doi: 10.1097/00001199-200605000-00005
6. Madsen T, Erlangsen A, Orlovska S, Mofaddy R, Nordentoft M, Benros ME, et al. Association between traumatic brain injury and risk of suicide. *JAMA.* (2018) 2018:320. doi: 10.1001/jama.2018.10211
7. Ponsford J, Downing MG, Olver J, Ponsford M, Acher R, Carty M, et al. Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *J Neurotrauma.* (2014) 31:64–77. doi: 10.1089/neu.2013.2997
8. Nijsse B, van Heugten CM, van Mierlo ML, Post MWM, de Kort PLM, Visser-Meily JMA. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. *Neuropsychol Rehabilit.* (2017) 27:99–115. doi: 10.1080/09602011.2015.1065280
9. Kimonides S, Cavuoto MG, De Silva L, Kinsella GJ. The role of subjective cognitive complaints and depressive symptoms in social re-integration following stroke: a mediation explanation in a cross-sectional sample. *Topics Stroke Rehabilit.* (2018) 25:514–20. doi: 10.1080/10749357.2018.1489570
10. Pickelsimer EE, Selassie AW, Sample PL, Heinemann A, Gu JK, Veldheer LC. Unmet service needs of persons with traumatic brain injury. *J Head Trauma Rehabilit.* (2007) 22:1–13. doi: 10.1097/00001199-200701000-00001
11. Andrew NE, Kilkenny M, Naylor R, Purvis T, Lalor E, Moloczij N, et al. Understanding long-term unmet needs in Australian survivors of stroke. *Int J Stroke.* (2014) 9:106–12. doi: 10.1111/ijs.12325
12. Gadidi V, Katz-Leurer M, Carmeli E, Bornstein NM. Long-term outcome poststroke: predictors of activity limitation and participation restriction. *Arch Phys Med Rehabilitation.* (2011) 92:1802–8. doi: 10.1016/j.apmr.2011.06.014
13. Stolwyk RJ, Mihaljcic T, Wong DK, Chapman JE, Rogers JM. Post-stroke cognitive impairment negatively impacts activity and participation outcomes: a systematic review and meta-analysis. *Stroke.* (2021) 52:748–60. doi: 10.1161/STROKEAHA.120.032215
14. Mole JA, Demeyere N. The relationship between early post-stroke cognition and longer term activities and participation: A systematic review. *Neuropsychol Rehabilit.* (2020) 30:346–70. doi: 10.1080/09602011.2018.1464934
15. Theadom A, Starkey N, Barker-Collo S, Jones K, Ameratunga S, Feigin V, et al. Population-based cohort study of the impacts of mild traumatic brain injury in adults four years post-injury. *PLoS ONE.* (2018) 13:e0191655. doi: 10.1371/journal.pone.0191655
16. Barker-Collo S, Feigin VL, Parag V, Lawes CM, Senior H. Auckland stroke outcomes study. Part 2: Cognition and functional outcomes 5 years poststroke. *Neurology.* (2010) 75:1608–16. doi: 10.1212/WNL.0b013e3181fb44c8
17. Wood RL, Rutterford NA. Demographic and cognitive predictors of long-term psychosocial outcome following traumatic brain injury. *J Int Neuropsychol Soc.* (2006) 12:350–8. doi: 10.1017/S1355617706060498
18. Feigin VL, Barker-Collo S, Parag V, Senior H, Lawes CM, Ratnasabapathy Y, et al. Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. *Neurology.* (2010) 75:1597–607. doi: 10.1212/WNL.0b013e3181fb44b3
19. Tse T, Linden T, Churilov L, Davis S, Donnan G, Carey LM. Longitudinal changes in activity participation in the first year post-stroke and association with depressive symptoms. *Disabillity Rehabilit.* (2018) 2018:1–8. doi: 10.1080/09638288.2018.1471742
20. Draper K, Ponsford J, Schonberger M. Psychosocial and emotional outcomes 10 years following traumatic brain injury. *J Head Trauma Rehabilit.* (2007) 22:278–87. doi: 10.1097/01.HTR.0000290972.63753.a7
21. Kutlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. *Int J Stroke.* (2014) 9:1026–36. doi: 10.1111/ijs.12356
22. Rastenyte D, Kranciukaite D. Poststroke depression and its impact on quality of life. *Medicina.* (2007) 43:1–9. doi: 10.3390/medicina43010001
23. De Wit L, Theuns P, Dejaeger E, Devos S, Gantenbein AR, Kerckhofs E, et al. Long-term impact of stroke on patients' health-related quality of life. *Disabillity Rehabilit.* (2017) 39:1435–40. doi: 10.1080/09638288.2016.1200676
24. World Health Organization. *International Classification of Functioning, Disability and Health: ICF*. Geneva: World Health Organization (2001).
25. Elliott M, Parente F. Efficacy of memory rehabilitation therapy: a meta-analysis of TBI and stroke cognitive rehabilitation literature. *Brain Injury.* (2014) 28:1610–6. doi: 10.3109/02699052.2014.934921

26. Velikonja D, Tate R, Ponsford J, McIntyre A, Janzen S, Bayley M. INCOG recommendations for management of cognition following traumatic brain injury, part V: memory. *J Head Trauma Rehabilit.* (2014) 29:369–86. doi: 10.1097/HTR.0000000000000069
27. das Nair R, Cogger H, Worthington E, Lincoln NB. Cognitive rehabilitation for memory deficits after stroke. *Cochrane Database Syst Rev.* (2016) 9:CD002293. doi: 10.1002/14651858.CD002293.pub3
28. Withiel TD, Wong D, Ponsford JL, Cadilhac DA, New P, Mihaljcic T, et al. Comparing memory group training and computerized cognitive training for improving memory function following stroke: A phase II randomized controlled trial. *J Rehabilit Med.* (2019) 51:343–51. doi: 10.2340/16501977-2540
29. Loetscher T, Potter KJ, Wong D, das Nair R. Cognitive rehabilitation for attention deficits following stroke. *Cochrane Database Syst Rev.* (2019) 2019:CD002842. doi: 10.1002/14651858.CD002842.pub3
30. Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, et al. Cognitive behavioral therapy for post-stroke depression: A meta-analysis. *J Affective Disord.* (2018) 235:589–96. doi: 10.1016/j.jad.2018.04.011
31. Gertler P, Tate RL, Cameron ID. Non-pharmacological interventions for depression in adults and children with traumatic brain injury. *Cochrane Database Syst Rev*. (2015) 2015:CD009871. doi: 10.1002/14651858.CD009871.pub2
32. Ponsford J, Lee NK, Wong D, McKay A, Haines K, Alway Y, et al. Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychol Med.* (2016) 46:1079–90. doi: 10.1017/S0033291715002640
33. Doering B, Exner C. Combining neuropsychological and cognitive-behavioral approaches for treating psychological sequelae of acquired brain injury. *Curr Opin Psychiatry*. (2011) 24:156–61. doi: 10.1097/YCO.0b013e328343804e
34. Wright CJ, Zeeman H, Biezaitis V. Holistic practice in traumatic brain injury rehabilitation: Perspectives of health practitioners. *PLoS ONE.* (2016) 11:e0156826. doi: 10.1371/journal.pone.0156826
35. Shany-Ur T, Bloch A, Salomon-Shushan T, Bar-Lev N, Sharoni L, Hoofien D. Efficacy of postacute neuropsychological rehabilitation for patients with acquired brain injuries is maintained in the long-term. *J Int Neuropsychol Soc.* (2020) 26:130–41. doi: 10.1017/S1355617719001024
36. Holleman M, Vink M, Nijland R, Schmand B. Effects of intensive neuropsychological rehabilitation for acquired brain injury. *Neuropsychol Rehabilit.* (2018) 28:649–62. doi: 10.1080/09602011.2016.1210013
37. Cicerone KD, Mott T, Azulay J, Sharlow-Galella MA, Ellmo WJ, Paradise S, et al. A randomized controlled trial of holistic neuropsychologic rehabilitation after traumatic brain injury. *Arch Phys Med Rehabilit.* (2008) 89:2239–49. doi: 10.1016/j.apmr.2008.06.017
38. Exner C, Doering BK, Conrad N, Künemund A, Zwick S, Kühl K, et al. Integrated neuropsychological and cognitive behavioural therapy after acquired brain injury: A pragmatic randomized clinical trial. *Neuropsychol Rehabilit*. (2021) 2021:1–35. doi: 10.1080/09602011.2021.1908902
39. Domensino A-F, Verberne D, Prince L, Fish J, Winegardner J, Bateman A, et al. Client experiences with holistic neuropsychological rehabilitation: "It is an ongoing process". *Neuropsychol Rehabilit*. (2021) 2021:1–23. doi: 10.1080/09602011.2021.1976222
40. Pais C, Ponsford JL, Gould KR, Wong D. Role of valued living and associations with functional outcome following traumatic brain injury. *Neuropsychol Rehabilit.* (2019) 29:625–37. doi: 10.1080/09602011.2017.1313745
41. Baseotto MC, Morris PG, Gillespie DC, Trevethan CT. Post-traumatic growth and value-directed living after acquired brain injury. *Neuropsychol Rehabilit.* (2020) 2020:1–20. doi: 10.1080/09602011.2020.1798254
42. Graham CD, Gouick J, Krahe C, Gillanders D. A systematic review of the use of Acceptance and Commitment Therapy (ACT) in chronic disease and long-term conditions. *Clin Psychol Rev.* (2016) 46:46–58. doi: 10.1016/j.cpr.2016.04.009
43. Sheppard SC, Forsyth JP, Hickling EJ, Bianchi J. A novel application of acceptance and commitment therapy for psychosocial problems associated with multiple sclerosis: Results from a half-day workshop intervention. *Int J MS Care.* (2010) 12:200–6. doi: 10.7224/1537-2073-12.4.200
44. Smout M, Davies M, Burns N, Christie A. Development of the Valuing Questionnaire (VQ). *J Context Behav Sci.* (2014) 3:164–72. doi: 10.1016/j.jcbs.2014.06.001
45. Van Bost G, Van Damme S, Crombez G. The role of acceptance and values in quality of life in patients with an acquired brain injury: a questionnaire study. *PeerJ.* (2017) 5:e3545. doi: 10.7717/peerj.3545
46. Whiting DL, Deane F, McLeod H, Ciarrochi J, Simpson G. Can acceptance and commitment therapy facilitate psychological adjustment after a severe traumatic brain injury? A pilot randomized controlled trial. *Neuropsychol Rehabilit.* (2020) 30:1348–71. doi: 10.1080/09602011.2019.1583582
47. Whiting DL, Deane FP, Simpson GK, Ciarrochi J, McLeod HJ. Acceptance and Commitment Therapy delivered in a dyad after a severe traumatic brain injury: A feasibility study. *Clin Psychol.* (2018) 22:230–40. doi: 10.1111/cp.12118
48. Sander AM, Clark AN, Arciniegas DB, Tran K, Leon-Novelo L, Ngan E, et al. A randomized controlled trial of acceptance and commitment therapy for psychological distress among persons with traumatic brain injury. *Neuropsychol Rehabilit.* (2021) 31:1105–29. doi: 10.1080/09602011.2020.1762670
49. McCoy T, Philp A, Kates-McElrath K. Acceptance and Commitment Therapy: A systematic review of psychological adjustment and reduction of psychological distress following a traumatic brain injury in adults. *J Addiction Psychiatry Mental Health.* (2021) 1:1–10.
50. Graham CD, Gillanders D, Stuart S, Gouick J. An acceptance and commitment therapy (ACT)-based intervention for an adult experiencing post-stroke anxiety and medically unexplained symptoms. *Clin Case Stud.* (2015) 14:83–97. doi: 10.1177/1534650114539386
51. Majumdar S, Morris R. Brief group-based acceptance and commitment therapy for stroke survivors. *Br J Clin Psychol.* (2019) 58:70–90. doi: 10.1111/bjc.12198
52. Large R, Samuel V, Morris R. A changed reality: Experience of an acceptance and commitment therapy (ACT) group after stroke. *Neuropsychol Rehabilit.* (2020) 30:1477–96. doi: 10.1080/09602011.2019.1589531
53. Gillanders S, Gillanders D. An acceptance and commitment therapy intervention for a woman with secondary progressive multiple sclerosis and a history of childhood trauma. *Neuro-Disability Psychother.* (2014) 2:19–40.
54. Hill G, Hynd N, Wheeler M, Tarran-Jones A, Carrabine H, Evans S. Living well with neurological conditions: Evaluation of an ACT-informed group intervention for psychological adjustment in outpatients with neurological problems. *Neuropsychologist.* (2017) 3:58–63.
55. Sathananthan N, Dimech-Betancourt B, Morris E, Vicendese D, Knox L, Gillanders D, et al. A single-case experimental evaluation of a new group-based intervention to enhance adjustment to life with acquired brain injury: VaLiANT (valued living after neurological trauma). *Neuropsychol Rehabilit.* (2021) 30:1348–71. doi: 10.1080/09602011.2021.1971094
56. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleŽa-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* (2013) 158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583
57. Orkin AM, Gill PJ, Ghersi D, Campbell L, Sugarman J, Emsley R, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA*. (2021) 326:257–65. doi: 10.1001/jama.2021.9941
58. Murray E, Power E, Togher L, McCabe P, Munro N, Smith K. The reliability of methodological ratings for speechBITE using the PEDro-P scale. *Int J Lang Commun Disord.* (2013) 48:297–306. doi: 10.1111/1460-6984.12007
59. Radford K, Say M, Thayer Z, Miller LA. *Making the Most of Your Memory: An Everyday Memory Skills Program*. Sydney: ASSBI Resources (2010).
60. Withiel TD, Stolwyk RJ, Ponsford JL, Cadilhac DA, Wong D. Effectiveness of a manualised group training intervention for memory dysfunction following stroke: a series of single case studies. *Disability Rehabilit.* (2020) 42:3033–42. doi: 10.1080/09638288.2019.1579260
61. O'Donoghue EK, Morris EMJ, Oliver JE, Johns LC. *ACT for Psychosis Recovery: A Practical Manual for Group-Based Interventions Using Acceptance and Commitment Therapy*. Oakland, CA: Context Press/New Harbinger Publications (2018).
62. Brassington L, Ferreira NB, Yates S, Fearn J, Lanza P, Kemp K, et al. Better living with illness: A transdiagnostic acceptance and commitment therapy group intervention for chronic physical illness. *J Context Behav Sci.* (2016) 5:208–14. doi: 10.1016/j.jcbs.2016.09.001

63. Wong D, Grace N, Baker K, McMahon G. Measuring clinical competencies in facilitating group-based rehabilitation interventions: development of a new competency checklist. *Clin Rehabilit.* (2019) 33:1079–87. doi: 10.1177/0269215519831048
64. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. *Health Q Life Outcomes.* (2007) 5:63. doi: 10.1186/1477-7525-5-63
65. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
66. Lovibond SH, Lovibond PF. *Manual for the Depression Anxiety Stress Scales*. Sydney: Psychology Foundation (1995).
67. Dahm J, Wong D, Ponsford J. Validity of the Depression Anxiety Stress Scales in assessing depression and anxiety following traumatic brain injury. *J Affect Disord.* (2013) 151:392–6. doi: 10.1016/j.jad.2013.06.011
68. Pearson N. *Advanced Clinical Solutions for WAIS-IV and WMS-IV: Administration and Scoring Manual*. San Antonio, TX: The Psychological Corporation (2009).
69. Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook*. Los Angeles, CA: Western Psychological Services (1996).
70. Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol.* (2004) 19:203–14. doi: 10.1016/S0887-6177(03)00039-8
71. Ricker JH, Axelrod BN. Analysis of an oral paradigm for the trail making test. *Assessment.* (1994) 1:47–51. doi: 10.1177/1073191194001001007
72. Lezak MD. *Neuropsychological Assessment*. Oxford: Oxford University Press (1995).
73. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Experi Psychiatry.* (2000) 31:73–86. doi: 10.1016/S0005-7916(00)00012-4
74. Wilson KG, Sandoz EK, Kitchens J, Roberts M. The Valued Living Questionnaire: defining and measuring valued action within a behavioral framework. *Psychol Rec.* (2010) 60:249–72. doi: 10.1007/BF03395706
75. Whiting DL, Deane FP, Ciarrochi J, McLeod HJ, Simpson GK. Validating measures of psychological flexibility in a population with acquired brain injury. *Psychol Assessment.* (2015) 27:415–23. doi: 10.1037/pas0000050
76. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A Report from the WHOQOL Group. *Q Life Res.* (2004) 13:299–310. doi: 10.1023/B:QURE.0000018486.91360.00
77. Tyerman A, Humphrey M. Changes in self-concept following severe head injury. *Int J Rehabilit Res.* (1984) 7:11–24. doi: 10.1097/00004356-198403000-00002
78. Willer B, Rosenthal M, Kreutzer JS, Gordon WA, Rempel R. Assessment of community integration following rehabilitation for traumatic brain injury. *J Head Trauma Rehabilit.* (1993) 8:75–87. doi: 10.1097/00001199-199308020-00009
79. Callaway L, Winkler D, Tippett A, Migliorini C, Herd N, Willer B. *The Community Integration Questionnaire-Revised (CIQ-R)*. Melbourne, VIC: Summer Foundation (2014).
80. Joseph S, Alex Linley P, Shevlin M, Goodfellow B, Butler LD. Assessing positive and negative changes in the aftermath of adversity: a short form of the Changes in Outlook Questionnaire. *J Loss Trauma.* (2006) 11:85–99. doi: 10.1080/15325020500358241
81. Radford K, Say M, Thayer Z, Miller L. *Making the Most of Your Memory: An Everyday Memory Skills Program*. Sydney, NSW: ASSBI Resources (2010).
82. Royle J, Lincoln NB. The everyday memory questionnaire - revised: development of a 13-item scale. *Disability Rehabilit.* (2008) 30:114–21. doi: 10.1080/09638280701223876
83. Huckans M, Pavawalla S, Demadura T, Kolessar M, Seelye A, Roost N, et al. A pilot study examining effects of group-based Cognitive Strategy Training treatment on self-reported cognitive problems, psychiatric symptoms, functioning, and compensatory strategy use in OIF/OEF combat veterans with persistent mild cognitive disorder and history of traumatic brain injury. *J Rehabil Res Dev.* (2010) 47:43–60. doi: 10.1682/JRRD.2009.02.0019
84. Torgerson DJ, Torgerson CJ. *Designing Randomised Trials in Health, Education and the Social Sciences: An Introduction*. Palgrave Macmillan (2008). doi: 10.1057/9780230583993
85. Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. *Neurology.* (2014) 82:77–9. doi: 10.1212/01.wnl.0000438226.10353.1c
86. Green P, MacLeod CJ. SIMR: an R package for power analysis of generalized linear mixed models by simulation. *Methods Ecol Evolution.* (2016) 7:493–8. doi: 10.1111/2041-210X.12504
87. Little RJA. A test of missing completely at random for multivariate data with missing values. *J Am Statist Assoc.* (1988) 83:1198–202. doi: 10.1080/01621459.1988.10478722
88. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol.* (2017) 17:162. doi: 10.1186/s12874-017-0442-1
89. John WT. The future of data analysis. *Ann Mathemat Statist.* (1962) 33:1–67. doi: 10.1214/aoms/1177704711
90. Tabachnick BG, Fidell LS. *Using Multivariate Statistics 7th ed*. Pearson (2018).
91. Love J, Selker R, Marsman M, Jamil T, Dropmann D, Verhagen J, et al. JASP: graphical statistical software for common statistical designs. *J Statist Softw.* (2019) 88:1 – 17. doi: 10.18637/jss.v088.i02
92. Crawford JR, Howell DC. Regression equations in clinical neuropsychology: an evaluation of statistical methods for comparing predicted and obtained scores. *J Clin Experi Neuropsychol.* (1998) 20:755–62. doi: 10.1076/jcen.20.5.755.1132
93. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol.* (1991) 59:12–9. doi: 10.1037/0022-006X.59.1.12

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.

frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 25 January 2022
doi: 10.3389/fresc.2021.793233

A Socially Assistive Robot for Stroke Patients: Acceptance, Needs, and Concerns of Patients and Informal Caregivers

Ayelet Dembovski[1], *Yael Amitai*[2,3] *and Shelly Levy-Tzedek*[3,4,5]*

[1] Department of Cognitive and Brain Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [2] Department of Physiology and Cell Biology, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [3] Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [4] Department of Physical Therapy, Faculty of Health Sciences, Recanati School for Community Health Professions, Ben-Gurion University of the Negev, Beer-Sheva, Israel, [5] Freiburg Institute for Advanced Studies (FRIAS), University of Freiburg, Freiburg im Breisgau, Germany

OPEN ACCESS

Edited by:
Elizabeth Skidmore,
University of Pittsburgh, United States

Reviewed by:
Manikandan Natarajan,
Manipal Academy of Higher Education, India
Nikmatul Fadilah,
Health Polytechnic of the Ministry of Health Surabaya, Indonesia

***Correspondence:**
Shelly Levy-Tzedek
shelly@bgu.ac.il

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: 11 October 2021
Accepted: 20 December 2021
Published: 25 January 2022

Citation:
Dembovski A, Amitai Y and Levy-Tzedek S (2022) A Socially Assistive Robot for Stroke Patients: Acceptance, Needs, and Concerns of Patients and Informal Caregivers. Front. Rehabilit. Sci. 2:793233. doi: 10.3389/fresc.2021.793233

Stroke patients often contend with long-term physical challenges that require treatment and support from both formal and informal caregivers. Socially Assistive Robots (SARs) can assist patients in their physical rehabilitation process and relieve some of the burden on the informal caregivers, such as spouses and family members. We collected and analyzed information from 23 participants (11 stroke patients and 12 informal caregivers) who participated in a total of six focus-group discussions. The participants responded to questions regarding using a SAR to promote physical exercises during the rehabilitation process: (a) the advantages and disadvantages of doing so; (b) specific needs that they wish a SAR would address; (c) patient-specific adaptations they would propose to include; and (d) concerns they had regarding the use of such technology in stroke rehabilitation. We found that the majority of the participants in both groups were interested in experiencing the use of a SAR for rehabilitation, in the clinic and at home. Both groups noted the advantage of having the constant presence of a motivating entity with whom they can practice their rehabilitative exercises. The patients noted how such a device can assist *formal* caregivers in managing their workload, while the informal caregivers indicated that such a system could ease *their own* workload and sense of burden. The main disadvantages that participants noted related to the robot not possessing human abilities, such as the ability to hold a conversation, to physically guide the patient's movements, and to express or understand emotions. We anticipate that the data collected in this study—input from the patients and their family members, including the similarities and differences between their points of view—will aid in improving the development of SARs for rehabilitation, so that they can better suit people who have had a stroke, and meet their individual needs.

Keywords: socially assistive robots, stroke, rehabilitation, focus groups, informal caregivers, patients, participatory design, co-design

INTRODUCTION

Nearly 795,000 strokes occur in the United States each year; on average, that means a stroke every 40 seconds (1). It is estimated that by 2030, approximately 3.4 million American adults over 50 will have suffered a stroke (2). With the increase in morbidity rates, the demand for professional, comprehensive, and intensive rehabilitative care tailored specifically to the patient and their injury will also increases (3–10).

Providing the necessary comprehensive care each patient needs can be challenging. Two thirds of stroke patients experience various deficits 6 months after the cessation of their rehabilitation process, and over 50% of them will still have significant disabilities relating to gross and fine motor ability, speech, perception, and cognition, affecting their daily lives and emotional state when evaluated 18 months after stroke (11–14).

When a patient is discharged from a hospital or a rehabilitation center, the balance of care abruptly switches from the formal professional arena to the informal-caregiving arena. Most often, this means a spouse, an adult child, or a friend taking on the burden of care (15, 16). The typical informal caregiver in the US is a 49.4-year-old woman who voluntarily assists a relative for 4.5 years for about 24 hours per week (17, 18). In 2017, it was estimated that family members provide 34 billion hours of treatment per year with an economic value of about $470 billion (16).

The most common needs of a stroke patient relate to daily activities such as bathing, dressing, and transportation, and less common needs relate to toileting and feeding (19) (see **Figure 1**). One of the main roles of family caregivers is providing transportation, with nearly 40% of informal caregivers reporting that they accompany patients to routine medical visits (20). The support that informal caregivers provide to patients allows individuals post-stroke to remain in their homes and communities for longer, thus postponing or even preventing institutionalization (20–22). Additionally, informal caregiving helps prevent or delay functional deterioration, reduces the use of medical services, and reduces expenses (20, 23, 24). There is no doubt that support given by informal caregivers is an integral factor in the healing processes of individuals post-stroke.

FIGURE 1 | Informal caregivers' roles. Some of roles undertaken by informal caregivers are depicted here, including help with feeding, dressing, traveling, shopping, cleaning, maintaining personal hygiene, and exercising. The breadth of functions many of them fill in the lives of the patients suggest that any improvement in patient independence has the potential to help alleviate some of the burden undertaken by the informal caregiver.

Lack of such support can have serious consequences: patients who receive inadequate assistance with Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) have been reported to require more physician visits, emergency room visits, and hospitalizations, and to suffer more often from depression (19, 25). Not attending medical appointments or being unable to obtain medical supplies may compromise the medical management of chronic health conditions, underlining the importance of the informal caregiver's role in transportation (19).

Alongside the clear benefits to the patients, this assistance can take a toll on the caregivers' physical and psychological health (26–28). Studies show that lack of caregiver preparation for their role can adversely affect their health, quality of live, and well-being. It has been demonstrated that caregivers face an increased risk of certain medical conditions, such as stroke, depression, fatigue, and more (29–33). It is, therefore, crucial to find ways to support these informal caregivers.

A variety of technological innovations are being developed to assist and ease the burden on professionals, informal caregivers, and patients (18, 34–36). For example, socially-assistive robots (SARs) have been developed to be used in hospitals and in the home, to perform various tasks, such as coaching an exercise session, aiding with ADLs, and encouraging exercise and emotional expression (15, 37–45). The purpose of SARs for rehabilitation is to support and expand independent functioning, reduce the support needed from caregivers, and motivate patients, caregivers, and therapists in coping with the intensive repetitive daily activities required to improve quality of life, health, and psychological well-being (46–50).

It is conceivable that a properly designed interaction with a SAR can offer benefits to both patients and their caregivers in the process of rehabilitation. We posit that it is essential to collect and incorporate these stakeholders' points of view into the process of designing effective interactions with robots for rehabilitation. Within the growing literature on the variety of SARs being developed, few studies explored the similarities and the differences in the needs, expectations and concerns of stroke patients and their informal caregivers, by directly asking the members of these stakeholder groups. For this reason, our goal in the current study was to examine the similarities and the differences in the attitudes, acceptance levels, needs, and concerns of individuals post-stroke and their primary informal caregivers regarding the use of a SAR to promote physical exercise in the rehabilitation process. We aimed to assess these stakeholders' initial reactions to the concept of SARs used in the home and at the clinic, with a focus on a robotic platform which will deliver a combination of cognitive and physical exercises. The current study is intended to complement and serve as a basis for immersive long-term interaction studies in these environments (home and clinic). Specifically, we asked:

(1) How do stroke patients and their informal caregivers perceive the notion of the patients performing rehabilitation exercises, coached by a SAR?
(2) What advantages and disadvantages do they see in such a practice?
(3) What changes or additions should be made to a specific implementation presented to them, so that it better meets patients' needs?
(4) What are their concerns regarding the use of a SAR in the rehabilitation process?

Understanding the needs and differences in opinions among individuals will help to optimize the rehabilitation system for all relevant stakeholders – clinicians [with whom we conducted focus groups in a previous study; see (51)], patients, and their informal caregivers. We expect that the higher the value the patients and their informal caregivers attribute to the SAR, the more likely they are to use it extensively for practicing rehabilitation exercises. Our intention is that the information gathered here will serve researchers, clinicians and engineers when designing interactions with a SAR for healthcare applications.

METHODS

Research Outline

We used the qualitative method of focus-groups discussions to collect information from patients and their caregivers. The focus groups enable an in-depth discussion that reveals the participants' positions, attitudes, and views regarding various subjects as well as a diversified view of any differences in opinions among the various group members (52–54). The methodology was based on the list of Consolidated Criteria for Reporting Qualitative Research (the COREQ list), which was developed to promote reporting transparency among researchers, while improving qualitative research reliability (55).

Experimental Protocol

Participants ($N = 23$, age: 68.3 $\pm$ 6.8 years; mean $\pm$ SD) took part in two experiments: one with individuals who have had a stroke and the other with informal caregivers of stroke patients. We held a total of six focus-group discussions— three with each population group. Participants were recruited using the convenience-sampling approach from Neeman, a nonprofit organization for post-stroke individuals and their families, which works to improve treatment, rehabilitation, and welfare of stroke patients and their families in Israel.

The criteria for inclusion in the study were: stroke patients or informal caregivers over 40 years old, Hebrew speaking. Stroke patients were recruited after the acute stage, if they experienced a rehabilitation process in a hospital, and had a motor impairment in their limbs which limits their movement. Caregivers were recruited if they cared for the individual post stroke three times per week or more. Exclusion criteria for patients were: significant impairment in their comprehension and verbal expression abilities (as assessed by the Neeman group coordinator), additional neurological conditions, undergoing rehabilitation at the time of the study. These criteria were communicated to the Neeman group coordinators, who then invited participants who meet these criteria to the focus-group discussions.

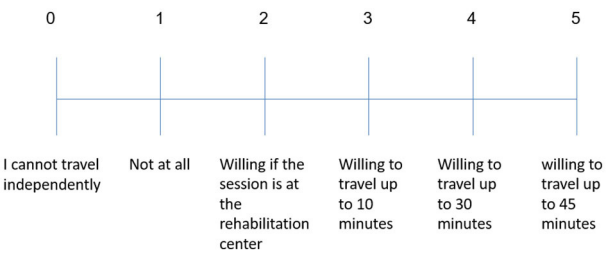
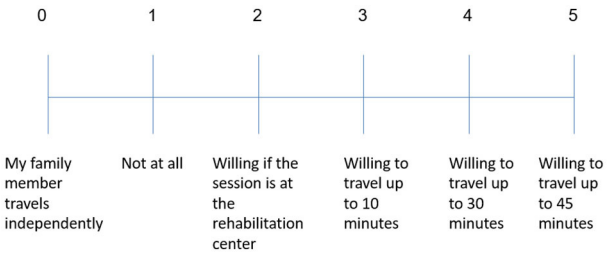
In recruiting participants, we strove to include diverse populations in terms of their geographic residence and socio-economic statuses, and accessibility to large rehabilitation centers.

All meetings were held face-to-face in the location where the Neeman group members usually meet (in Eilat, Hadera and Ofakim), except for the ones located in Haifa which were held using the Zoom video-conferencing software. The moderator had no prior acquaintance with any of the participants, and each participant attended a single focus-group discussion.

Group discussions were held between September 2020 and January 2021. Each discussion lasted between 45–90 min and was videotaped with HC-VX980 Panasonic and DJI OSMO cameras and audiotaped with a ZOOM H1N audio recorder, for further analysis. All discussions were moderated by the first author, a speech-language pathologist, who was a master's student at the time. In addition to the moderator, an assistant from the research team was present in one of the meetings with patients (in Ofakim), and took field notes, and a family-group coordinator was present in one of the meetings with family members (in Eilat); all three are female. At the beginning of each session, the moderator explained the overarching goal of the project: the long-term rehabilitation of stroke patients using a humanoid robot for upper-limb practice; and the specific goal of the focus-group discussions: to get feedback and understand their perceptions regarding SARs for rehabilitation in general, and regarding the specific implementation our research group has developed (15). Our team developed a robot-based gamified exercise platform for long-term post-stroke rehabilitation; the platform uses the humanoid robot Pepper (Softbank Robotics Aldebaran), and includes seven gamified sets of exercises, which are based on functional tasks from the everyday life of the patients, such as reaching to a cup, or turning a key in a lock. Each exercise set comprises a combination of cognitive and physical components. The platform gives the patients instructions, as well as feedback on their performance, and can track their performance over time. Following a brief overview of the platform, and an explanation about the format of the focus-group discussion, participants watched a two-minute video in which healthy participants were seen practicing five different exercise games with the robot. The video shows individuals sitting in front of the robot with a worktable between them. On the table are various everyday objects (e.g., keys, cups) which they are asked to grasp, manipulate and arrange, according to instructions provided by the robot.

The exercise games presented in the video were the Cup Game, the Target Game, the Keys Game, and the Escape Room Game [see (15)]. The video shows the individuals completing the exercise sets and receiving feedback from the robot, having successfully completed the task. The robot's responses included, inter alia: hand clapping, victorious arm gestures, and a jovial waving of the hands. After the participants watched the video, the moderator led a discussion based on 11 questions for the

TABLE 1 | Discussion questions - Patient groups and Informal-caregiver groups.

The questions presented in the focus groups	
Patient groups	**Informal-caregiver groups**
What are your thoughts and feelings regarding the video you just watched?	
Would you be interested in practicing with Pepper during your rehabilitation process?	Would you be interested in your family member practicing with Pepper during their rehabilitation process?
What advantages do you think practicing with Pepper has, compared to practicing alone?	
What disadvantages do you think practicing with Pepper has, compared to practicing alone?	
What would you add or change for the system to meet your needs?	**What would you add or change for the system to meet your family member's needs?**
How do you think Pepper could aid and assist you in your rehabilitation?	How do you think Pepper could aid and assist your family member's rehabilitation?
Do you think there are needs that Pepper cannot address?	
Do you think there are limitations that could prevent you from practicing with Pepper?	Can you think of any reason why your family member could not practice with Pepper?
Do you depend on someone else to drive you to your usual treatments?	**Are you the one driving your family member to their usual treatments?**
If you are arriving independently to treatments, please rate the level of effort you would be willing to invest in traveling for treatments with Pepper.	Please rate the level of effort you would be willing to invest to drive your family member for treatments with Pepper.
	
	Do you think your family member's practicing with Pepper could affect you? If so, in what ways?
Is there anything you would like to add?	

post-stroke patient groups and 12 questions for the family-member groups (see **Table 1**) which were formulated by the research team, and tested for clarity with members of the extended research group. Participants were asked to describe their personal experiences and note their thoughts and feelings regarding the robotic rehabilitation system, including any perceived advantages and disadvantages, beneficial elements, and what they would have liked to add, upgrade, or change in the system to improve it to suit their needs.

The video and audio recordings were transcribed and open-coded (applying the inductive approach) by hand using the Framework Method (56). In the thematic analysis process, common themes from the different groups were identified and categorized, as detailed in the Results section below.

After conducting two focus-group sessions, of stroke patients and of informal caregivers (a total of four), it was evident that there was a repetition of the main themes, and data saturation was reached. Therefore, another focus-group discussion was held for each of the two population groups, after which data collection ceased (57). No new variables were noted in the third and final session of each population group. The experimental protocol was approved by the Ben Gurion University of the Negev's ethics committee. All participants gave their written informed consent to participate.

RESULTS

Experiment 1—Stroke Patients

In Experiment 1 ($n = 11$, 10 males, 1 female; ages 57-85 years; 69.8 $\pm$ 6.7 years [mean $\pm$ SD]), the participants were stroke patients (11.2 $\pm$ 5.6 years; mean $\pm$ SD) 2-20 years post stroke (see **Table 2**). Three focus groups were held in three different centers: Ofakim ($N = 3$), Eilat ($N = 3$), and Hadera ($N = 5$). The letter in a participant's code in **Table 2**, as well as in the Results section, indicates the location at which the focus-group session was held.

The thematic analysis of the data from the patients' focus groups revealed five main themes: (i) attitudes toward the robot; (ii) motivation for use and feedback; (iii) perceived disadvantages; (iv) adaptability to patients' specific needs; and (v) the use of a SAR as supplementary to standard treatment. Listed below are the details for each of the themes, interlaced with direct quotes from the group discussions; see **Table 4** for a summary of the main issues brought up by the two study populations.

TABLE 2 | Participant demographics—Individuals with stroke ($N = 11$).

Participant	Age (years)	Years since the stroke	Gender
O1	57	17	Male
O2	85	5	Male
O3	71	5	Male
E1	69	2	Female
E2	67	10	Male
E3	69	12	Male
H1	66	9	Male
H2	67	16	Male
H3	68	20	Male
H4	78	18	Male
H5	71	10	Male
Average	69.8	11.2	

The upper-case letter in a participant's code indicates the location of the focus-group session to which they were recruited (O- Ofakim, E- Eilat, H- Hadera).

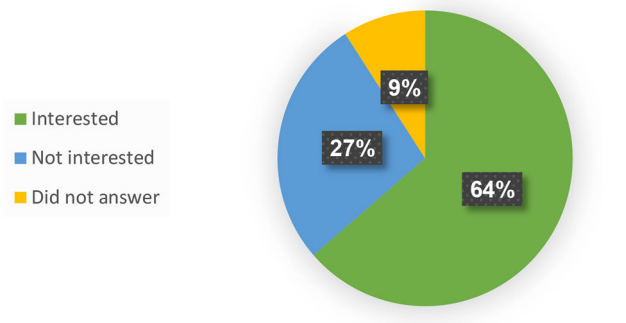


FIGURE 2 | Interest of individuals post-stroke in practicing with a robot as part of the rehabilitation process.

Attitudes Toward the Robot

Attitudes toward the robot were mixed. Thirty-six percent of the patients ($N = 4$) stood out for their positive attitude: they thought the robot was interesting, positive, and helpful. Two of those four participants did not see any drawbacks in the system. Thirty-six percent of the patients ($N = 4$) were ambivalent, and 28% of the patients ($N = 3$) opposed the use of the robotic rehabilitation system, saying it lacked the human qualities required in the process of rehabilitation. When they were asked if they would want to use Pepper during their rehabilitation process, most participants (seven, 64%) said they would, three replied they would not, and one abstained (see **Figure 2**).

Motivation for Use and Feedback

Three of the participants noted that discipline and inner motivation were crucial in the process of rehabilitation. Four participants (36%) said the robot could motivate and encourage stroke patients to perform rehabilitation exercises. They indicated that it is exceedingly physically and mentally challenging to do exercises alone and that they often give up as a result, but that they do believe the robot could encourage them to exercise.

> "After a stroke, you get occupational therapy [for] 12 treatments. That's it for the whole year … Pepper can help you get more… rehabilitation hours… [and] motivate you even by saying 'keep going, slowly, slowly… You don't know how much it [the feedback] has an effect, because it's hard [the rehabilitation process]…" (H2)

However, two participants emphasized the difference between the encouragement and support of a robot and the support, and level of feedback that a human can provide.

> "There's a huge difference [between a human therapist and a robot assistant]. I prefer people. A person needs feedback" (O2)

See also quote from H2 in the section titled The Human Aspect, below.

Five participants stated that they consider the robot to be an authoritative figure that could supervise them and help them commit to the process. Participant H3, however, did not agree, claiming that the robot could not offer the kind of support that a human therapist can:

> "…[the robot] doesn't touch you… it can't really *move* your hands… it took me a long time to put on socks or zip up my pants… It was all done with the help of a therapist…"

Four participants saw the advantages of doing exercises with the robot and also mentioned that it may serve to assist the professionals who already take care of them.

> "This thing can take the load off of many people, especially [off the] physical therapists" (O1)

Two of the 11 patients noted that their motivation for treatments in general, and with Pepper in particular, would depend on the support of their family and friends. One mentioned that if their family encouraged them to try this treatment with the robot, they would be happy to do so.

> "It also depends on the family… you need the family… as support… The family needs to give you the motivation [to experiment with the robot] … That's very important" (H2)

Two of the participants saw the SAR's value in encouraging the patient to do group exercises, as well.

Perceived Disadvantages

The Human Aspect

Nine of the 11 patients (82%) expressed their dissatisfaction with the robot's lack of humanity. They referred to its inability to provide guidance and direction, real conversation, empathy, and genuine human contact and interaction.

> "[When] a human being… instructs [me] to do something and it's hard for me, they try to help me … a robot won't help me, it will

only give instructions, tell me if [what I did] was good or not. But a person who can see that I'm struggling with something would …. help me out" (E3)
"It doesn't have emotions. You need feedback. [A] personal connection is better… A good word is sometimes more important than the entire treatment" (H2)

Help With Physical Needs

Participants from the patient group reported a lack of balance, constant falling, and an inability to perform routine actions, such as standing, walking, sitting etc., which require physical support and assistance by caregivers. Six of the participants thought that the robot could not provide this kind of support. Two participants stated that, given an opportunity to practice with technology, they would prefer aid technology (technology that is attached to injured body parts and provides electrical stimulation) which they perceive as more effective.

"I need help with my left hand… physically… Pepper wouldn't have helped me [with that]…" (H2)

Adaptability to Patient Disability

General Adaptability

The participants made suggestions regarding exercising with Pepper. One suggestion was that the robot gives clear vocal instructions at an appropriate volume. Five participants noted the need to adjust Pepper to accommodate to their physical disabilities. They would have wanted the robot to assist them in standing, sitting, opening doors, and more (see Part 3.5). Two participants referred to Pepper's inability to perform a demonstration after giving instructions. They said that watching a video is not enough for them to understand the exercise and that a physical illustration is mandatory in their view.

"[There should be] a demonstration and then a …video so that a person can understand what [Pepper] wants and then it will be easier… It should be mobile, easy to operate…" (H2)

Individual Adaptability

The participants suggested specific adjustments per their individual impairments which they would want programmed into the robot. Seven noted that they would like the robot to help practice motor skills, three noted cognitive skills, and four noted communication skills.

"I think if it should help with everything! With speaking, too" (E3)

Robots for Supplementary Practice

Seven participants (64%) stressed that exercising with the robot should not replace conventional treatments with a human therapist, but be done in addition to treatments with a human therapist. Three said that until they have successfully learned how to operate the system, another person should be present during their practice. Three participants stressed that someone must be present in order to mediate and help, at least during the first few sessions.

TABLE 3 | Participant demographics—Informal caregivers of individuals with stroke ($N = 12$).

Participant	Age (years)	Years caring for the individual with stroke	Gender	Relation
o1	70	4	Female	Spouse
o2	72	5	Male	Close friend
o3	63	10	Female	Spouse
o4	62	5	Female	Spouse
e1	69	2	Male	Spouse
e2	48	10	Female	Spouse
h1	67	21	Female	Spouse
h2	70	25	Female	Spouse
h3	70	14	Female	Spouse
h4	66	19	Female	Spouse
h5	73	20	Female	Spouse
h6	74	4	Female	Spouse
Average	**67**	**11.5**		

The lower-case letter in the participants' code indicates the location of the focus-group session to which they were recruited (o- Ofakim, e- Eilat, h- Haifa).

"[If] I got Pepper, I think it would be good for me, but not as a replacement for someone who helps and guides you… You could [practice with Pepper in rehabilitation], but after a person finishes their part. Human first and Pepper later, [and] not at the same time!" (H3)
"It's better to start with a human… You need someone to guide you on the bigger things like walking, or shopping…" (H1)
"… a person is better … but if I were in a situation where I can have the robot or have nothing, I would prefer having the robot" (O3)

Experiment 2—Informal Caregivers

In Experiment 2 ($N = 12$, 2 males, 10 females), the participants were informal caregivers of individuals after stroke (ages 48–74 years; 67 ± 6.7 years [mean ± SD]) who have been caring for a stroke patient for 11.5 ± 7 years (mean ± SD; see **Table 3**). Three focus groups of informal caregivers recruited from the Ofakim ($N = 4$), Eilat ($N = 2$), and Haifa centers ($N = 6$), were held via Zoom video chat due to COVID-19 restrictions.

The thematic analysis of the data from the informal caregivers' focus groups (the family-member groups) revealed four main themes, which correspond with the main themes from the patient groups: (i) attitudes toward the robot; (ii) motivation for use and feedback; (iii) perceived disadvantages; (iv) adaptability to patient needs; and (v) the use of a SAR as supplementary to standard treatment; see **Table 4** for a summary of the main issues brought up by the two study populations.

Attitudes Toward the Robot

Compared with the stroke patients, the informal caregivers had a more optimistic attitude toward using the robot in the rehabilitation process, especially the Ofakim focus group. They expressed great confidence in the robotic system and believed

TABLE 4 | The main similarities and differences between the two population groups.

Issues that came up in the focus-group discussions	
Patients	**Informal caregivers**
View the robot-based system as an innovative, interesting, and intriguing technology that can motivate the patients to commit to the rehabilitation process	
Perceive the added value of the system to be: a way of helping to reduce the load from their *formal* caregivers	Perceive the added value of the system to be: it could provide them with more time for self-care and everyday chores, and help prevent friction and disagreements with patients
Concerned that practice with a robot will *replace* the care given by formal caregivers; See the value in the robotic system, but refuse to accept it as a *substitute* for the standard care	
Mainly want this new technology to assist them with motor needs, primarily with physical support (e.g., balancing, getting up from a chair)	Believe that the gamified exercise system could inspire them and give them ideas for further practice to better facilitate their family member's rehabilitation process
Think the system should be adapted to the specific needs and capabilities of stroke patients, e.g.,: ease of operation; instructions and feedback written in large lettering, and spoken using a loud voice; repetition of instructions; personalization of difficulty levels; practice of communication, cognition, and memory skills	
Perceive system's disadvantages to be the robot's inability to: physically demonstrate the instructions; identify and respond to nuances in patient's behavior (e.g., indicators of exhaustion, lack of understanding, etc.); converse with the patients	
Would like physical contact with the robot, as a means to better practice movement (a guiding touch)	**Would like the robot to provide comforting physical contact, such as a hug, or a reassuring touch**

it could perform a wide range of activities and provide care for their spouses.

All informal caregivers who took part in the study, when asked if they would be interested in their family member exercising with Pepper during the rehabilitation process, said "yes". It became apparent that they were willing to try any exercise or treatment that might improve the stroke patients' condition or at least keep it from deteriorating.

> "I think it's good, … alongside the 12 [treatments] a year he receives, it would [give him] more [practice] time. I think he can do it at home. During COVID-19 we were not [at the rehabilitation center] a lot and it's harder for him to walk, and [when he exercised] on the bicycle – he said that it was harder than before [because there had been a long break from treatments]" (o2)

Motivation for Use and Feedback

The robot was perceived as being an interesting, novel, and an innovative new way to do rehabilitation exercises. Most participants (10 out of 12) thought that the robot had a significant advantage over self-practice because it could motivate patients into action, thus promoting progress. One participant noted that they perceived the robot as an authoritative figure that could aid their spouse in committing to and persisting in their practice. One of the participants in the Haifa focus group mentioned that motivation for exercising could also come from group practice with the robot, a statement with which all five of the group members agreed.

Four participants noted that Pepper could reduce costs, since it can be used at any time and for an unlimited number of treatment sessions.

> *"… Therapists … cost more money … [The robot] is one more thing [they can use] … in rehabilitation. From what I know, the more you practice the better… [Pepper] can add interest and provide another form of rehabilitation"* (o4)

It seems that the informal caregivers were motivated to have their spouses use the robot not only because it can encourage the performance of exercises that can improve the patients' condition, but also because the system can give them (the family members) ideas for how to practice with the patient. They noted it may also provide them with an indication of their spouses' progress and allow them to have some free time, thus helping to prevent friction and conflict.

> "It really gives us ideas on how to carry on… gives us some confidence" (o1)
> "I'm skeptical regarding the ability of [a person with] cognitive limitations to understand what the robot wants, its instructions… on the other hand, I think it can spare us, the caregiving spouses, a lot of negative interactions with our partners because … our involvement with treatments created a lot of antagonism, resistance, and … anger. If someone else can do the work, I think it's good because even in the [traditional] treatments, … when we went to occupational therapy, the therapist would give us something to do … and I was the one who had to deal with him and give him instructions. If a robot can do that, it would reduce some of the friction and I see that as a positive thing" (h4)
> "It can set us free. We could leave them with Pepper for 40 minutes and come back to see what they had done" (h5)

On the other hand, two of the participants were quite concerned that the stroke patients would not want to use or cooperate with the robot due to fear of or indifference toward technology (both patients were 57 years old when the stroke occurred).

Six of the participants (all of the Haifa group) saw the SAR's potential in motivating the patient to do group exercises, as well. It should be noted that the topic of using the SAR for group exercises was brought up by the participants, and was not in response to a question by the group mediator.

Perceived Disadvantages

Human Aspects

Seven of the 12 informal caregivers emphasized that the robot was missing the human capacity to understand the patient. They believe that Pepper will miss small gestures that stroke patients use due to speech and communication impairments and might fail to clarify instructions when misunderstandings arise.

"… [the caregiver] need[s] to know how to hug and smile… the fact that it's a robot and not a human … would not [make my spouse] happy to cooperate" (h5)

Adaptability to Patient Disability

The issue of adaptability of the robot, which came up both in the patient groups and in the family-member groups, is comprised of two components: general adaptability –features that must be in all rehabilitation robots; and individual adaptability –features that can be customized for the individual's medical needs.

General Adaptability

The informal caregivers noted that the stroke patients may suffer from significant cognitive injuries and that their auditory comprehension and ability to understand instructions may be compromised. Four of the participants opined that the robot would not be suitable for their spouses due to cognitive impairments that make it difficult to understand oral instructions. Three participants mentioned that the robot must provide physical demonstrations of the required activities in order for the patients to understand their instructions; one mentioned that written instructions should be in a large font; and three others mentioned that the robot must have a relatively long waiting time for a response from the patient.

Individual Adaptability

Specific adjustments need to be made in the robot's system to suit each stroke patient's particular difficulties. The most common adjustments mentioned were intended to accommodate impairments in communication, writing, reading, retrieval, and memory. Three of the informal caregivers would have liked for the robot to help practice motor skills; five mentioned cognitive skills; four mentioned communication skills; and four participants mentioned social contexts (reading a book or a newspaper to the patient), as well as activities of daily living (such as getting dressed).

"It is hard for my husband to read quickly, and he needs big lettering… [H]e can't hear well, so we got him headphones to raise the volume. There are so many [types of] injuries… [E]ach is different… [T]he treatment should be individually tailored" (o4)

One of the participants noted that she would have liked a SAR to help her husband in re-training his emotional-communication skills. She gave the example of reminding him to smile, since he is often in a bad mood, and she hopes that smiling will make him feel better:

"Sometimes he is in such a bad mood, I … say to him 'Hello, smile;… it's healthy for the body, to smile.' (o1)

Five of the informal caregivers stated that it was difficult for them to assess the robotic system based on the video presented at the beginning of the focus group discussion.

Robots as Supplementary Practice

Eight of the informal caregivers emphasized that the robot should be used to supplement, rather than replace, the work of clinicians.

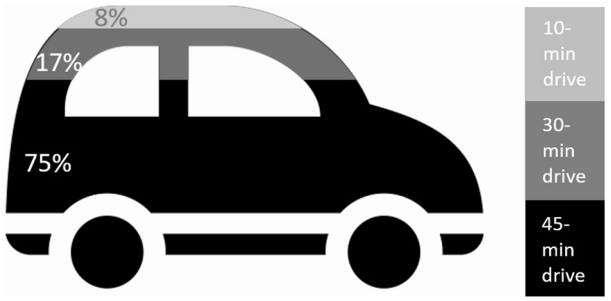


FIGURE 3 | Willingness of informal caregivers to drive the patients specifically for training sessions with the robot. One hundred percent of the participants in the informal caregivers' groups drive their family members to errands and treatments. One hundred percentage of them indicated that they will be willing to drive them specifically for training sessions with the robot, with 92% of them willing to drive 30–45 min for that purpose.

Three of them stressed that someone must accompany it to mediate and help, at least in the first few sessions.

"[The robot should only be] extra help… only if it is in addition to the [standard] treatments… [I]f it's just the robot, then it's not relevant… after the [standard] treatments are done and then there's an option for [practicing with] a robot. I think that could happen" (e2)

Informal Caregivers' Extent of Effort

All the family members who participated in the focus groups were the informal caregivers who did most of the driving of stroke patients to their various treatments. We asked the family members how long they would be willing to drive the patients to practice with a robot, as a proxy for assessing the extent of effort they were willing to put into getting their family members to sessions with the robot. The possible responses were: "unwilling", "willing if the treatment [with the robot] is at the treatment center" (i.e., the rehabilitation center where all other treatments are given), and "willing to travel up to 30/45 minutes" (to a location separate from where the standard treatments take place). The results showed that 100% of the informal caregivers were willing to drive the patients for practice sessions with the robot, with 92% of those willing to drive between 30–45 mins for that purpose (the maximum driving time we asked about was 45 min; see **Figure 3**). Those who said that they would prefer to travel <45 min mentioned that they do not like or are unable to travel long distances. One mentioned that she would prefer first to check whether her spouse would even want to cooperate with this practice, and only then would she be willing to make the necessary effort.

DISCUSSION

The aim of the research was to study and analyze the attitudes of stroke patients and their informal caregivers toward the use of SARs during the rehabilitation process. We therefore

conducted two sets of focus groups—one comprised of stroke patients and the other of informal caregivers (family members)—to explore the projected levels of use and acceptance, and to understand the two groups' needs and concerns with regards to the rehabilitative system we developed, which presents to the participants a combination of cognitive and physical challenges (15, 51).

The analysis of the data we collected revealed a number of parameters that impact the projected acceptance and use of the robot in the rehabilitation process. These parameters can be divided into two categories: those that relate to the stroke patients and their informal caregivers, and those that relate to the robot.

Parameters Relating to the Individual

Attitudes Toward the Robot

Almost two-thirds (64%) of the participants in the patient groups expressed their desire to exercise with the robot, and those who were reluctant to do so, explained that it was because the robot lacked human qualities and could not meet their physical needs. The attitude expressed by the majority corresponds with results we reported from a user questionnaire (USEQ) administered to 10 patients who had the robot-based rehabilitative system we developed over a five-to-seven-week period, for a total of 15 sessions each; they indicated their wish to continue training with the platform with a score of 4.3 ± 1.0 (out of 5; 15). In a series of in-depth interviews we conducted with nine of those patients, they indicated that their motivation to continue using the system was primarily affected by the perceived functional benefit[1]; this finding was echoed by a strong correlation we found between participants' evaluation of the contribution of the system to their rehabilitation and their willingness to keep training with it (15): "…it is not the mere use of technology that increases the motivation of the person to practice, but rather it is the appreciation of the technology's effectiveness and its perceived contribution to the rehabilitation process". The minority attitude in the current study reflects the other side of this spectrum: a lack of belief in the functional benefit that training with the robot would bring, leads them to express disinterest in the training.

All participants in the family-member groups expressed interest in having the patient do exercises with the robot, indicating their belief that *any* practice may serve to advance the patients' medical condition. The stroke patients, on the other hand, focused on the functionality of the treatment tool, what it can or cannot do, and formulated their opinion based on this factor. It is important to understand this attitude that functionality dictates use, as it will ultimately impact whether patients will try to use the system. Indeed, it has been previously shown that users that view the robot positively will want to use it and will do so often (58, 59).

Motivation and Feedback

Both stroke patients and their informal caregivers view the system as an innovative, interesting, and intriguing technology that can motivate the patients to commit to the rehabilitation process. Only the stroke patients saw added value in the system in so far as it could reduce the workload for their formal caregivers. Indeed, studies have shown that SARs and assistive technologies can ease the load of both formal and informal caregivers (35, 60, 61). Frennert et al. (62) specifically showed that robots were perceived as beneficial to the working conditions of formal caregivers, as a resource for decreasing health costs, and as a way to increase the quality of treatment, seeing as robots can work around the clock without sleeping or being distracted by personal matters.

As for the informal caregivers, the motivation for using the robot was twofold: (1) the positive contribution of the training toward their spouse's rehabilitation; and (2) the benefit of using the robot to them (the family members). They indicated that this gamified exercise system could inspire them and give them ideas for further practice to better facilitate their family member's rehabilitation process. Furthermore, they believed that training with the robot could provide them with more time for self-care or everyday chores and might even reduce friction and disagreements.

Indeed, the notion that the social robot can alleviate some of the burden—be it physical or emotional—from informal caregivers came up in a study by Moharana et al. (63), who designed assistive robots for collaboration with informal caregivers of patients with dementia. One of the caregivers who participated in this study wished that the robot would "take the role of a bad guy" by telling the patient they have to stop eating unhealthy food, thus preventing an argument between the spouses.

These insights provided by the informal caregivers—on how a robot may help patients not only directly, but also indirectly, by helping their caregivers, and easing some of the potential tensions that may develop between them during a long rehabilitation process—highlight the importance of including the informal caregivers in the process of designing assistive technology for the benefit of patients.

Robots as a Supplementary Practice

The participants were worried that practicing with a robot would replace the human care given by formal caregivers and made it very clear that while they see the value in training with the robot, they refuse to use it as a substitute for standard treatments, but rather in addition to those.

Technological Experience

The informal caregivers raised concerns regarding the cooperation of their family members with the robot over time. Their reasons included indifference to technology, difficulty in understanding how to operate the robot, and a lack of trust in technology, which may lead to avoidance (64, 65). It should be noted that these concerns did not arise from the stroke patients. The informal caregivers mentioned that at least during the first few sessions, until patients gain experience, a person must be present in order to mediate and help, before patients practice alone with the robot. The finding that family members were concerned about the technological barrier to using the robot echoes the findings of Frennert et al. (66) which aimed to assess how different users—adults and their informal caregivers—see

[1]Koren Y, Feingold Polak R, Levy-Tzedek S. Extended interviews with stroke patients over a long-term rehabilitation using human-robot or human-computer interactions (unpublished data).

or envision the potential role of a robot in their lives. They found that all the informal caregivers thought the relatives in their care (their adult parents) could not learn how to use and operate the robot. It may be that this concern is misplaced: in our long-term study with patients, they responded to the question "Was the information provided by the system clear to you?" with a score of 4.9 out of 5, and to the question "Were you able to control the system?" with a score of 4.8 out of 5 (15).

Parameters Relating to the Robot

Adaptability

Previous studies have indicated that for a robot to meet the needs of the individual, it should be user-friendly, safe, reliable, with a human voice, and moderate movement (66–70). These desired characteristics were echoed by participants in the current study, who indicated that they would have liked for the robot to have the following attributes and functions: mobility; ease of operation; instructions written in large lettering; a loud voice and repetition of instructions with suitable intonation to emphasize parts of the sentence; adjustments to different levels of difficulty; capacity for longer response times by the user; and practice for language and communication impairments (speech, reading, and writing), cognition, memory, social contexts (like reading books) and other motor impairments specific to their injuries (such as hemispatial neglect). This expectation for a multi-modal assistive device echoes studies that show that a combined approach improves function—e.g., in upper-limb function (71) and in gait parameters (72) post-stroke.

Our research group previously assessed the opinions and recommendations of expert clinicians regarding the rehabilitation platform that developed with the Pepper robot for people recovering from a stroke (68). Both the participants of the current study and the expert clinicians (formal caregivers) from the Feingold Polak et al. study (68) mentioned the topics of flexibility and an encouraging reward system. The experts stated that the robot should be customizable to patients' unique needs and conditions; one of the ways to do this, they suggested, is to assure that instructions are spoken clearly and slowly and to have the robot say/express kind words of encouragement (68). While the participants in the current study did not mention anything regarding the response times of the robot, the clinicians in Feingold Polak et al. (68) indicated that the robot should respond quickly. Indeed, patients who used this robotic platform over a 5–7 week period noted that they wish it would react as quickly as a human would (15); they also noted their desire that the robotic platform would be tailored to their individual needs.

One of the main perceived disadvantages of the robot in the current study was its inability to perform a physical demonstration of the instructions to patients, and its inability to notice small nuances; to "read" the patient in certain situations, such as lack of understanding, exhaustion, reluctance to continue exercising, etc. Stroke patients noted they want the technology to also assist them with motor needs: physical support, balancing, and lifting.

In addition, the stroke patients in the current study indicated their need for physical contact. The issue of contact was also mentioned by the informal caregivers, but unlike the stroke patients, who mentioned they needed the physical contact for movement guidance, the informal caregivers referred to the human ability to encourage and support. The informal caregivers used a hug as an example of a significant and useful human expression. Indeed, studies with SARs like "KASPAR" and "Paro" have suggested that humans seek some physical contact when interacting with a robot in social situations (73) and that physical contact with a robot can improve mood and relieve physical pain (74). It is possible that the participants in the current study expected human-like qualities (physical assistance, touch, interaction, and expression of emotion) from this technological platform (75), as they are yet unfamiliar with non-human social platforms which may assist in other ways in the process of rehabilitation.

Human Aspects

Both population groups stressed the lack of human traits in the robot; some perceived it as a cold machine, unable to express or understand emotions, converse, or react to a changing situation. They saw it as an automated object with specific, preset answers or instructions that preclude natural conversation and expression of emotion. They mentioned the need to have some sort of social connection with the robot. Interestingly, these issues were not brought up by patients who had trained with the system over a 5–7 week period (15), suggesting that exposure to the benefits the system has – in terms of improving upper-limb function – may change the a-priori perceptions of what the system's characteristics should be. This notwithstanding, it seems it would be advantageous if the system could provide both the training platform and a more human-like connection; Busso et al. (76) suggested that when a system can recognize facial expressions and decipher their meaning, it can assist the user and meet their needs more accurately.

Personality

It has been found that a robot with a caring, empathetic, and friendly personality encourages more interaction between it and the individual (77–79). Goetz and Kiesler (80) presented the idea that the robot's personality must match its purpose; the results of their study demonstrate that the participants enjoyed interacting (while engaging in strenuous exercise) with the "playful robot" more than with the "serious, concerned robot". However, they were less inclined to perform the "playful robot's" requests, and as a result, practiced less with it. These results suggest that users require care and empathy, but also authoritativeness and assertiveness that will motivate them to continue and persevere with their physically straining exercises. It is thus encouraging that both the patients and the informal caregivers in the present study perceived the robot as an authoritative figure that would motivate the users to exercise.

The Extent of Effort the Informal Caregivers Were Willing to Exert

All the patients in this study rely on their informal caregiver's transportation to arrive at their treatments or doctor appointments, and all of the informal caregivers in this study drive their spouses. Means of transportation and distance

from medical centers are considered potential major barriers to the accessibility and utilization of medical care (81). It has been found that those who have an informal caregiving support system that provides them with transportation visit their health care services 1.6 times more than those who do not (81). Distance has been studied mainly in the context of rural areas with low population density versus urban areas and was found to be one of the most influential parameters affecting health outcomes and one of the most significant barriers to health care accessibility (82, 83). The greater the distance from treatment centers is the less frequent are patients' visits (81, 84–86).

In this study we wanted to test whether distance-time is one of the factors that will influence the informal caregivers' decision to drive or not to drive the patients for sessions with the robotic platform. We found that 100% of the informal caregivers were indeed willing to make the effort to drive their family members for treatments with the SAR; 92% of them were willing to drive between 30–45 mins for that purpose (the maximum driving time we asked about was 45 min).

SAR for At-Home Rehabilitation

We conducted the study in 2020, the year that COVID-19 was declared a global pandemic (87). The informal caregivers indicated that during this period, the standard treatments were canceled or reduced in volume and that patients were left without rehabilitation for an extended period. This disruption to the rehabilitation process may have hampered their recovery. Both stroke patients and informal caregivers saw the added value in having such a guided-exercise system in their own homes, especially during a global pandemic.

Summary of the Main Differences Between the Responses of the Two Study Populations

While there were similarities between the responses of the participants in the patient groups and in the informal-caregivers groups, there were some notable differences as well, which we summarize below:

1. All (100%) of the informal caregivers were interested in having their family member practice with the SAR, while 64% of the stroke patients expressed their desire to exercise with the robot; those who were reluctant claimed the robot lacked human qualities and would not meet their physical needs.
2. The informal caregivers suggested that any kind of practice could aid the patients and improve their function. The stroke patients, on the other hand, were more cautious and sought to establish the functionality of the treatment tool prior to use.
3. Beyond the perceived benefits to patients, the informal caregivers saw the benefit that using the SAR offered the caregivers themselves (mainly providing them with more free time), while the stroke patients indicated the benefit it offered the *formal* caregivers (mainly reducing their workload).
4. The informal caregivers expressed a concern that indifference to technology, or inability to effectively operate it may lead patients to avoid using it. This concern was not noted by any of the stroke patients.
5. Both groups indicated the importance of physical contact in rehabilitation; The caregivers stressed the importance of emotional touch, and that the robot lacks the ability to touch and hug the patients as a sign of encouragement, while the stroke patients stressed the importance of a guiding touch, and that the robot lacks the ability to indicate to them the correct movement by physically moving their body in the desired way.
6. The participants in the patient groups noted they expected technological tools to provide them physical assistance with standing, sitting, walking etc., and the robot's inability to provide such physical assistance was perceived as a significant disadvantage. This disadvantage was not mentioned by any of the informal caregivers.

Study Limitations

This study had several limitations. First, the sample size was relatively small; the study was conducted during the COVID-19 pandemic, which limited the ability to gather people together for a discussion session due to lockdowns, cancellations of support group meetings, and social distancing regulations. Some potential participants were reluctant to attend in-person discussion groups due to their at-risk statuses. The total number of participants in our study was 23: 11 stroke patients and 12 informal caregivers. Ideally, future research would include a larger sample size.

Second, there was no equal representation of gender in the focus groups. In the patient groups there was only one woman, and in the family-member groups (the informal caregivers) there were only two men.

Third, it was not possible to mobilize the robot and provide hands-on experience. Instead, the participants were shown a short, two-minute video of the robot doing exercises with healthy individuals. The participants noted it was hard for them to evaluate the robot's abilities and imagine it in action, since they had no first-hand experience with the technology. Notably, despite this limitation, most stroke patients were interested in using a SAR for their rehabilitation. The current study serves to complement the 2-year in-clinic long-term interaction study we conducted with patients using the robotic rehabilitation platform we developed (15), as well as focus-group discussions we held with formal caregivers of individuals post-stroke (51).

Fourth, the level of the stroke patients' physical impairment was not examined on an individual basis; it is, therefore, unknown whether different impairment levels were represented.

Lastly, as in any focus-group discussion, it is possible that not everyone felt comfortable expressing their genuine thoughts and opinions, especially if they differed from the rest of the group members' views. It is possible that if personal interviews had been conducted, different opinions would have emerged.

Summary and Conclusions

We found that both population groups (patients and family members) had a positive attitude toward using robotic technology in rehabilitation; specifically, a platform that provides a multi-modal intervention, combining cognitive and

physical training. They thought that the SAR could motivate, encourage, and help users commit to the long process of rehabilitation, while stressing the importance of personalized adaptation of the robot's behavior to their needs. Participants also noted that they would like the robot to have human-like qualities alongside an authoritative personality to help users comply with their exercise regimen. They thought the robot should be able to react to the individual, provide proper feedback, guide, reflect, demonstrate, converse, and express emotions. As many SARs are designed to help users but do not provide this full range of functionalities, we suggest that it is important to speak openly to patients and their informal caregivers about their specific goals and how they can fit within the range of abilities of the assistive robot.

The participants in the focus groups opined that a SAR would be effective at their rehabilitation facility as well as their home; they expressed that the robot could help its users improve their movement skills and give them additional ideas for activities, freeing up blocks of time for the caregivers, thereby easing their sense of burden. As the "care gap"—the gap between the care that people need and what the healthcare system can offer them (which only widened during the COVID-19 pandemic)—widens, SARs offer patients additional training time in the clinic or at home, and the caregivers generally seemed pleased with the idea (88–91).

This study provided the informal caregivers with a rare platform to express their views, thoughts, and opinions on robotic technology for rehabilitation using qualitative tools, which allowed them to shed some light on and delve deeper into their own experiences. The informal caregivers may be affected mentally, physically, and financially in a process that could go on for years after the event. They hold first-hand knowledge of the injury and the needs of the patient, which is why it is important to collect and analyze information from this population to get a fuller picture of how stroke patients can be treated better and how the caregivers' burdens could be eased.

We hope that this work can serve as a basis for future works developing technological tools for rehabilitation.

Future Recommendations

Further studies should test which factors have a greater effect on the level of acceptance and use of the robot: factors that derived from the individual as opposed to factors that derive from the robot. It would be interesting to test whether the age of the patients affects their acceptance and use patterns of this technology, and whether these attitudes change over time within a long-term interaction. Finally, it is important to investigate the potential benefits and disadvantages of using a SAR in the home and at the clinic, using a combination of qualitative data collection with objective outcome measures, such as clinical scores.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further data are not publicly available so as not to compromise the privacy of research participants.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ben Gurion University of the Negev's Ethics Committee. 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

AD and SL-T designed the experiment. AD collected the patient data, analyzed and interpreted the patient data, and wrote the manuscript. SL-T supervised the experiment and the writing of the manuscript. SL-T and YA secured the funds for the study. YA reviewed and critically commented on the manuscript. All authors read and approved the final manuscript.

FUNDING

The research was partially supported by the Helmsley Charitable Trust through the Agricultural, Biological and Cognitive Robotics Initiative, by the Marcus Endowment Fund, and the Paul Ivanier Center for Production Management, all at the Ben-Gurion University of the Negev. Financial support was provided by the Rosetrees Trust, the Borten Family Foundation, the Robert Bergida bequest, and the Consolidated Anti-Aging Foundation. This research was also supported by grant no. 3000017258 from the Chief Scientist Office of the Israeli Ministry of Health, by the National Insurance Institute of Israel, and received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754340.

ACKNOWLEDGMENTS

The authors wish to thank Ronit Feingold Polak for making comments on a previous version of the manuscript and Gili Mayo for her assistance with running one of the focus-group meetings.

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics–2018 update: a report from the American Heart Association. *Circulation.* (2018) 137:e67–e492. doi: 10.1161/CIR.0000000000000558
2. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke.* (2013) 44:2361–75. doi: 10.1161/STR.0b013e31829734f2
3. Bloom DE, Canning D, Lubet A. Global population aging: Facts, challenges, solutions and perspectives.

Daedalus. (2015) 144:80–92. doi: 10.1162/DAED_a_00332
4. Brackenridge J, Bradnam VL, Lennon S, Costi J J, Hobbs AD. A review of rehabilitation devices to promote upper limb function following stroke. *Neurosci. Biomed. Eng.* (2016) 4:25–42. doi: 10.2174/2213385204666160303220102
5. Combs SA, Finley MA, Henss M, Himmler S, Lapota K, Stillwell D. Effects of a repetitive gaming intervention on upper extremity impairments and function in persons with chronic stroke: a preliminary study. *Disabil Rehabil.* (2012) 34:1291–8. doi: 10.3109/09638288.2011.641660
6. Hubbard I, Parsons M. The conventional care of therapists as acute stroke specialists: a case study. *Int J Ther Rehabil*. (2007). 14:357–362. doi: 10.12968/ijtr.2007.14.8.24355
7. Koch P, Schulz R, Hummel FC. Structural connectivity analyses in motor recovery research after stroke. *Ann Clin Transl Neurol.* (2016) 3:233–44. doi: 10.1002/acn3.278
8. Qian Z, Bi Z. Recent development of rehabilitation robots. *Adv Mech Eng.* (2015) 7:563062. doi: 10.1155/2014/563062
9. Umeki N, Murata J, Higashijima M. (2019) Effects of training for finger perception on functional recovery of hemiplegic upper limbs in acute stroke patients. *Occup Ther Int*. (2019) 2019: 6508261. doi: 10.1155/2019/6508261
10. Wu DY, Guo M, Gao YS, Kang YH, Guo JC, Jiang XL, et al. Clinical effects of comprehensive therapy of early psychological intervention and rehabilitation training on neurological rehabilitation of patients with acute stroke. *Asian Pac J Trop Med.* (2012) 5:914–6. doi: 10.1016/S1995-7645(12)60171-0
11. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* (2009) 8:741–54. doi: 10.1016/S1474-4422(09)70150-4
12. Magnusson C, Anastassova M, Paneels S, Rassmus-Gröhn K, Rydeman B, Randall G, et al. Stroke and universal design. In Proceedings of Universal Design and Higher Education in Transformation Congress. (2018) p. 854.
13. Singh RJ, Chen S, Ganesh A, Hill MD. Long-term neurological, vascular, and mortality outcomes after stroke. *Int J Stroke.* (2018) 13:787–96. doi: 10.1177/1747493018798526
14. Welmer AK, Holmqvist LW, Sommerfeld DK. Limited fine hand use after stroke and its association with other disabilities. *J Rehabil Med.* (2008) 40:603–8. doi: 10.2340/16501977-0218
15. Feingold Polak R, Barzel O, Levy-Tzedek S, A. robot goes to rehab: a novel gamified system for long-term stroke rehabilitation using a socially assistive robot—methodology and usability testing. *J Neuroeng Rehabil.* (2021) 18:1–18. doi: 10.1186/s12984-021-00915-2
16. Reinhard S, Feinberg LF, Houser A, Choula R, Evans M. *Valuing the Invaluable: 2019 Update – Charting a Path Forward.* Washington, DC: AARP Public Policy Institute. doi: 10.26419/ppi.00082.001
17. AARP and National Alliance for Caregiving in the United States 2020. Washington, DC: AARP. (2020).
18. Aldehaim AY, Alotaibi FF, Uphold CR, Dang S. The impact of technology-based interventions on informal caregivers of stroke survivors: a systematic review. *Telemedicine e-Health.* (2016) 22:223–31. doi: 10.1089/tmj.2015.0062
19. Allen SM, Mor V. The prevalence and consequences of unmet need: Contrasts between older and younger adults with disability. *Medical Care*. (1997) 1132–48 doi: 10.1097/00005650-199711000-00005
20. Feinberg L, Reinhard SC, Houser A, Choula R. *Valuing the Invaluable: 2011 Update, the Growing Contributions and Costs of Family Caregiving.* Washington, DC: AARP Public Policy Institute (2011). p. 32.
21. Bakas T, Clark PC, Kelly-Hayes M, King RB, Lutz BJ, Miller EL. Evidence for stroke family caregiver and dyad interventions: a statement for healthcare professionals from the American Heart Association and American Stroke Association. *Stroke.* (2014) 45:2836–52. doi: 10.1161/STR.0000000000000033
22. Camak DJ. Addressing the burden of stroke caregivers: a literature review. *J Clin Nurs.* (2015) 24:2376–82. doi: 10.1111/jocn.12884
23. Harris JE, Eng JJ, Miller WC, Dawson AS. The role of caregiver involvement in upper-limb treatment in individuals with subacute stroke. *Phys Ther.* (2010) 90:1302–10. doi: 10.2522/ptj.20090349
24. Van Houtven CH, Norton EC. Informal care and Medicare expenditures: testing for heterogeneous treatment effects. *J Health Econ.* (2008) 27:134–56. doi: 10.1016/j.jhealeco.2007.03.002
25. Xu H, Covinsky KE, Stallard E, Thomas III J, Sands LP. Insufficient help for activity of daily living disabilities and risk of all-cause hospitalization. *J Am Geriatr Soc.* (2012) 60:927–33. doi: 10.1111/j.1532-5415.2012.03926.x
26. Cecil R, Thompson K, Parahoo K, McCaughan E. Towards an understanding of the lives of families affected by stroke: a qualitative study of home carers. *J Adv Nurs.* (2013) 69:1761–70. doi: 10.1111/jan.12037
27. Kokorelias KM, Lu FK, Santos JR, Xu Y, Leung R, Cameron JI. "Caregiving is a full-time job" impacting stroke caregivers' health and well-being: A qualitative meta-synthesis. *Health Social Care Commun.* (2020) 28:325–340 doi: 10.1111/hsc.12895
28. Liu H, Lou VW. Transitioning into spousal caregiving: contribution of caregiving intensity and caregivers' multiple chronic conditions to functional health. *Age Ageing.* (2019) 48:108–14. doi: 10.1093/ageing/afy098
29. Capistrant BD, Moon JR, Berkman LF, Glymour MM. Current and long-term spousal caregiving and onset of cardiovascular disease. *J Epidemiol Community Health.* (2012) 66:951–6. doi: 10.1136/jech-2011-200040
30. Haley WE, Roth DL, Howard G, Safford MM. Caregiving strain and estimated risk for stroke and coronary heart disease among spouse caregivers: differential effects by race and sex. *Stroke.* (2010) 41:331–6. doi: 10.1161/STROKEAHA.109.568279
31. McLennon SM, Bakas T, Jessup NM, Habermann B, Weaver MT. Task difficulty and life changes among stroke family caregivers: relationship to depressive symptoms. *Arch Phys Med Rehabil.* (2014) 95:2484–90. doi: 10.1016/j.apmr.2014.04.028
32. McPherson CJ, Wilson KG, Chyurlia L, Leclerc C. The caregiving relationship and quality of life among partners of stroke survivors: A cross-sectional study. *Health Qual Life Outcomes.* (2011) 9:1–10. doi: 10.1186/1477-7525-9-29
33. van Campen C, de Boer AH, Iedema J. Are informal caregivers less happy than noncaregivers? Happiness and the intensity of caregiving in combination with paid and voluntary work. *Scand J Caring Sci.* (2013) 27:44–50. doi: 10.1111/j.1471-6712.2012.00998.x
34. Joo H, Dunet DO, Fang J, Wang G. Cost of informal caregiving associated with stroke among the elderly in the United States. *Neurology.* (2014) 83:1831–7. doi: 10.1212/WNL.0000000000000986
35. Madara Marasinghe K. Assistive technologies in reducing caregiver burden among informal caregivers of older adults: a systematic review. *Disabil Rehabil Assist Technol.* (2016) 11:353–60. doi: 10.3109/17483107.2015.1087061
36. Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. *Lancet Neurol.* (2020) 19:348–60. doi: 10.1016/S1474-4422(19)30415-6
37. Broadbent E, Garrett J, Jepsen N, Ogilvie VL, Ahn HS, Robinson H, et al. Using robots at home to support patients with chronic obstructive pulmonary disease: pilot randomized controlled trial. *J Med Internet Res.* (2018) 20:e8640. doi: 10.2196/jmir.8640
38. Céspedes Gómez N, Irfan B, Senft E, Cifuentes CA, Gutierrez LF, Rincon-Roncancio M, et al. A Socially Assistive Robot for Long-Term Cardiac Rehabilitation in the Real World. *Front Neurorobot.* (2021) 15:21. doi: 10.3389/fnbot.2021.633248
39. Chen TL, Ciocarlie M, Cousins S, Grice PM, Hawkins K, Hsiao K, et al. Robots for humanity: using assistive robotics to empower people with disabilities. *IEEE Robotics and Automation Magazine.* (2013) 20:30–9. doi: 10.1109/MRA.2012.2229950
40. Eizicovits D, Edan Y, Tabak I, Levy-Tzedek S. Robotic gaming prototype for upper limb exercise: Effects of age and embodiment on user preferences and movement. *Restor Neurol Neurosci.* (2018) 36:261–74. doi: 10.3233/RNN-170802
41. Fasola J, Mataric MJ. Using socially assistive human–robot interaction to motivate physical exercise for older adults. *Proceedings of the IEEE.* (2012) 100:2512–26. doi: 10.1109/JPROC.2012.2200539
42. Kashi S, Levy-Tzedek S. Smooth leader or sharp follower? Playing the mirror game with a robot. *Restor Neurol Neurosci.* (2018) 36:147–59. doi: 10.3233/RNN-170756
43. Kubota A, Riek LD. Methods for robot behavior adaptation for cognitive neurorehabilitation. *Annu Rev Control Robot Auton Syst.* (2021) 5 doi: 10.1146/annurev-control-042920-093225
44. Matarić MJ, Eriksson J, Feil-Seifer DJ, Winstein CJ. Socially assistive robotics for post-stroke rehabilitation. *J Neuroeng Rehabil.* (2007) 4:5. doi: 10.1186/1743-0003-4-5

45. Mucchiani C, Cacchione P, Johnson M, Mead R, Yim M. Deployment of a socially assistive robot for assessment of COVID-19 symptoms and exposure at an elder care setting. In 2021 30th IEEE International Conference on Robot and Human Interactive Communication (RO-MAN). *IEEE.* (2021) 1189–95. doi: 10.1109/RO-MAN50785.2021.9515551
46. Demain S, Burridge J, Ellis-Hill C, Hughes AM, Yardley L, Tedesco-Triccas L, et al. Assistive technologies after stroke: self-management or fending for yourself? A focus group study. *BMC Health Services Res.* (2013) 13:334. doi: 10.1186/1472-6963-13-334
47. Feingold Polak R, Elishay A, Shahar Y, Stein M, Edan Y, Levy-Tzedek S. Differences between young and old users when interacting with a humanoid robot: A qualitative usability study. *Paladyn, Journal of Behavioral Robotics.* (2018) 9:183–92. doi: 10.1515/pjbr-2018-0013
48. Langer A, Levy-Tzedek S. Emerging roles for social robots in rehabilitation: current directions. *ACM Trans Hum-Robot Interact.* (2021) 10:1–4. doi: 10.1145/3462256
49. Piezzo C, Suzuki K. Feasibility study of a socially assistive humanoid robot for guiding elderly individuals during walking. *Future Internet.* (2017) 9:30. doi: 10.3390/fi9030030
50. Swift-Spong K, Short E, Wade E, Matarić MJ. Effects of comparative feedback from a socially assistive robot on self-efficacy in post-stroke rehabilitation. In 2015 IEEE International Conference on Rehabilitation Robotics (ICORR). *IEEE.* (2015) 764–9. doi: 10.1109/ICORR.2015.7281294
51. Polak FR, Levy-Tzedek S. Social robot for rehabilitation expert clinicians and post-stroke patients' evaluation following a long-term intervention. In: *Proceedings of the 2020 ACM/IEEE International Conference on Human-Robot Interaction* (2020). doi: 10.1145/3319502.3374797. p. 151–60.
52. Gill P, Stewart K, Treasure E, Chadwick B. Methods of data collection in qualitative research: interviews and focus groups. *Br Dent J.* (2008) 204:291. doi: 10.1038/bdj.2008.192
53. Tausch AP, Menold N. Methodological aspects of focus groups in health research: results of qualitative interviews with focus group moderators. *Glob Qual Nurs Res.* (2016) 3:2333393616630466. doi: 10.1177/2333393616630466
54. van Teijlingen E, Pitchforth E. Focus group research in family planning and reproductive health care. *J Fam Plann Reprod Health Care.* (2006) 32:30. doi: 10.1783/147118906775275299
55. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
56. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol.* (2013) 13:1–8. doi: 10.1186/1471-2288-13-117
57. Hollis V, Openshaw S, Goble R. Conducting focus groups: Purpose and practicalities. *Br J Occup Ther.* (2002) 65:2–8. doi: 10.1177/030802260206500102
58. Heerink M, Kröse B, Wielinga BJ, Evers V. Studying the acceptance of a robotic agent by elderly users. *Int J Adv* Robot *Syst.* (2006) 7:33–43.
59. Chu L, Chen HW, Cheng PY, Ho P, Weng IT, Yang PL, et al. Identifying features that enhance older adults' acceptance of robots: a mixed methods study. *Gerontology.* (2019) 65:441–50. doi: 10.1159/000494881
60. Louie WYG, Li J, Vaquero T, Nejat G. A focus group study on the design considerations and impressions of a socially assistive robot for long-term care. In The 23rd IEEE international symposium on robot and human interactive communication. *IEEE.* (2014) 237–42. doi: 10.1109/ROMAN.2014.6926259
61. Mortenson WB, Demers L, Fuhrer MJ, Jutai JW, Lenker J, DeRuyter F. How assistive technology use by individuals with disabilities impacts their caregivers: a systematic review of the research evidence. *Am J Phys Med Rehabil.* (2012) 91:984. doi: 10.1097/PHM.0b013e318269eceb
62. Frennert S, Östlund B. How do older people think and feel about robots in health-and elderly care?. In International Conference on Inclusive Robotics for a better Society. Springer, Cham. (2018) p. 167–74 doi: 10.1007/978-3-030-24074-5_28
63. Moharana S, Panduro AE, Lee HR, Riek LD. Robots for joy, robots for sorrow: community based robot design for dementia caregivers. In 2019 14th ACM/IEEE International Conference on Human-Robot Interaction (HRI). IEEE. (2019) p. 458–67. doi: 10.1109/HRI.2019.8673206
64. Kellmeyer P, Mueller O, Feingold Polak R, Levy-Tzedek S. Social robots in rehabilitation: A question of trust. *Sci Robot.* (2018). 3(21):?. doi: 10.1126/scirobotics.aat1587
65. Langer A, Feingold Polak R, Mueller O, Kellmeyer P, Levy-Tzedek S. Trust in socially assistive robots: Considerations for use in rehabilitation. *Neurosci Biobehav Rev.* (2019) 104:231–9. doi: 10.1016/j.neubiorev.2019.07.014
66. Frennert S, Eftring H, Östlund B. What older people expect of robots: A mixed methods approach. In International conference on social robotics Springer, Cham. (2013) p. 19–29 doi: 10.1007/978-3-319-02675-6_3
67. Broadbent E, Stafford R, MacDonald B. Acceptance of healthcare robots for the older population: review and future directions. *Int J Soc Robot.* (2009) 1:319. doi: 10.1007/s12369-009-0030-6
68. Feingold Polak R, Bistritsky A, Gozlan Y, Levy-Tzedek S. Novel gamified system for post-stroke upper-limb rehabilitation using a social robot: focus groups of expert clinicians. In 2019 International Conference on Virtual Rehabilitation (ICVR). IEEE (2019). p. 1–7.
69. Wu YH, Wrobel J, Cornuet M, Kerhervé H, Damnée S, Rigaud AS. Acceptance of an assistive robot in older adults: a mixed-method study of human–robot interaction over a 1-month period in the Living Lab setting. *Clin Interv Aging.* (2014) 9:801. doi: 10.2147/CIA.S56435
70. Hutson S, Lim SL, Bentley PJ, Bianchi-Berthouze N, Bowling A. Investigating the suitability of social robots for the wellbeing of the elderly. In International Conference on Affective Computing and Intelligent Interaction. Springer, Berlin, Heidelberg (2011). doi: 10.1007/978-3-642-24600-5_61. p. 578–87.
71. Aminov A, Rogers JM, Middleton S, Caeyenberghs K, Wilson PH. What do randomized controlled trials say about virtual rehabilitation in stroke? A systematic literature review and meta-analysis of upper-limb and cognitive outcomes. *J Neuroeng Rehabil.* (2018) 15:1–24. doi: 10.1186/s12984-018-0370-2
72. Huber SK, Knols RH, Arnet P, de Bruin. ED. Motor-cognitive intervention concepts can improve gait in chronic stroke, but their effect on cognitive functions is unclear: A systematic review with meta-analyses. *Neurosci Biobehav Rev.* (2021) S0149-7634(21)00506-6. doi: 10.1016/j.neubiorev.2021.11.013
73. Silvera-Tawil D, Rye D, Velonaki M. Artificial skin and tactile sensing for socially interactive robots: A review. *Rob Auton Syst.* (2015) 63:230–43. doi: 10.1016/j.robot.2014.09.008
74. Geva N, Uzefovsky F, Levy-Tzedek S. Touching the social robot PARO reduces pain perception and salivary oxytocin levels. *Sci Rep.* (2020) 10:1–15. doi: 10.1038/s41598-020-66982-y
75. Henschel A, Laban G, Cross ES. What Makes a Robot Social? A review of social robots from science fiction to a home or hospital near you. *Current Robotics Reports.* (2021) 1–11. doi: 10.1007/s43154-020-00035-0
76. Busso C, Deng Z, Yildirim S, Bulut M, Lee CM, Kazemzadeh A, et al. Analysis of emotion recognition using facial expressions, speech and multimodal information. In Proceedings of the 6th international conference on Multimodal interfaces. (2004) p. 205–11. doi: 10.1145/1027933.1027968
77. Damiano L, Dumouchel P, Lehmann H. Towards human–robot affective co-evolution overcoming oppositions in constructing emotions and empathy. *Int J Social Robot.* (2015) 7:7–18. doi: 10.1007/s12369-014-0258-7
78. Ring L, Shi L, Totzke K, Bickmore T. Social support agents for older adults: longitudinal affective computing in the home. *J Multimodal User Interfaces.* (2015) 9:79–88. doi: 10.1007/s12193-014-0157-0
79. Stahl BC, McBride N, Wakunuma K, Flick C. The empathic care robot: A prototype of responsible research and innovation. *Technol Forecast Soc Change.* (2014) 84:74–85. doi: 10.1016/j.techfore.2013.08.001
80. Goetz J, Kiesler S. Cooperation with a robotic assistant. In CHI'02 Extended Abstracts on Human Factors in Computing Systems. (2002) p. 578–9. doi: 10.1145/506443.506492
81. Arcury TA, Gesler WM, Preisser JS, Sherman J, Spencer J, Perin J. The effects of geography and spatial behavior on health care utilization among the residents of a rural region. *Health Serv Res.* (2005) 40:135–56. doi: 10.1111/j.1475-6773.2005.00346.x
82. Buzza C, Ono SS, Turvey C, Wittrock S, Noble M, Reddy G, et al. Distance is relative: unpacking a principal barrier in rural healthcare. *J Gen Intern Med.* (2011). 26:648. doi: 10.1007/s11606-011-1762-1
83. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an

impact on health outcomes? A systematic review. *BMJ open.* (2016) 6:e013059. doi: 10.1136/bmjopen-2016-013059
84. Goodman DC, Fisher E, Stukel TA. Chang CH. The distance to community medical care and the likelihood of hospitalization: is closer always better? *Am J Public Health.* (1997) 87:1144–50. doi: 10.2105/AJPH.87.7.1144
85. Mishra S, Sahu PK, Sarkar AK, Mehran B, Sharma S. Geo-spatial site suitability analysis for development of health care units in rural India: Effects on habitation accessibility, facility utilization and zonal equity in facility distribution. *J Transp Geogr.* (2019) 78:135–49. doi: 10.1016/j.jtrangeo.2019.05.017
86. Nemet GF, Bailey AJ. Distance and health care utilization among the rural elderly. *Soc Sci Med.* (2000) 50:1197–208. doi: 10.1016/S0277-9536(99)00365-2
87. World Health Organization. *WHO Director-General's opening remarks at the media briefing on COVID-19 Geneva*: WHO. (2020). Available online at: https://www.who.int/dg/speeches/detail/who-directorgeneral-s-opening-remarks-at-the-media-briefing-oncovid-
88. Aiken LH, US. nurse labor market dynamics are key to global nurse sufficiency. *Health Serv Res.* (2007) 42:1299–320. doi: 10.1111/j.1475-6773.2007.00714.x
89. Mandizvidza V, London L, Bryer A. Shortfall in stroke care: A study of ischaemic stroke care practices in a South African metropole. *S Afr Med J.* (2021) 111:215–9. doi: 10.7196/SAMJ.2021.v111i3.15104
90. Peek ST, Wouters EJ, Van Hoof J, Luijkx KG, Boeije HR, Vrijhoef HJ. Factors influencing acceptance of technology for aging in place: a systematic review. *Int J Med Inform.* (2014) 83:235–48. doi: 10.1016/j.ijmedinf.2014.01.004
91. Pestine-Stevens A, Greenfield EA. The need for community practice to support aging in place during COVID-19. *J Gerontol Soc Work.* (2020) 63:631–4. doi: 10.1080/01634372.2020.1789258

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.

frontiers in Rehabilitation Sciences

REVIEW
published: 10 February 2022
doi: 10.3389/fresc.2022.795335

Predicting Individual Treatment Response to rTMS for Motor Recovery After Stroke: A Review and the CanStim Perspective

Franziska E. Hildesheim[1,2,3], *Alexander N. Silver*[1,2,3], *Adan-Ulises Dominguez-Vargas*[2,4,5], *Justin W. Andrushko*[2,6], *Jodi D. Edwards*[2,7,8], *Numa Dancause*[2,4,5] *and Alexander Thiel*[1,2,3]*

[1] *Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, QC, Canada,* [2] *Canadian Platform for Trials in Non-Invasive Brain Stimulation (CanStim), Montréal, QC, Canada,* [3] *Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada,* [4] *Centre interdisciplinaire de recherche sur le cerveau et l'apprentissage (CIRCA), Université de Montréal, Montréal, QC, Canada,* [5] *Département de Neurosciences, Faculté de Médecine, Université de Montréal, Montréal, QC, Canada,* [6] *Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada,* [7] *University of Ottawa Heart Institute, Ottawa, ON, Canada,* [8] *School of Epidemiology and Public Health, University of Ottawa Heart Institute, Ottawa, ON, Canada*

Background: Rehabilitation is critical for reducing stroke-related disability and improving quality-of-life post-stroke. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulation technique used as stand-alone or adjunct treatment to physiotherapy, may be of benefit for motor recovery in subgroups of stroke patients. The Canadian Platform for Trials in Non-Invasive Brain Stimulation (CanStim) seeks to advance the use of these techniques to improve post-stroke recovery through clinical trials and pre-clinical studies using standardized research protocols. Here, we review existing clinical trials for demographic, clinical, and neurobiological factors which may predict treatment response to identify knowledge gaps which need to be addressed before implementing these parameters for patient stratification in clinical trial protocols.

Objective: To provide a review of clinical rTMS trials of stroke recovery identifying factors associated with rTMS response in stroke patients with motor deficits and develop research perspectives for pre-clinical and clinical studies.

Methods: A literature search was performed in PubMed, using the Boolean search terms *stroke* AND *repetitive transcranial magnetic stimulation* OR *rTMS* AND *motor* for studies investigating the use of rTMS for motor recovery in stroke patients at any recovery phase. A total of 1,676 articles were screened by two blinded raters, with 26 papers identified for inclusion in this review.

Results: Multiple possible factors associated with rTMS response were identified, including stroke location, cortical thickness, brain-derived neurotrophic factor (*BDNF*) genotype, initial stroke severity, and several imaging and clinical factors associated with a relatively preserved functional motor network of the ipsilesional hemisphere. Age, sex, and time post-stroke were generally not related to rTMS response. Factors associated with greater response were identified in studies of both excitatory ipsilesional and inhibitory contralesional rTMS. Heterogeneous study designs and contradictory data exemplify the need for greater protocol standardization and high-quality controlled trials.

OPEN ACCESS

Edited by:
Gail A. Eskes,
Dalhousie University, Canada

Reviewed by:
Luca Sebastianelli,
Hospital of Vipiteno, Italy
Sandeep K. Subramanian,
The University of Texas Health Science Center at San Antonio, United States

***Correspondence:**
Alexander Thiel
alexander.thiel@mcgill.ca

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *14 October 2021*
Accepted: *17 January 2022*
Published: *10 February 2022*

Citation:
Hildesheim FE, Silver AN, Dominguez-Vargas A-U, Andrushko JW, Edwards JD, Dancause N and Thiel A (2022) Predicting Individual Treatment Response to rTMS for Motor Recovery After Stroke: A Review and the CanStim Perspective. Front. Rehabilit. Sci. 3:795335. doi: 10.3389/fresc.2022.795335

Conclusion: Clinical, brain structural and neurobiological factors have been identified as potential predictors for rTMS response in stroke patients with motor impairment. These factors can inform the design of future clinical trials, before being considered for optimization of individual rehabilitation therapy for stroke patients. Pre-clinical models for stroke recovery, specifically developed in a clinical context, may accelerate this process.

Keywords: repetitive transcranial magnetic stimulation, stroke, motor recovery, rehabilitation, prediction, review

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique with the potential to modify cortical excitability in localized brain regions directly under the stimulation coil, as well as in distal brain regions connected to the stimulation site (1). Brief electrical currents are induced through strong magnetic fields (1, 2). By varying the number, frequency and intensity of magnetic pulses, different effects can be induced in the brain. Generally, low-frequency pulse rates of $\leq$ 1 Hz have inhibitory effects on underlying brain tissue by reducing the excitability of neurons, whereas high-frequency pulse rates $\geq$5 Hz have excitatory effects [see Ridding and Rothwell (3) for a more detailed review]. Another rTMS protocol, theta-burst stimulation (TBS), uses multiple short bursts of 50 Hz pulses (4). Depending on whether these pulse trains are applied intermittently (iTBS) or continuously (cTBS), TBS can act as either excitatory or inhibitory stimulus. rTMS is considered safe, with the only common adverse effect being minor local reactions, such as headache or scalp discomfort. The most serious adverse effect reported in literature is induction of generalized seizures. The risk is however considered very low, even among those taking drugs acting on the central nervous system (5). Updated guidelines for the therapeutic use of rTMS to maximize patient safety and minimize the risk of severe adverse events have recently been published (5).

rTMS has been claimed to have benefits in a wide variety of psychiatric and neurological conditions (3), however, major unipolar depression and obsessive-compulsive disorder are currently the only indications with FDA approval (6). The use of rTMS as an adjunct to physical therapy for recovery of motor function in stroke has received particular attention, due to the high prevalence of stroke and residual disability of function, even with current standard of care rehabilitation treatment (7). Two general types of rTMS protocols are used in stroke rehabilitation (**Figure 1**). In the first approach, excitatory high-frequency rTMS stimulation is applied over the ipsilesional primary motor cortex (M1) or adjacent brain areas. The mechanism by which this promotes motor recovery over time is not fully understood, but may involve strengthening of synaptic connections in descending motor pathways (3). In the second approach, inhibitory low-frequency rTMS is applied over contralesional M1, which may reduce interhemispheric inhibition from the contralesional M1 onto the ipsilesional M1, and thereby promote cortical reorganization in the ipsilesional hemisphere.

Both excitatory and inhibitory rTMS protocols have been shown to improve motor recovery in post-stroke patients in the acute, subacute and chronic phase of recovery (12–15). However, inter-individual variability in response to rTMS treatment remains high, and evidence regarding factors that may contribute to this variability is fragmentary. Identifying factors causing this variability is thus key to improve the identification of patients most likely to benefit from rTMS treatment and to recruit more homogeneous populations into clinical trials. The purpose of this review is to identify potential predictive factors from the literature which could be subject to future targeted validation studies to inform implementation into clinical trial protocols.

METHODS

A literature search was performed in PubMed for the identification of articles published prior to July 2021. The database was searched using the Boolean search terms *stroke* AND *repetitive transcranial magnetic stimulation* OR *rTMS* AND *motor*. Only full-text articles were considered for inclusion. Studies were included based on the following inclusion criteria: (1) diagnosis of ischemic or hemorrhagic stroke in human subjects, (2) patients are reported to suffer from upper or lower extremity deficits, (3) study assesses and reports upper or lower limb motor function or associated electrophysiological parameters before and after rTMS intervention, and (4) study reports statistical analysis results (e.g., ANOVA, multivariate regression model, etc.) of patient factors associated with differential rTMS response. Both studies including rTMS as a stand-alone treatment and those combining rTMS with physiotherapy or occupational therapy programs were included. Studies with patients of all age, sex and education level, as well as patients in all phases post-stroke (acute, subacute, chronic), were considered for study inclusion. Exclusion criteria included non-therapeutic use of TMS and use of another invasive or non-invasive neuromodulation technique (e.g., transcranial direct current stimulation [tDCS]). Review articles, meta-analyses, editorials, and guidelines, as well as articles not available in English, French, or German were also excluded.

A total of 1,676 articles were found with this initial search protocol. For article organization, the open-access review software Rayyan was used (www.rayyan.ai). After removal of duplicates, the titles and abstracts of remaining articles were screened by two independent blinded raters (F.E.H. and J.W.A.), to determine their relevance for the research question of this review. After article screening, the results were unblinded.

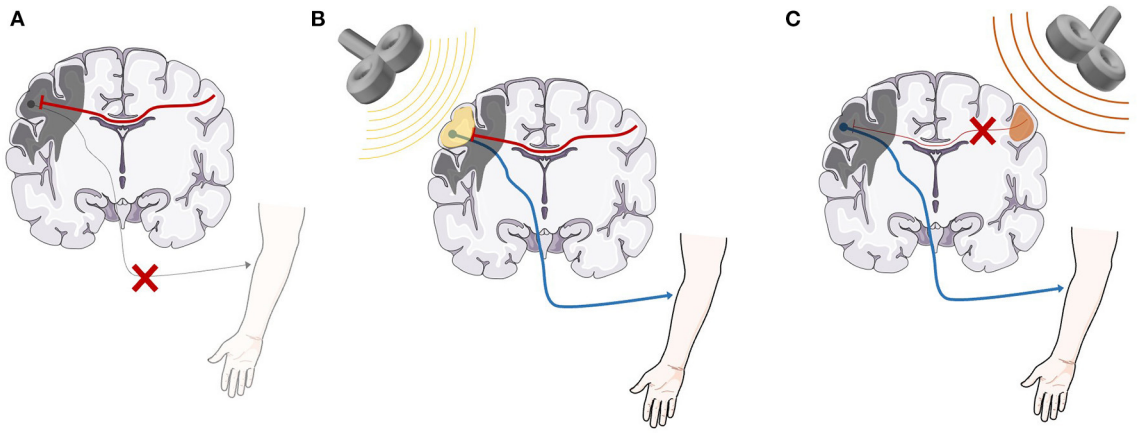


FIGURE 1 | A representation of the basic neurobiological model underlying rTMS as an adjunct treatment for stroke recovery. **(A)** After stroke, direct damage to the primary motor cortex as well as inhibitory signaling from the contralesional motor cortex are both likely involved in lack of functional recovery (8–11). **(B)** High-frequency (>5 Hz) rTMS applied over the ipsilesional hemisphere strengthens the descending motor pathway, facilitating motor recovery. **(C)** Low-frequency (<1 Hz) rTMS applied over the contralesional hemisphere reduces inhibitory signals from the contralesional motor cortex, promoting beneficial cortical reorganization and motor recovery (3). rTMS, repetitive transcranial magnetic stimulation. Anatomical images adapted from smart.servier.com.

Mismatched papers were reviewed by a third independent rater (A.N.S.) and disagreements were resolved through consensus (F.E.H., J.W.A. and A.N.S).

RESULTS

A total of 1,676 articles were identified, and with duplicates removed, 1,673 articles remained to be screened for inclusion by the two raters. The agreement between reviewers on study inclusion was 98.2%, with a categorization mismatch in 30/1,673 articles (1.79%) and 18/1,673 (1.07%) articles identified for inclusion by both raters before unblinding. After review of the mismatched papers by the third rater, 26 articles with a total of 3,975 participants were identified as relevant and included in this review (**Figure 2**).

Table 1 provides an overview of included studies, and **Figure 3** illustrates the variation in study design, rTMS protocol, time post-stroke and number of sessions across studies. Half of the included studies (13/26), encompassing a large majority of the patient population, were single-arm, non-randomized retrospective or prospective studies (21–32, 36). Eleven studies included a sham-control condition either in a crossover or parallel-group design (16, 20, 33–35, 37–42). Of the 11 sham-controlled trials, only four were randomized, double-blind trials (19, 20, 35, 38).

In terms of rTMS protocols, 10 studies used excitatory rTMS (17, 21, 22, 33, 34, 36, 39) or iTBS (18, 37, 38) targeting ipsilesional M1 (17, 18, 21, 22, 34, 36–39) or ipsilesional S1 (33), with either a single session (18, 33, 34, 36, 37, 39) or a total of 10 sessions (17, 21, 22, 38) of intervention. A total of 13 studies used inhibitory rTMS over contralesional M1, with a range from 5 up to 30 intervention sessions (19, 20, 23–32, 41). Two studies used both inhibitory contralesional, as well as excitatory ipsilesional rTMS over M1 (35, 40), and a single study measured the effects of a single session of excitatory contralesional rTMS on M1, dorsal premotor cortex (dPMC), and anterior intraparietal sulcus (aIPS) (16). rTMS/iTBS was either used as a stand-alone intervention, paired with conventional physiotherapy/occupational therapy respecting the core standards of practice or task-specific training of the affected limb (e.g., index finger tapping).

Clinical assessment of motor outcome varied greatly, with different studies using the Fugl-Meyer Assessment (FMA), Wolf Motor Function Test (WMFT), Box and Block Test (BBT), Barthel Index, index finger tapping frequency, maximal grip force, reaction time tasks, and others. The timing of the motor assessment also varied, with eight studies examining immediate effects after a single rTMS session (16, 18, 32–35, 37, 39), 13 studies examining motor improvement after a prescribed series of sessions (17, 19, 21, 24–31, 38, 41), and 5 studies examining improvement from 1 week to 6 months after completion of rTMS treatment (20, 22, 23, 36, 40).

For the purpose of this review, we defined acute stroke as < 2 weeks since stroke onset, chronic stroke as > 6 months since stroke onset, and subacute stroke as falling in between these two categories (12). Over half of the studies (16/26) included chronic patients only (23–38), three studies included subacute, as well as chronic patients (39–41), four studies included subacute patients only (19–22), and three studies included acute patients (16–18). The female to male ratio of all patients included in the studies was approximately 1:2 (males $n = 2{,}596$, 65.31%), with one study not reporting the sex of participants (40).

Clinical Factors

Demographics

The majority of included studies described no association between certain demographic variables, such as age and sex, and treatment response (21, 22, 30–33). A single study of 12 chronic stroke patients found that increasing age was correlated with

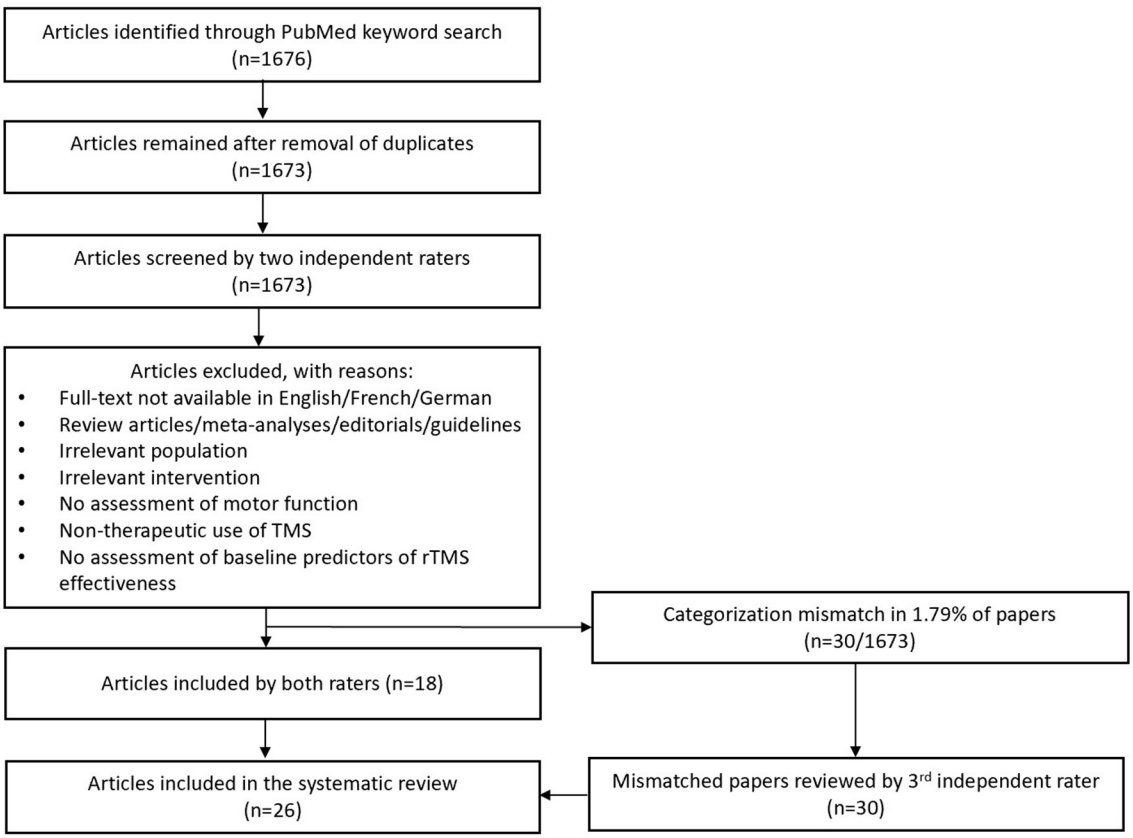


FIGURE 2 | Study selection procedure. rTMS, repetitive transcranial magnetic stimulation.

less recovery of motor function, as reflected by less increase in grip strength 1 h after a single session of excitatory rTMS over ipsilesional M1 (36).

Time Post-stroke

rTMS was shown to promote increased motor function when administered in the acute (<2 weeks), subacute (2 weeks−6 months), and chronic (>6 months) phase. Only a few studies directly examined time since stroke as a covariate for rTMS response and no association was found between time post-stroke and motor recovery after rTMS intervention (22, 30–32, 38). However, acute and subacute stroke patients were underrepresented, with 73% of studies investigating chronic patients.

Baseline Motor Impairment

Stroke patients with better motor function at baseline were more likely to respond to rTMS in several studies applying different rTMS protocols (29, 32). In a study by Emara et al. (40) subjects with better baseline motor function showed functional improvement, assessed by the Activity Index, after inhibitory 1 Hz rTMS over contralesional M1. In contrast, patients with worse baseline function showed no improvement (40). However, in the same study, when applying excitatory 5 Hz rTMS over ipsilesional M1 in a different cohort, these patients showed significant functional improvement following the intervention regardless of their baseline motor function (40). Recent clinical guideline recommendations indicate a superior efficacy of inhibitory contralesional rTMS over excitatory ipsilesional rTMS (12). However, in the study of Emara et al. (40) more heavily affected patients responded to excitatory ipsilesional rTMS only, which leads to this rTMS protocol appearing more efficient.

Similarly, Hamaguchi et al. (27) retrospectively investigated 1,254 stroke patients who received inhibitory 1 Hz rTMS over contralesional M1. They reported that stroke patients with severe and moderate initial motor impairment were more likely than patients with mild initial motor impairment to show improvement in the FMA after an rTMS intervention (27). The authors suggested that functional improvement resulting from rTMS based treatment is in general lower in patients with better baseline function. However, in a more recent study, the same research group retrospectively analyzed 1,716 stroke patients receiving the same rTMS protocol (inhibitory 1 Hz rTMS over contralesional M1) and reported that the level of initial motor impairment was not significantly associated with rTMS response

TABLE 1 | Overview of studies included in this review.

References	*n*	Phase post-stroke	rTMS protocol	Study design	Primary outcome measures	Factors associated with rTMS response
Hensel et al. (16)	13	Acute	Excitatory 10 Hz, contralesional dPMC, M1 & aIPS; single session	Crossover (sham vs. rTMS), single-blind, randomized	Index finger tapping	Connectivity between frontal motor regions and aIPS
Chang et al. (17)	44	Acute	Excitatory 10 Hz, ipsilesional M1, 10 sessions	Parallel-group (Val/Val vs. Met allele), double-blind	FMA, BBT	Val/Val *BDNF* genotype
Di Lazzaro et al. (18)	20	Acute	iTBS, ipsilesional M1, single session	Parallel-group (Val/Val vs. Met allele), double-blind	Changes in cortical excitability (RMT, MEP, AMT)	Val/Val *BDNF* genotype
Kim et al. (19)	73	Subacute	Inhibitory 1 Hz, contralesional M1, 10 sessions	Parallel-group (sham vs. rTMS), double-blind, randomized	BBT	Subcortical vs. cortical involvement
Ludemann-Podubecka et al. (20)	40	Subacute	Inhibitory 1 Hz, contralesional M1, 15 sessions	Parallel-group (sham vs. rTMS), double-blind, randomized	WMFT, MESUPES, index finger tapping, cortical excitability (MEP)	Lesion in dominant vs. non-dominant hemisphere
Chang et al. (21)	62	Subacute	Excitatory 10 Hz, ipsilesional M1, 10 sessions	Single-arm	FMA	Val/Val *BDNF* genotype, MEP response at BL
Lee et al. (22)	29	Subacute	Excitatory 10 Hz, ipsilesional M1, 10 sessions	Single-arm	FIM, K-MBI	Subcortical vs. cortical involvement, aphasia, mental status
Demirtas-Tatlidede et al. (23)	10	Chronic	Inhibitory 1 Hz, contralesional M1, 10 sessions	Single-arm	FMA, WMFT, mAS, hand grip strength	Integrity of transcallosal fibers
Ueda et al. (24)	25	Chronic	Inhibitory 1 Hz, contralesional M1, 12 sessions	Single-arm	WMFT	Cortical thickness
Ueda et al. (25)	30	Chronic	Inhibitory 1 Hz, contralesional M1, 10 sessions	Single-arm	FMA, WMFT, BRS	Laterality index in motor area
Ueda et al. (26)	25	Chronic	Inhibitory 1 Hz, contralesional M1, 12 sessions	Single-arm	FMA, WMFT	Integrity of CST
Hamaguchi et al. (27)	1,254	Chronic	Inhibitory 1 Hz, contralesional M1, 15 sessions	Single-arm, retrospective analysis	FMA	BL residual hand function
Tamashiro et al. (28)	59	Chronic	Inhibitory 1 Hz, contralesional M1, 21 sessions	Single-arm	FMA, WMFT, mAS	Hemispheric dominance
Kakuda et al. (29)	52	Chronic	Inhibitory 1 Hz, contralesional M1, 22 sessions	Single-arm, retrospective analysis	FMA, WMFT	BL residual hand function
Kakuda et al. (30)	204	Chronic	Inhibitory 1 Hz, contralesional M1, 22 sessions	Single-arm	FMA, WMFT	No effect of stroke subtype
Tatsuno et al. (31)	1,716	Chronic	Inhibitory 1 Hz, contralesional M1, 30 sessions	Single-arm, retrospective analysis	FMA	No effect of BL stroke severity
Carey et al. (32)	12	Chronic	Inhibitory 1 Hz with intermittent 6 Hz priming, contralesional M1, 5 sessions	Single-arm	Performance time in single hand component of TEMPA	PLIC volume, Beck Depression Inventory score

(Continued)

TABLE 1 | Continued

References	*n*	Phase post-stroke	rTMS protocol	Study design	Primary outcome measures	Factors associated with rTMS response
Brodie et al. (33)	22	Chronic	Excitatory 5 Hz, ipsilesional S1, single session	Parallel-group (sham vs. rTMS), single-blind, pseudo-randomized	Response time of goal-directed visuo-motor serial targeting task	White matter volume of ipsilesional S1
Uhm et al. (34)	22	Chronic	Excitatory 10 Hz, ipsilesional M1, single session	Crossover (sham vs. subthreshold rTMS vs. suprathreshold rTMS), rater-blinded, randomized	Cortical excitability (MEP)	Val/Val *BDNF* genotype
Kindred et al. (35)	14	Chronic	Excitatory 10 Hz, ipsilesional M1 AND inhibitory 1 Hz, contralesional M1, 3 sessions	Crossover (sham vs. inhibitory rTMS vs. excitatory rTMS), double-blind, randomized	Cortical excitability (RMT, MEP), walking speed	Structural connectivity of CST via tractography
Yozbatiran et al. (36)	12	Chronic	Excitatory 20 Hz, ipsilesional M1, single session	Single-arm	FMA, Barthel Index, ARAT, hand grip strength, 9-hole peg test, motion range of index finger and wrist	Age
Diekhoff-Krebs et al. (37)	14	Chronic	iTBS, ipsilesional M1, single session	Crossover (sham vs. rTMS)	JTT, index finger tapping, hand grip strength	Extent of CST damage, inhibition level from ipsilesional M1, excitation level from ipsilesional SMA
Lai et al. (38)	72	Chronic	iTBS, ipsilesional M1, 10 sessions	Parallel-group (sham vs. rTMS), double-blind, randomized	WFMT, Functional Ability Scale, reaction time task, index finger tapping	BL residual hand function
Ameli et al. (39)	29	Subacute + chronic	Excitatory 10 Hz, ipsilesional M1, single session	Crossover (sham vs. rTMS)	Index finger tapping & hand tapping	Subcortical vs. cortical involvement, lesion extension, fMRI activity of lesioned region
Emara et al. (40)	60	Subacute + chronic	Excitatory 5 Hz, ipsilesional M1 OR inhibitory 1 Hz, contralesional M1, 10 sessions	Parallel-group (sham vs. contralesional rTMS vs. ipsilesional rTMS), randomized	Activity Index	Subcortical vs. cortical involvement, total anterior circulation stroke
Niimi et al. (41)	62	Subacute + chronic	Inhibitory 1 Hz, contralesional M1, 22 sessions	Parallel-group (sham vs. rTMS), non-randomized	FMA, WMFT	pro*BDNF* level at BL

rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta-burst stimulation; M1, primary motor cortex; S1, primary somatosensory cortex; aIPS, anterior intraparietal sulcus; dPMC, dorsal premotor cortex; PLIC, posterior limb of the internal capsule; SMA, supplementary motor area; CST, corticospinal tract; BDNF, brain-derived neurotrophic factor; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; MEP, motor-evoked potential; RMT, resting motor threshold; AMT, active motor threshold; FMA, Fugl-Meyer Assessment; BBT, Box and Block Test; WMFT, Wolf Motor Function Test; MESUPES, Motor Evaluation Scale for Upper Extremity in Stroke Patients; FIM, Functional Independence Measure; K-MBI, Korean version of the modified Barthel Index; mAS, modified Ashworth Scale; BRS, Brunnstrom Recovery Stage; TEMPA, upper extremity performance test for elderly; ARAT, Action Research Arm Test; JTT, Jebsen Taylor Hand Function Test; BL, baseline.

(31). Patients with low to high levels of baseline motor capacity showed significant motor improvement in the FMA after rTMS intervention, and no significant difference was found between patients with low or high baseline functioning (31).

Structural Imaging Factors

Subcortical vs. Cortical Lesion Location

The beneficial effect of rTMS for promoting motor recovery in stroke patients has been suggested to be associated with the specific lesion location (19, 39, 40). In general, stroke patients with purely subcortical lesions and a spared cortex tend to show greater beneficial effects of rTMS than stroke patients with additional cortical involvement (19, 39, 40).

In a recent study by Kim et al. (19) 10 sessions of inhibitory (1 Hz) rTMS over contralesional M1 had a beneficial effect on upper limb motor recovery in the BBT in stroke patients with purely subcortical lesions. A significant improvement on the Brunnstrom stage of the affected hand immediately after rTMS

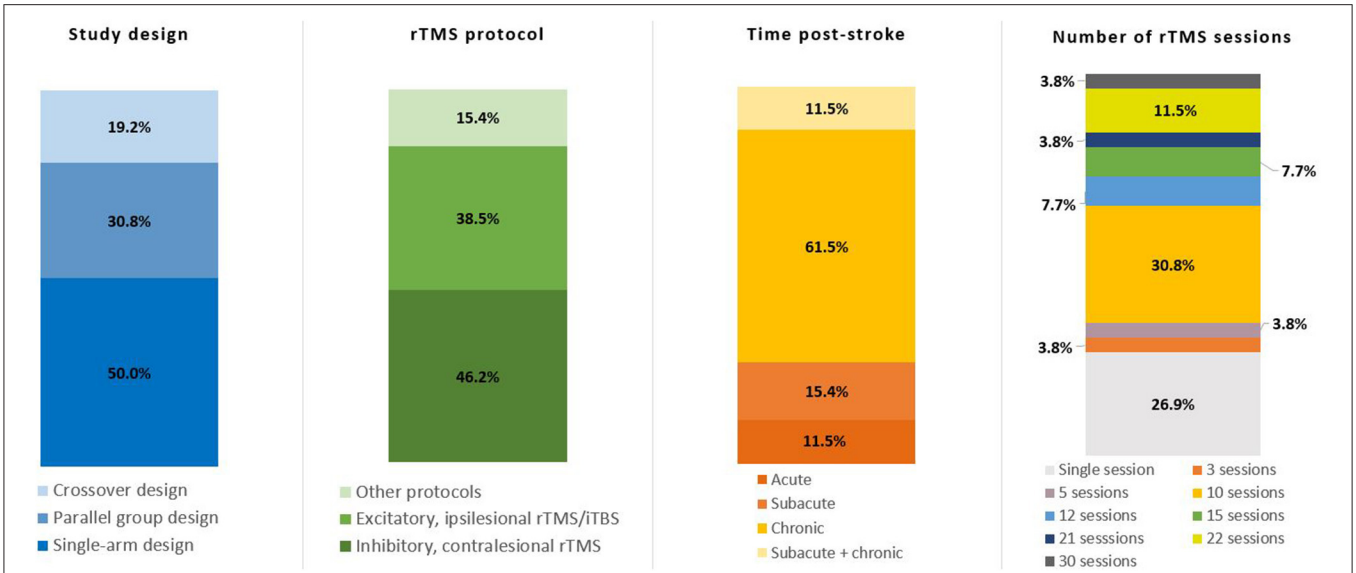


FIGURE 3 | Key details of included studies. Total number of studies $n = 26$. rTMS, repetitive transcranial magnetic stimulation; iTBS, intermittent theta burst stimulation.

intervention and at 1-month of follow-up were reported in the subgroup of subcortical stroke patients. In patients with additional cortical involvement, no beneficial effects of rTMS were seen (19).

In another study using a high-frequency rTMS protocol of 10 Hz over ipsilesional M1, beneficial rTMS-effects on frequency and amplitude of index finger tapping and hand tapping of the affected hand were seen in 14 of 16 purely subcortical stroke patients, while recovery was only seen in 7 of 13 patients with additional cortical involvement (39). In fact, a slight, non-significant dexterity deterioration of the affected hand was seen after rTMS intervention in the latter group (39).

Emara et al. (40) applied excitatory rTMS (5 Hz) over ipsilesional M1 and reported a beneficial rTMS effect on functional recovery, measured via the Activity Index, in subcortical, as well as cortical stroke patients. In the same study, a different set of patients received inhibitory 1 Hz rTMS over contralesional M1 and only patients with purely subcortical lesions showed a beneficial rTMS effect. Patients with cortical involvement did not respond to rTMS treatment. In this study, the authors distinguished between total anterior circulation stroke, partial anterior circulation stroke, posterior circulation stroke and lacunar stroke, rather than specifying the exact location of the lesion. Patients were categorized based on the presence or absence of cortical lesion involvement as assessed via MRI. The authors proposed that for the restoration of interhemispheric balance through contralesional rTMS, an intact ipsilesional cortex is a prerequisite, which is not given in stroke patients with cortical involvement (40). However, this proposition has to be considered carefully, as it is questionable whether the ipsilesional cortex of a patient with a stroke in a non-cortical area can truly be considered "intact," due to the effects of diaschisis (43).

All three studies examining the effect of lesion location on rTMS response have shown that rTMS seems to have a more beneficial effect in subcortical stroke patients than in patients with additional cortical involvement. However, none of the three studies adjusted their statistical analyses for lesion size. Future studies need to control for lesion size to rule out that the more beneficial rTMS effect in subcortical patients is not driven by an overall smaller lesion size in those patients compared to patients with cortical lesion extension.

Lesion Extension, Gray Matter, and White Matter

Several structural brain properties, such as lesion extension, cortical thickness, and white matter (WM) characteristics have been proposed to be associated with the degree of rTMS response in stroke patients with motor deficits (24, 32, 33, 39, 40).

A negative association between lesion extension and rTMS response was reported in a study applying excitatory rTMS over ipsilesional M1 (39). In that study, a larger lesion extension with involvement of cortical motor areas was related to poorer motor improvement after rTMS intervention, as measured via index finger and hand tapping. The influence of lesion extension on rTMS response was supported in another study reporting that patients with total anterior circulation stroke (i.e., a cortical stroke affecting brain areas supplied by the anterior branches of the middle as well as anterior cerebral artery resulting in a large lesion volume) showed a significantly lower level of motor recovery, measured using the Activity Index, after rTMS compared to patients with partial posterior middle cerebral artery stroke, posterior circulation stroke, and lacunar stroke (40).

Further, a positive correlation between cortical thickness of the postcentral and supramarginal gyrus of the affected hemisphere and improved motor recovery, assessed using the WMFT, after rTMS intervention was reported in a recent study

applying inhibitory 1 Hz rTMS over contralesional M1 (24). The lesioned hemisphere showed a significant thinner cortical thickness compared to the unaffected hemisphere. However, this association was only reported for cortical thickness but not for the overall GM volume.

After excitatory rTMS over the ipsilesional primary somatosensory cortex (S1), a positive correlation was observed between residual WM volume of the ipsilesional S1 and motor improvement of a goal-directed visuo-motor serial targeting task (33). No association was found between the degree of motor improvement and residual WM volume of ipsilesional M1, residual GM volume of ipsilesional S1 and residual GM volume of ipsilesional M1. In a combined linear regression model including age and GM volume, as well as WM volume of ipsilesional S1, 72% of the variance could be explained ($p = 0.042$), while no statistical significance was reached when excluding WM volume of ipsilesional S1 ($r^2 = 0.244$, $p = 0.376$) (33).

The association between WM preservation and motor recovery after rTMS was further investigated in a study using low-frequency (1 Hz) rTMS over contralesional M1. Each 1 Hz rTMS session was preceded by a session of 10 min of intermittent 6 Hz rTMS over the same motor hotspot (32). Priming the motor hotspot with 6 Hz stimulation was previously reported to accentuate the effects of low-frequency rTMS in healthy subjects (44). The authors found a positive association between the preserved volume of the ipsilesional posterior limb of the internal capsule (PLIC) and the level of rTMS response, as measured by performance time in a single-hand component of the TEMPA performance test. The preservation of other ipsilesional motor network regions [i.e., M1, S1, premotor cortex (PMC) and supplementary motor area (SMA)] was not associated with rTMS response (32). However, this study from Carey et al. (32) is the only one included in this review performing a priming prior to the rTMS session. Primed rTMS is a rarely used approach in the rTMS literature and its benefits over unprimed rTMS remain unclear.

Connectivity and Functional Imaging Factors

Corticospinal and Transcallosal Tract Integrity

Although stroke is classically described as causing neurological deficits by affecting localized, specific brain areas (45), a growing body of research demonstrates the importance of network effects resulting from disruption of communication between distant brain regions (46–48). Techniques such as diffusion weighted imaging (DWI) or diffusion tensor imaging (DTI), correlations between functional magnetic resonance imaging (fMRI) signals in different regions, and assessment of the amplitude and latency of motor-evoked potentials (MEPs) from TMS can be used to assess the structural and functional connectivity of different cortical and subcortical structures (48). Several studies applying those techniques have found that the integrity of corticospinal and transcallosal tracts are specifically associated with response to rTMS (16, 23, 26, 35, 37).

Corticospinal tract (CST) integrity appears to be a particularly important clinical marker for the ability to respond to rTMS intervention. In a study of chronic stroke patients, Kindred et al. (35) showed that higher baseline structural connectivity between M1 and the CST, measured as the sum of streamlines assessed by DTI, was positively associated with a greater decrease in MEP latency after a single session of inhibitory or excitatory rTMS. Similarly, Ueda et al. (26) demonstrated that certain DTI measures of CST integrity (mean and radial diffusivity) showed a positive correlation with motor improvement on the FMA and WMFT after 12 sessions of inhibitory 1 Hz rTMS over the contralesional M1, although no correlations were seen with other key measures, such as fractional anisotropy. A study using a single session of excitatory iTBS over ipsilesional M1 showed a significant negative correlation between the degree of CST damage and improvement of motor function in multiple measures (i.e., Jebsen-Taylor Hand Function Test [JTT], index finger tapping, hand grip) (37). CST damage was estimated based on the individual lesion intersection volume, relative to the total CST volume.

Baseline presence and strength of MEPs following TMS stimulation of the motor cortex, an electrophysiological measure that depends on CST integrity, has also been shown to be significantly associated with improvement of motor function after both excitatory iTBS and excitatory 10 Hz rTMS (21, 22, 38). Specifically, Chang et al. (21) found that patients who had an MEP response at baseline were 2.14 times as likely to have clinically meaningful motor improvement as assessed with the FMA ($p = 0.044$) after 10 Hz rTMS over ipsilesional M1 than patients with no MEP response. They did, however, not find an equivalent correlation between motor improvement and DTI measures of CST integrity (21), suggesting that physiological measures using single pulse TMS may be more sensitive than current anatomical imaging measures.

A positive linear relationship was reported between motor improvement (assessed with the FMA) after inhibitory 1 Hz rTMS over contralesional M1, and transcallosal fiber integrity between contralesional M1 and ipsilesional M1 (23). Higher fractional anisotropy values were associated with better motor recovery, highlighting the crucial role of interhemispheric communication for neural reorganization and motor recovery after stroke.

Diekhoff-Krebs et al. (37) combined several fMRI, TMS and clinical assessment parameters in a multivariate prediction model to assess which parameters allow the best prediction of motor improvement after a single session of excitatory iTBS over ipsilesional M1. They came to the conclusion that dynamic causal modeling (DCM) of endogenous connectivity parameters in a motor network, consisting of bihemispheric M1, PMC and SMA, and the clinical deficits assessed prior to stimulation with ARAT, allowed the best prediction of motor improvement after iTBS, explaining 82% of the variance ($p = 0.016$) (37). Those results indicate that brain connectivity parameters and initial motor function are stronger predictors for individual's motor recovery after iTBS than any TMS parameters, which did not further improve the prediction model (37). However, this model has

yet to be validated as a predictor of rTMS response in studies evaluating long-term recovery.

Other Functional Imaging Factors

Baseline activity of motor areas, individual connectivity patterns within the sensorimotor network prior to rTMS treatment, and hemispheric dominance have been associated with motor improvement after rTMS and can be measured via fMRI and functional near-infrared spectroscopy (fNIRS) (20, 25, 28, 37, 39).

Initial activity of ipsilesional M1 prior to rTMS intervention was positively correlated with motor improvement of index finger tapping after excitatory rTMS over that area (39). At baseline, patients that responded positively to rTMS showed widespread blood oxygen level dependent (BOLD) activation in the ipsilesional, as well as contralesional hemisphere during movements of the affected hand in a task-based fMRI design. The BOLD signal is a ratio between oxygenated and deoxygenated hemoglobin and is therefore a measure of neuronal metabolism that is highly correlated with and often used synonymously with neuronal activation (49). In contrast, patients that did not respond to rTMS showed weaker neural activity in both hemispheres, especially in ipsilesional M1, during hand movement (39). In another study, Diekhoff-Krebs et al. (37) reported that both stronger excitatory coupling between ipsilesional M1 and ipsilesional SMA and stronger inhibitory effects of ipsilesional M1 on contralesional M1 at baseline were associated with better motor recovery (measured using JTT, hand grip, and index finger tapping) following iTBS.

The individual activity of S1, PMC, and SMA prior to treatment was also associated with motor outcomes after rTMS. Patients with dominant neural activity of those motor areas of the unaffected hemisphere had significantly better motor recovery in the FMA, WMFT, and modified Ashworth Scale after inhibitory contralesional rTMS compared to patients with a dominant motor network activity in the lesioned hemisphere (28). Hemispheric dominance was assessed by calculating laterality indices based on changes in oxy-hemoglobin during a motor task-based fNIRS assessment. Consistent with previous fNIRS findings, a more recent fMRI study supports the more beneficial effect of inhibitory rTMS over contralesional M1 on the FMA, WMFT, and Brunnstrom stage in patients with dominant motor network activity in the unaffected hemisphere, in contrast to patients with dominant motor network activity in the lesioned hemisphere (25).

A stroke lesion in the hemisphere, representing the dominant hand of the subject, was associated with poor motor recovery in the sham condition as assessed by the WMFT, Motor Evaluation Scale for Upper Extremity in Stroke Patients (MESUPES), index finger tapping, and MEPs, but showed better motor recovery after rTMS, as reported in a study using inhibitory rTMS over contralesional M1 (20). In contrast, patients with a lesion in the hemisphere representing the non-dominant hand, showed equal motor recovery in the sham and the rTMS condition.

Genetic Factors

Brain-derived neurotrophic factor (*BDNF*) is a neurotrophic protein involved in a variety of key neurological processes, including memory consolidation and neuroplasticity (50). A relatively common single-nucleotide polymorphism (Val66Met) in the *BDNF* gene has been associated with decreased neuroplasticity in response to TMS and TBS. This *BDNF* gene polymorphism is thus a promising candidate for a negative clinical predictive factor (51). Indeed, MEP amplitudes in response to 10 Hz rTMS over ipsilesional M1 were higher in stroke patients homozygous for the Val-allele in contrast to heterozygous patients or patients homozygous for the Met-allele (34).

In a study of clinical motor improvement, Chang et al. (17) reported significantly greater improvement in upper limb motor function (FMA and BBT) at up to 2 months in Val/Val patients following 10 sessions of 10 Hz rTMS over ipsilesional M1 vs. those with at least one Met allele. Similarly, they reported in a separate study that patients with the Val/Val genotype were 1.8 times more likely ($p = 0.016$, odds ratio: 6.05, 95% confidence interval: 1.39–26.27) to show improved motor function using the FMA following 10 sessions of 10 Hz rTMS over ipsilesional M1 (21). Along the same lines, patients with low baseline serum levels of pro-*BDNF*, the precursor form of *BDNF*, were significantly more likely to respond to 1 Hz rTMS over contralesional M1 compared to patients with high levels of pro-*BDNF*, as measured by the FMA and WMFT. This was possibly due to having a greater proportion of activated *BDNF* (41).

However, Niimi et al. (41) found no effect of *BDNF* genotype on response to rTMS treatment in the FMA and WMFT in a study of contralesional 1 Hz rTMS. It thus appears that the efficacy of ipsilesional rTMS protocols is affected more by the Val66Met polymorphism.

Miscellaneous Factors

Several included studies investigated the effect of baseline functional status and comorbidities, showing negative correlations between rTMS efficacy in promoting motor recovery and the presence of aphasia, a lower Mini-Mental State Examination (MMSE) score (indicating lower function), and a higher score on the Beck Depression Inventory (indicating greater severity of comorbid depression) (22, 32).

DISCUSSION

The purpose of this review was to identify clinical, structural, and neurobiological factors in human subjects that may be associated with greater response to rTMS for stroke rehabilitation. Factors most consistently associated with rTMS response were biomarkers of structural and functional integrity of motor networks whereas the role of clinical, demographic and genetic factors is less certain (**Figure 4**). We discuss trends and conclusions we can draw from the current literature and how we can move further the state of knowledge, specifically how the identification of potential predictors could be accelerated by efficiently combining pre-clinical and clinical research efforts.

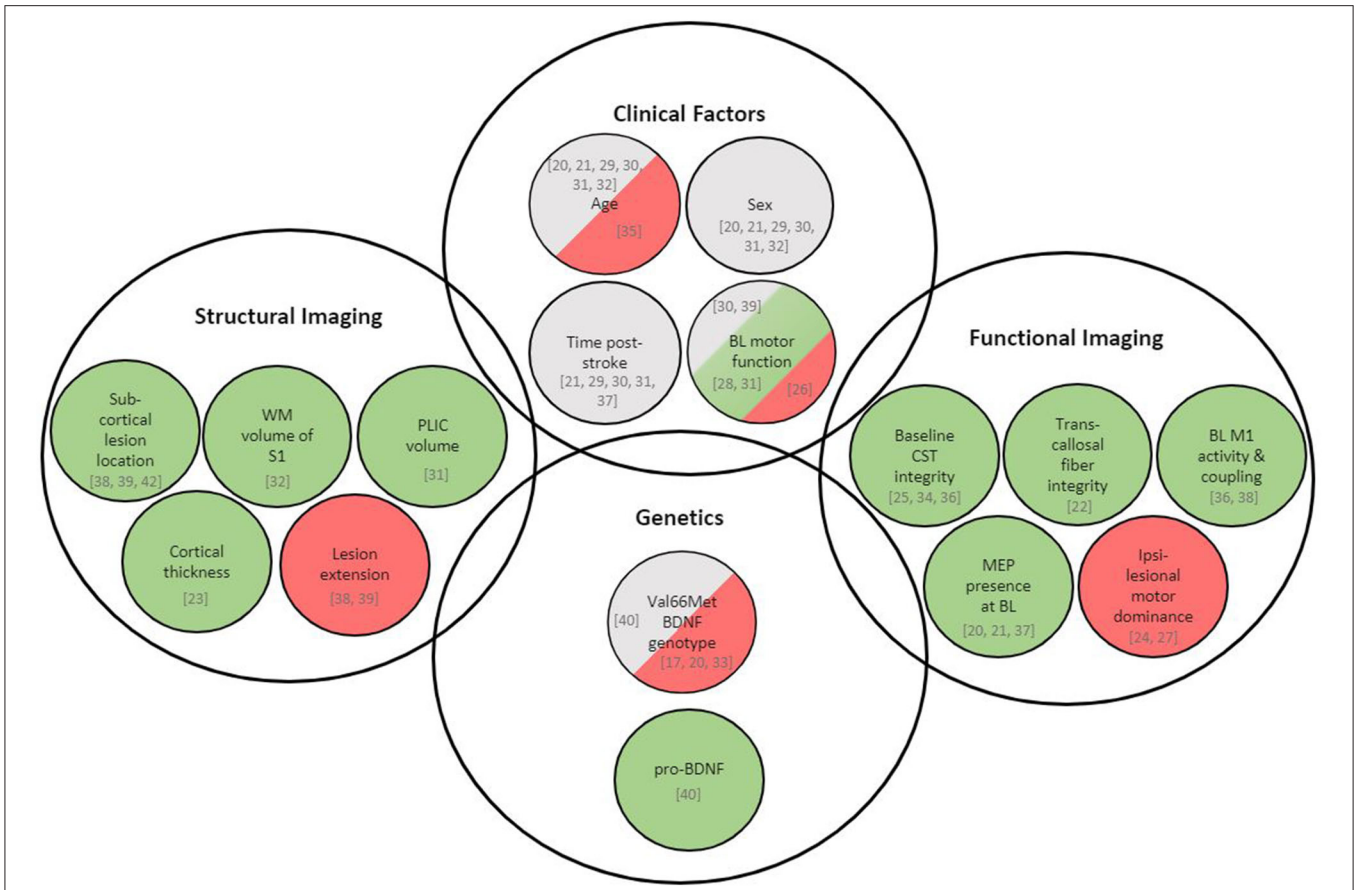


FIGURE 4 | Overview of variables associated with rTMS-induced recovery in stroke patients. Green represents variables being positively associated with rTMS response, red represents variables being negatively associated with rTMS response, and gray represents variables showing no association with rTMS response. Respective literature is specified in square brackets. *BDNF*, brain-derived neurotrophic factor; BOLD, blood oxygen level dependent; CST, corticospinal tract; MEP, motor-evoked potential; M1, primary motor cortex; PLIC, posterior limb of internal capsule; S1, primary somatosensory cortex; WM, white matter; BL, baseline.

Predictive Factors for rTMS Response

Clinical and Demographic Factors

It is well known that older age (≥65 years) and female sex increase the probability of severe deficits and poorer functional outcomes in stroke patients in general (52, 53). Whether and how these risk factors translate into a differential response to specific rehabilitation interventions in general and specifically to brain stimulation interventions remains unclear. The studies reviewed here report heterogeneous effects of age and no effect of sex on the response to TMS interventions. One study reports a positive association between increasing age and less recovery of motor function after rTMS (36). However, increasing age is generally associated with worse baseline motor impairment after stroke (54). Therefore, it needs to be further investigated whether the reported negative association between age and rTMS response remains significant after adjusting for baseline motor impairment. None of the reported studies were specifically designed or sufficiently powered to investigate the role of age and sex on rTMS response. Specifically designing future studies to directly examine potential effects of sex and age on rTMS response might reveal associations that may have been missed when including those parameters as covariates only.

Not only the effect of age and sex, but also the impact of baseline motor impairment remains uncertain based on the reviewed studies. While most studies performing contralesional inhibitory rTMS report better improvements in mild to moderately affected patients (29, 32, 40), such a relationship has not been established for other protocols. Two studies report no effect of baseline impairment or even report better improvement in more severely affected patients (27, 31). The impact of baseline motor impairments on the potential efficacy of rTMS treatment for stroke recovery is thus equivocal and it remains unclear if results may be related to evaluation tools sensitivity and ceiling effects.

Pre-clinical studies have provided clear evidence linking cortical lesion volume and location, behavioral recovery and reorganization in distant spared brain areas (55–57). After small lesions in the motor cortex that induce mild deficits, there is a decrease of cortical territory from which hand movements can be elicited in both the ipsi- and contralesional hemisphere. In contrast, more impaired animals with bigger lesions show larger

motor representations in the same areas. Thus, the role of spared motor areas, such as the contralesional M1, and consequently the effect on recovery of rTMS treatment targeting these motor areas, are very likely to vary based on lesion characteristics and impairments. In fact, when considering the impact of these factors on the physiological reorganization of spared motor areas in animal studies, one could predict that a given treatment (i.e., 1 Hz inhibitory protocol over the contralesional M1) should have opposite effects in mildly and severely affected patients. It has been shown for example that excitatory stimulation of the contralesional cortex in rats with corticospinal tract lesions favors anatomical rewiring and behavioral recovery (58). Excitatory stimulation of the contralesional hemisphere may thus be the preferred approach in cases where lesions largely or completely disconnect the ipsilesional hemisphere from the contralateral spinal cord.

Integrity of Motor Network

Several aspects of structural and functional motor network integrity appeared throughout the reviewed studies as areas in which further research may be able to identify robust predictive factors (**Figure 4**). Specifically, a relatively preserved ipsilesional M1 with its intra- and interhemispheric connectivity seems to be related to a favorable rTMS response. Stroke can lead to a disruption of neural signal transmission due to changes in axon diameter and changes in the myelination of white matter tracts (39). It has been hypothesized that this disruption of structural and functional connectivity may hinder the propagation of rTMS-modulated cortical activity from the site of stimulation throughout the motor network (39, 42, 59). A certain degree of preserved descending white matter projections, as well as functional motor network connectivity, may thus be needed for rTMS-induced changes in neural activity to manifest into improved motor behavior (39). The importance of white-matter integrity for recovery is also supported by pre-clinical data. In monkeys, the extent of recovery of hand and digit function correlates to both white and gray matter volume damage (60). However, recovery is slower after brain injuries that include frontal white matter in comparison to lesions of similar or even greater volumes, but restricted to gray matter (60). For the assessment of structural network integrity with respect to rTMS response, white matter markers thus appear to be more important than markers of gray matter. Not surprisingly, large lesions and the presence of extensive cortical damage limit the effect of TMS (as would be the case with any rehabilitation intervention). However, for less extensive or mainly subcortical lesions, measures of WM integrity such as WM volume of the CST, the internal capsule or transcallosal fibers seem to be better markers.

Transcallosal fiber integrity between contralesional M1 and ipsilesional M1 has a positive linear relationship with motor improvement, assessed via the FMA, after inhibitory 1 Hz rTMS over contralesional M1 (23). Fractional anisotropy (FA), a diffusion tensor imaging-based parameter reflecting the orientation of white matter fiber bundles by measuring water diffusivity, was used to examine microstructural damage of transcallosal motor fibers between ipsilesional and contralesional M1. Higher FA values were associated with better motor improvement after rTMS (23), reflecting a potential predictive role of the integrity of the corpus callosum in rTMS response. Several other studies have reported lower corpus callosum FA to be associated with poorer motor outcomes (61–65), highlighting the important role of transcallosal fiber integrity in motor recovery and interhemispheric reorganization post-stroke.

Future studies specifically targeting the predictive role of transcallosal fiber integrity in rTMS-elicited motor improvement are necessary. A systematic review from Bertolucci et al. (66) specifically looked at interhemispheric effects after stroke, assessed with TMS, and the relationship with motor recovery. The authors suggest that the modulation of transcallosal inhibition could be of benefit for stroke patients with good residual motor function and strong interhemispheric inhibition, but less for patients with poor residual motor function and weak interhemispheric inhibition (66). For assessment of transcallosal fiber integrity, two electrophysiological TMS approaches have been used: (a) the ipsilateral silent period (iSP) of single TMS pulses, in which a longer iSP duration and a higher iSP magnitude represent more transcallosal fiber damage, and (b) the TMS double pulse paradigm (66). The measurement of TMS-induced electrophysiological response with a combined TMS-EEG technique provides an alternative approach for assessing interhemispheric inhibition and transcallosal fiber damage (67).

Several of the identified studies in this review showed that patients with purely subcortical stroke were more likely to have a greater response to rTMS intervention than patients with cortical involvement. In cortical stroke, intracortical inhibition is suppressed (42, 68). Reduced inhibition in the ipsilesional hemisphere drives a downregulation of inhibitory activity in the contralesional hemisphere through axonal connections (69). The loss of intracortical inhibition is associated with enhanced excitatory activity in the immediate neighborhood of the cortical lesion (68). Those changes in inhibitory as well as excitatory mechanisms in the cortex might play a role in the inferior rTMS response in patients with cortical stroke compared to patients with subcortical stroke (19, 39). However, it needs to be taken into account that some rTMS studies report no significant association between lesion location and motor improvement after rTMS intervention in stroke patients (21, 30, 38).

These findings highlight that our current understanding of the effects of lesion location and volume on rTMS treatment efficacy is still quite limited. These interactions are likely to be very complex given the heterogeneity of lesion characteristics across patients. They might therefore benefit from pre-clinical studies that can better isolate and dissect the variables involved. As stated above, lesion location and volume affect the physiological reorganization in distant areas, within the ipsi- and contralesional motor network. Thus, perhaps the most reliable biomarkers of the effectiveness of rTMS approaches will be based on assessment of the functional state of spared areas in the motor network.

Only a few studies examined the predictive role of functional imaging on rTMS response. An association between stronger overall BOLD activation at baseline (39), as well as stronger intrahemispheric excitatory coupling between motor areas (37)

and rTMS response, have been reported in two studies using fMRI. An association between dominant neuronal activity in the unaffected in contrast to the lesioned hemisphere and rTMS response has been shown in an fNIRS study (28) and was confirmed in another fMRI study (25). The number of studies using functional neuroimaging techniques such as fMRI and fNIRS for rTMS response prediction is limited and more studies are needed in order to draw solid conclusions from these findings.

Three studies reported that stroke patients with the presence of motor-evoked potentials (MEPs) of the paretic *first dorsal interosseous* muscle (FDI) (21, 38) or the *abductor pollicis brevis* muscle (APB) (22) after single-pulse TMS at baseline are more likely to have clinically meaningful motor improvement after rTMS intervention than patients with no initial MEP response. The presence or absence of MEPs informs about the functional integrity as well as cortical excitability of the motor network and the cerebrospinal tract (21, 22, 38).

BDNF and Synaptic Plasticity

The only genetic factor for rTMS response investigated was the presence of the Val66Met *BDNF* polymorphism, which was shown in several studies to be negatively associated with motor response to excitatory ipsilesional rTMS (17, 21, 34). Given the known role of *BDNF* in brain plasticity (50) and the theorized importance of modifying synaptic connections in the rTMS-aided recovery process from stroke (70), it is reasonable that a loss-of-function mutation in this gene would be associated with a smaller response to the treatment. This concept is strengthened by the evidence that a greater proportion of activated *BDNF* in the circulation seems to be associated with greater response to rTMS (17, 21).

This association between *BDNF* genotype and rTMS response has however not been confirmed in a separate study utilizing inhibitory contralesional rTMS (41). Some evidence from pre-clinical studies in rats seems to suggest that non-invasive brain stimulation may directly increase the expression of *BDNF*, facilitate neurogenesis (71) and enhance *BDNF* affinity for tyrosine receptor kinase B (TrkB), a neurotrophin receptor (72). This would result in a direct modulation of synaptic plasticity mediated by *BDNF*-TrkB-NDMA receptors (73). Such mechanisms may be of greater relevance in the perilesional cortex, but much less so in the contralesional unaffected cortex. If so, they would provide a pathophysiological rational for a possible link between the stimulation protocol and the specific genotype effect. Further research will be needed to ascertain if this association between genotype and rTMS protocol is valid and TMS studies in animal models may be a more efficient way to reliably demonstrate this specific interaction than clinical trials.

Stand-Alone vs. Combined rTMS Approach

The majority of studies included in this review ($n = 19/26$) used some form behavioral intervention in addition to rTMS. Standardized physical or occupational therapy was used in 13 studies (19, 21, 24–31, 38, 40, 41) and 6 studies combined rTMS with task-specific training (e.g., index finger tapping practice, visuomotor serial targeting task) (16, 20, 32, 33, 35, 39). Only 7 studies used rTMS as stand-alone therapy without any additional behavioral intention (17, 18, 22, 23, 34, 36, 37). Up to date, no study directly investigated, if the value of potential predictive factors for rTMS response differs depending on whether rTMS is used in a stand-alone or a combined approach.

Basic neuroimaging studies on the effect of non-invasive brain stimulation on cerebral activity seem to suggest that a modulatory effect of non-invasive brain stimulation on cerebral activity is caused by the interaction of stimulation and physiological recruitment of cortical neuronal activity. In a previous neuroimaging study of the motor system, it has been shown that tDCS stimulation alone has no effect on cortical activity but inhibitory or excitatory modulation was demonstrated in healthy subjects while simultaneously performing a motor task (74). Similar physiological neuromodulatory effects have also been reported for the language system, where a change in cerebral blood flow as surrogate marker of cortical activity was only observed as interaction between rTMS and a verb generation task, but not when applying rTMS alone (75).

Based on those findings, it is reasonable to assume that the potential predictive factors reported in this review apply more to rTMS used in a combined approach than rTMS as a stand-alone intervention. Since the literature evidence for rTMS as stand-alone therapy is inconclusive, it has been recommended for future studies to combine rTMS with some form of standardized therapy given to sham as well as intervention groups to minimize variability arising from non-standardized forms and doses of therapy and clearly isolate the add-on effect of brain stimulation (12).

Limitations of Existing Data

Only a few large, controlled studies that investigate predictive factors for rTMS response in stroke patients with motor deficits currently exist. More than half (14/26) of the included studies had a small sample size ($n \leq 30$), and more than 60% (16/26) of studies had no sham control condition. Only three of the included studies were randomized controlled trials with an adequate control group. Difficulties with patient recruitment, feasibility, and financial resources make carrying out these studies difficult. The lack of large, controlled trials limits the conclusions that can be drawn from the data, especially with the heterogeneity of study design and large variability in methodology.

rTMS protocols used in the included studies varied regarding stimulation frequency and intensity, targeted brain region, stimulated hemisphere, and number of therapeutic sessions (ranging between 1 and 30). All these factors are known to affect the extent of cortical excitation, and presumably underlying molecular mechanisms (76–78). Besides heterogeneous study protocols and designs, the inclusion and exclusion criteria for patient selection also varied between studies. Some studies excluded patients with aphasia, cognitive impairment, comorbidities, or ongoing medication usage, while in others these patients were included. While pre-clinical studies examining these factors are sparse, they can have effects on rTMS protocol efficacy. For example, the cognitive state of aged rats prior to the

rTMS protocol was shown to affect the impact of the treatment on behavioral performance (79).

Additionally, outcome measures and timing of assessment varied greatly between studies. While some studies measured motor activity immediately after a single rTMS session, others measured motor improvement after finishing the whole set of rTMS sessions. Five studies investigated long-term effects of rTMS by assessing the recovery status at 1 up to 4 follow-up appointments, between 1 week up to 6 months after rTMS treatment (20, 22, 23, 36, 40). However, time interval between rTMS intervention and follow-up session, motor outcome measures as well as statistical tests in data analyses strongly varied. All these factors can be considered as potential biases. Most studies used clinical assessment tools for evaluation of motor function. However, other studies used change in cortical excitability through resting motor threshold (RMT), MEP and active motor threshold (AMT) as surrogate for motor function. Clinical assessment of motor function included among others the FMA, WMFT, BBT, Barthel Index, index finger tapping frequency, maximal grip force, and reaction time tasks. However, it should be noted that the majority of these tests measure the degree of motor impairment. Only four studies (22, 36, 38, 40) used evaluations of restriction in activities and participation, which is often a more relevant measure for a patient's daily functioning (80). Future studies should use measures of both motor impairment and evaluations of restriction in activities and participation in daily life, in order to better quantify the benefit of rTMS intervention for patients. In particular, they should include standardized measures of sensorimotor recovery after stroke (81).

It should also be noted that 25/26 included studies examined upper limb motor function, while only a single study assessed gait and lower limb function (35). The lack of studies assessing the effect of rTMS on lower limb performance post-stroke needs to be addressed in future studies.

Finally, in some of the included studies, rTMS was used as the sole intervention (17, 18, 22, 23, 34, 36, 37) without concurrent physiotherapy, occupational therapy or specific task-based training. In animals, treatments that promote plasticity and recovery after central nervous system injuries are typically more effective when combined with rehabilitation (82). All of these widely differing design parameters across the studies make it difficult to directly compare findings and interpret the results as a unified whole.

This review includes two retrospective studies with a large stroke patient population of $n = 1{,}254$ (27) and $n = 1{,}716$ (31). However, both studies were conducted in the same research group and included patients from the same data pool, receiving inhibitory 1 Hz rTMS over contralesional M1. When investigating differences in potential predictive factors between different rTMS protocols, it has to be taken into account that the two above-mentioned studies account for nearly 75% of the total patient population included in this review, leading to an over-representation of the inhibitory contralesional rTMS protocol and the potential repetition of data.

Over half of the included studies in this review (14/26) were conducted by research groups in Japan and South Korea, demonstrating the leading contributions of these nations in rTMS research. As only studies in English, French, or German were considered for inclusion in this review, relevant studies published in other languages may have been missed.

Finally, it must be stated that it was not the purpose of this paper to provide a comprehensive and systematic review of all possible predictive factors, but rather to identify factors that may be good candidates to be further explored in targeted studies. As such the scope of the review was limited to only one database.

Future Perspectives

The high variability in study design and rTMS parameters between studies reveals the importance of standardization and homogenization of rTMS trials in the future. Findings can only be compared properly if study design and rTMS parameters, such as stimulation intensity and frequency, number of sessions, targeted brain area and hemisphere, and outcome measures are consistent between studies. To ensure such standardization, the design of future rTMS trials in stroke patients with motor deficits should be informed by expert consensus such as the *CanStim consensus recommendations for rTMS in upper extremity motor stroke rehabilitation trials* (12) regarding patient population, rehabilitation interventions, outcome measures, and stimulation parameters.

Similar expert recommendations are available e.g., for the use of kinematic and kinetic movement quantification tools as well as qualitative measures of motor performance of the upper limb as developed by the Second *Stroke Recovery and Rehabilitation Roundtable* (83).

This review has revealed several knowledge gaps that should be addressed in future clinical trials. *BDNF* genotype has been shown to be associated with motor recovery after excitatory ipsilesional rTMS, but not after inhibitory contralesional rTMS. Future clinical trials need to address the differential response to these two procedures in patients with *BDNF* polymorphism and reveal potential associations between applied rTMS protocol and *BDNF* genotype.

As the majority of stroke patients included in this review were in the chronic phase (73%, **Figure 3**), more studies in acute and subacute stroke patients are needed to further investigate predictive factors for rTMS response on recovery in those earlier stages post-stroke, specifically since stroke rehabilitation in most health care systems is provided during these early phases. Moreover, in the majority of patients in this review, the effect of rTMS on recovery was assessed immediately after finishing all intervention sessions. Follow-up assessment of motor function was only performed across a few trials. Future trials should ensure that patients are monitored longitudinally to potentially identify associations between predictive clinical and imaging baseline factors and longitudinal motor outcomes.

Finally, perhaps the most disconcerting realization at this stage of implementation is the apparent lack of understanding of the mechanisms through which rTMS protocols can increase recovery after stroke. We believe that it is likely that pre-clinical research may be the most needed and useful to answer these

questions. For example, it was recently shown that high-frequency rTMS can reduce apoptotic cell death and promote neuronal sprouting of cortical projections in mice after stroke (84). Using invasive methods, animal models can also inform about the effects of rTMS on the neural network activity and how these effects may vary following different types of strokes. These efforts will need to include models that reflect the complexity of the human sensorimotor cortical network (85, 86). Treatment parameters and selection criteria for human trials could thus be based on the directly measured effects of rTMS on the brain in suitable pre-clinical models rather than behavioral outcomes derived from clinical observations. In our view, such a systematic approach, could accelerate the translation process and make it more efficient because only such selection criteria are subject to clinical evaluation which are based on valid pathophysiological mechanisms with documented rTMS effects on the brain.

While it is unlikely that a single parameter will be sufficient to separate stroke patients likely to benefit from rTMS intervention from patients likely not to show rTMS response, the ultimate goal would be the development of a multivariate predictive model for rTMS response in stroke patients with motor deficits in order to optimize patient selection for specific rTMS interventions. By combining multiple predictive factors that may individually have low-to-moderate predictive ability, a more complete individual prediction model for rTMS response can be developed. The multivariate models developed by Diekhoff-Krebs et al. (37) for behavioral iTBS response combined endogenous connectivity parameters and clinical deficits at baseline and explained 82% of variance. Further development of such models, including other potential predictive factors identified in this review could enable a scoring system to be developed and validated for likelihood of response to rTMS, facilitating patient selection for clinical trial purposes.

However, it also needs to be considered that imaging techniques such as DWI/DTI, fMRI, and fNIRS are time-consuming and expensive procedures and thus difficult to implement in clinical settings. To be clinically useful, potential predictive factors should be easily determinable, preferably through routine structural imaging or blood lab tests.

A first attempt for a potential algorithm could be more general predictive scores for stroke recovery, such as the Predict Recovery Potential 2 (PREP2). This algorithm has a relatively good predictive accuracy (>70%), and can be calculated with clinical measures such as Shoulder Abduction and Finger Extension (SAFE) score and NIHHS score combined with TMS MEP measurements, thus allowing for calculation even when MRI or more complex imaging techniques are unavailable (87). Exploring the ability of modified versions of such algorithms to predict response to rTMS specifically may be another direction for further research.

CONCLUSION

This review evaluated evidence for demographic, clinical, and neurobiological factors to distinguish stroke patients with motor deficits who are more likely to respond to rTMS intervention. Purely subcortical lesions, factors associated with an at least partially preserved ipsilesional motor network (undamaged M1, proper intra- and interhemispheric integrity of M1, well-preserved WM volume under the site of stimulation, and PLIC volume), as well as cortical thickness, motor network dominance in the unaffected hemisphere, and the absence of the Val66Met *BDNF* polymorphism are promising predictive factors. Based on the high variability in rTMS protocol and experimental design between studies, these findings need to be further investigated and confirmed in future research.

AUTHOR CONTRIBUTIONS

FH, JA, and AS contributed to the literature search. FH and AS contributed to drafting the manuscript, figures, and tables. A-UD-V and ND provided the portions of the manuscript regarding pre-clinical and animal data. AT, JE, and ND contributed to the concept of the review. AT supervised the project. All authors contributed to the revision and approval of the manuscript.

FUNDING

This work was supported by the Canadian Partnership for Stroke Recovery and a Platform Support Grant of the Brain Canada Foundation. A-UD-V was supported by a postdoctoral fellowship from CONACYT, Mexico (CVU-330898).

ACKNOWLEDGMENTS

We thank Edward Bein, PhD, for aid in statistical interpretation of several studies.

REFERENCES

1. George MS, Wassermann EM, Post RM. Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *J Neuropsychiatry Clin Neurosci.* (1996) 8:373–82. doi: 10.1176/jnp.8.4.373
2. Gates JR. Transcranial magnetic stimulation. *Neuroimaging Clin N Am.* (1995) 5:711–20.
3. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? *Nat Rev Neurosci.* (2007) 8:559–67. doi: 10.1038/nrn2169
4. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron.* (2005) 45:201–6. doi: 10.1016/j.neuron.2004.12.033
5. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert guidelines. *Clin Neurophysiol.* (2021) 132:269–306. doi: 10.1016/j.clinph.2020.10.003
6. Chail A, Saini RK, Bhat PS, Srivastava K, Chauhan V. Transcranial magnetic stimulation: a review of its evolution and current applications. *Ind Psychiatry J.* (2018) 27:172–80. doi: 10.4103/ipj.ipj_88_18

7. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract.* (2020) 2:17. doi: 10.1186/s42466-020-00060-6
8. Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. *Neuroimage.* (2010) 50:233–42. doi: 10.1016/j.neuroimage.2009.12.029
9. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol.* (2004) 55:400–9. doi: 10.1002/ana.10848
10. Takeuchi N, Izumi S. Maladaptive plasticity for motor recovery after stroke: mechanisms and approaches. *Neural Plast.* (2012) 2012:359728. doi: 10.1155/2012/359728
11. Volz LJ, Vollmer M, Michely J, Fink GR, Rothwell JC, Grefkes C. Time-dependent functional role of the contralesional motor cortex after stroke. *Neuroimage Clin.* (2017) 16:165–74. doi: 10.1016/j.nicl.2017.07.024
12. Edwards JD, Black SE, Boe S, Boyd L, Chaves A, Chen R, et al. Canadian platform for trials in noninvasive brain stimulation (CanStim) consensus recommendations for repetitive transcranial magnetic stimulation in upper extremity motor stroke rehabilitation trials. *Neurorehabil Neural Repair.* (2021) 35:103–16. doi: 10.1177/1545968320981960
13. Xiang H, Sun J, Tang X, Zeng K, Wu X. The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. *Clin Rehabil.* (2019) 33:847–64. doi: 10.1177/0269215519829897
14. Zhang L, Xing G, Fan Y, Guo Z, Chen H, Mu Q. Short- and long-term effects of repetitive transcranial magnetic stimulation on upper limb motor function after stroke: a systematic review and meta-analysis. *Clin Rehabil.* (2017) 31:1137–53. doi: 10.1177/0269215517692386
15. O'Brien AT, Bertolucci F, Torrealba-Acosta G, Huerta R, Fregni F, Thibaut A. Non-invasive brain stimulation for fine motor improvement after stroke: a meta-analysis. *Eur J Neurol.* (2018) 25:1017–26. doi: 10.1111/ene.13643
16. Hensel L, Tscherpel C, Freytag J, Ritter S, Rehme AK, Volz LJ, et al. Connectivity-related roles of contralesional brain regions for motor performance early after stroke. *Cereb Cortex.* (2021) 31:993–1007. doi: 10.1093/cercor/bhaa270
17. Chang WH, Bang OY, Shin YI, Lee A, Pascual-Leone A, Kim YH, et al. polymorphism and differential rTMS effects on motor recovery of stroke patients. *Brain Stimul.* (2014) 7:553–8. doi: 10.1016/j.brs.2014.03.008
18. Di Lazzaro V, Pellegrino G, Di Pino G, Corbetto M, Ranieri F, Brunelli N, et al. Val66Met BDNF gene polymorphism influences human motor cortex plasticity in acute stroke. *Brain Stimul.* (2015) 8:92–6. doi: 10.1016/j.brs.2014.08.006
19. Kim WS, Kwon BS, Seo HG, Park J, Paik NJ. Low-frequency repetitive transcranial magnetic stimulation over contralesional motor cortex for motor recovery in subacute ischemic stroke: a randomized sham-controlled trial. *Neurorehabil Neural Repair.* (2020) 34:856–67. doi: 10.1177/1545968320948610
20. Ludemann-Podubecka J, Bosl K, Theilig S, Wiederer R, Nowak DA. The effectiveness of 1 Hz rTMS over the primary motor area of the unaffected hemisphere to improve hand function after stroke depends on hemispheric dominance. *Brain Stimul.* (2015) 8:823–30. doi: 10.1016/j.brs.2015.02.004
21. Chang WH, Uhm KE, Shin YI, Pascual-Leone A, Kim YH. Factors influencing the response to high-frequency repetitive transcranial magnetic stimulation in patients with subacute stroke. *Restor Neurol Neurosci.* (2016) 34:747–55. doi: 10.3233/RNN-150634
22. Lee JH, Kim SB, Lee KW, Kim MA, Lee SJ, Choi SJ. Factors associated with upper extremity motor recovery after repetitive transcranial magnetic stimulation in stroke patients. *Ann Rehabil Med.* (2015) 39:268–76. doi: 10.5535/arm.2015.39.2.268
23. Demirtas-Tatlidede A, Alonso-Alonso M, Shetty RP, Ronen I, Pascual-Leone A, Fregni F. Long-term effects of contralesional rTMS in severe stroke: safety, cortical excitability, and relationship with transcallosal motor fibers. *NeuroRehabilitation.* (2015) 36:51–9. doi: 10.3233/NRE-141191
24. Ueda R, Yamada N, Abo M, Senoo A. Correlation analysis of motor function improvement and brain structure for upper limb paralysis. *Neuroreport.* (2019) 30:77–81. doi: 10.1097/WNR.0000000000001160
25. Ueda R, Yamada N, Abo M, Ruwan PW, Senoo A. MRI evaluation of motor function recovery by rTMS and intensive occupational therapy and changes in the activity of motor cortex. *Int J Neurosci.* (2019) 130:309–17. doi: 10.1080/00207454.2019.1680553
26. Ueda R, Yamada N, Abo M, Senoo A. White matter changes follow low-frequency repetitive transcranial magnetic stimulation plus intensive occupational therapy for motor paralysis after stroke: a DTI study using TBSS. *Acta Neurol Belg.* (2021) 121:387–96. doi: 10.1007/s13760-019-01150-2
27. Hamaguchi T, Yamada N, Hada T, Abo M. Prediction of motor recovery in the upper extremity for repetitive transcranial magnetic stimulation and occupational therapy goal setting in patients with chronic stroke: a retrospective analysis of prospectively collected data. *Front Neurol.* (2020) 11:581186. doi: 10.3389/fneur.2020.581186
28. Tamashiro H, Kinoshita S, Okamoto T, Urushidani N, Abo M. Effect of baseline brain activity on response to low-frequency rTMS/intensive occupational therapy in poststroke patients with upper limb hemiparesis: a near-infrared spectroscopy study. *Int J Neurosci.* (2019) 129:337–43. doi: 10.1080/00207454.2018.1536053
29. Kakuda W, Abo M, Kobayashi K, Takagishi T, Momosaki R, Yokoi A, et al. Baseline severity of upper limb hemiparesis influences the outcome of low-frequency rTMS combined with intensive occupational therapy in patients who have had a stroke. PM R. (2011) 3:516–22. doi: 10.1016/j.pmrj.2011.02.015
30. Kakuda W, Abo M, Shimizu M, Sasanuma J, Okamoto T, Yokoi A, et al. A multi-center study on low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis in post-stroke patients. *J Neuroeng Rehabil.* (2012) 9:4. doi: 10.1186/1743-0003-9-4
31. Tatsuno H, Hamaguchi T, Sasanuma J, Kakita K, Okamoto T, Shimizu M, et al. Does a combination treatment of repetitive transcranial magnetic stimulation and occupational therapy improve upper limb muscle paralysis equally in patients with chronic stroke caused by cerebral hemorrhage and infarction?: a retrospective cohort study. *Medicine.* (2021) 100:e26339. doi: 10.1097/MD.0000000000026339
32. Carey JR, Deng H, Gillick BT, Cassidy JM, Anderson DC, Zhang L, et al. Serial treatments of primed low-frequency rTMS in stroke: characteristics of responders vs. *nonresponders Restor Neurol Neurosci.* (2014) 32:323–35. doi: 10.3233/RNN-130358
33. Brodie SM, Borich MR, Boyd LA. Impact of 5-Hz rTMS over the primary sensory cortex is related to white matter volume in individuals with chronic stroke. *Eur J Neurosci.* (2014) 40:3405–12. doi: 10.1111/ejn.12717
34. Uhm KE, Kim YH, Yoon KJ, Hwang JM, Chang WH. BDNF genotype influence the efficacy of rTMS in stroke patients. *Neurosci Lett.* (2015) 594:117–21. doi: 10.1016/j.neulet.2015.03.053
35. Kindred JH, Wonsetler EC, Charalambous CC, Srivastava S, Marebwa BK, Bonilha L, et al. Individualized responses to ipsilesional high-frequency and contralesional low-frequency rTMS in chronic stroke: a pilot study to support the individualization of neuromodulation for rehabilitation. *Front Hum Neurosci.* (2020) 14:578127. doi: 10.3389/fnhum.2020.578127
36. Yozbatiran N, Alonso-Alonso M, See J, Demirtas-Tatlidede A, Luu D, Motiwala RR, et al. Safety and behavioral effects of high-frequency repetitive transcranial magnetic stimulation in stroke. *Stroke.* (2009) 40:309–12. doi: 10.1161/STROKEAHA.108.522144
37. Diekhoff-Krebs S, Pool EM, Sarfeld AS, Rehme AK, Eickhoff SB, Fink GR, et al. Interindividual differences in motor network connectivity and behavioral response to iTBS in stroke patients. *Neuroimage Clin.* (2017) 15:559–71. doi: 10.1016/j.nicl.2017.06.006
38. Lai CJ, Wang CP, Tsai PY, Chan RC, Lin SH, Lin FG, et al. Corticospinal integrity and motor impairment predict outcomes after excitatory repetitive transcranial magnetic stimulation: a preliminary study. *Arch Phys Med Rehabil.* (2015) 96:69–75. doi: 10.1016/j.apmr.2014.08.014
39. Ameli M, Grefkes C, Kemper F, Riegg FP, Rehme AK, Karbe H, et al. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol.* (2009) 66:298–309. doi: 10.1002/ana.21725

40. Emara T, El Nahas N, Elkader HA, Ashour S, El Etrebi A. MRI can Predict the Response to Therapeutic Repetitive Transcranial Magnetic Stimulation (rTMS) in Stroke Patients. *J Vasc Interv Neurol.* (2009) 2:163–8.
41. Niimi M, Hashimoto K, Kakuda W, Miyano S, Momosaki R, Ishima T, et al. Role of brain-derived neurotrophic factor in beneficial effects of repetitive transcranial magnetic stimulation for upper limb hemiparesis after stroke. *PLoS ONE.* (2016) 11:e0152241. doi: 10.1371/journal.pone.0152241
42. Kim JY, Boudier-Reveret M, Chang M. Can repetitive transcranial magnetic stimulation enhance motor outcomes in cerebral infarct patients? *J Integr Neurosci.* (2020) 19:119–23. doi: 10.31083/j.jin.2020.01.20
43. Ko SB, Yoon BW. Mechanisms of functional recovery after stroke. *Front Neurol Neurosci.* (2013) 32:1–8. doi: 10.1159/000346405
44. Iyer MB, Schleper N, Wassermann EN. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *J Neurosci.* (2003) 23:10867–72. doi: 10.1523/JNEUROSCI.23-34-10867.2003
45. Broca P. Remarks on the seat of the faculty of articulated language, following an observation of aphemia (loss of speech). *Bulletin de la Société Anatomique.* (1861) 6:330–57.
46. Carrera E, Tononi G. Diaschisis: past, present, future. *Brain.* (2014) 137:2408–22. doi: 10.1093/brain/awu101
47. Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. *Hum Brain Mapp.* (2008) 29:802–9. doi: 10.1002/hbm.20579
48. Guggisberg AG, Koch PJ, Hummel FC, Buetefisch CM. Brain networks and their relevance for stroke rehabilitation. *Clin Neurophysiol.* (2019) 130:1098–124. doi: 10.1016/j.clinph.2019.04.004
49. Golkowski D, Ranft A, Kiel T, Riedl V, Kohl P, Rohrer G, et al. Coherence of BOLD signal and electrical activity in the human brain during deep sevoflurane anesthesia. *Brain Behav.* (2017) 7:e00679. doi: 10.1002/brb3.679
50. Aicardi G, Argilli E, Cappello S, Santi S, Riccio M, Thoenen H, et al. Induction of long-term potentiation and depression is reflected by corresponding changes in secretion of endogenous brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A.* (2004) 101:15788–92. doi: 10.1073/pnas.0406960101
51. Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J Physiol.* (2008) 586:5717–25. doi: 10.1113/jphysiol.2008.159905
52. Bushnell CD, Reeves MJ, Zhao X, Pan W, Prvu-Bettger J, Zimmer L, et al. Sex differences in quality of life after ischemic stroke. *Neurology.* (2014) 82:922–31. doi: 10.1212/WNL.0000000000000208
53. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. Stroke. (2003) 34:122–6. doi: 10.1161/01.str.0000047852.05842.3c
54. Roy-O'Reilly M, McCullough LD. Age and sex are critical factors in ischemic stroke pathology. *Endocrinology.* (2018) 159:3120–31. doi: 10.1210/en.2018-00465
55. Dancause N, Barbay S, Frost SB, Zoubina EV, Plautz EJ, Mahnken JD, et al. Effects of small ischemic lesions in the primary motor cortex on neurophysiological organization in ventral premotor cortex. *J Neurophysiol.* (2006) 96:3506–11. doi: 10.1152/jn.00792.2006
56. Jeffers MS, Touvykine B, Ripley A, Lahey G, Carter A, Dancause N, et al. Poststroke impairment and recovery are predicted by task-specific regionalization of injury. *J Neurosci.* (2020) 40:6082–97. doi: 10.1523/JNEUROSCI.0057-20.2020
57. Touvykine B, Mansoori BK, Jean-Charles L, Deffeyes J, Quessy S, Dancause N. The effect of lesion size on the organization of the ipsilesional and contralesional motor cortex. *Neurorehabil Neural Repair.* (2016) 30:280–92. doi: 10.1177/1545968315585356
58. Carmel JB, Berrol LJ, Brus-Ramer M, Martin JH. Chronic electrical stimulation of the intact corticospinal system after unilateral injury restores skilled locomotor control and promotes spinal axon outgrowth. *J Neurosci.* (2010) 30:10918–26. doi: 10.1523/JNEUROSCI.1435-10.2010
59. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. *Neuroimage.* (2003) 20:1685–96. doi: 10.1016/j.neuroimage.2003.07.028
60. Darling WG, Pizzimenti MA, Rotella DL, Peterson CR, Hynes SM, Ge J, et al. Volumetric effects of motor cortex injury on recovery of dexterous movements. *Exp Neurol.* (2009) 220:90–108. doi: 10.1016/j.expneurol.2009.07.034
61. Wang LE, Tittgemeyer M, Imperati D, Diekhoff S, Ameli M, Fink GR, et al. Degeneration of corpus callosum and recovery of motor function after stroke: a multimodal magnetic resonance imaging study. *Hum Brain Mapp.* (2012) 33:2941–56. doi: 10.1002/hbm.21417
62. Lench DH, Hutchinson S, Woodbury ML, Hanlon CA. Kinematic measures of bimanual performance are associated with callosum white matter change in people with chronic stroke. *Arch Rehabil Res Clin Transl.* (2020) 2:100075. doi: 10.1016/j.arrct.2020.100075
63. Stewart JC, Dewanjee P, Tran G, Quinlan EB, Dodakian L, McKenzie A, et al. Role of corpus callosum integrity in arm function differs based on motor severity after stroke. *Neuroimage Clin.* (2017) 14:641–7. doi: 10.1016/j.nicl.2017.02.023
64. Stewart JC, O'Donnell M, Handlery K, Winstein CJ. Skilled reach performance correlates with corpus callosum structural integrity in individuals with mild motor impairment after stroke: a preliminary investigation. *Neurorehabil Neural Repair.* (2017) 31:657–65. doi: 10.1177/1545968317712467
65. Li Y, Wu P, Liang F, Huang W. The microstructural status of the corpus callosum is associated with the degree of motor function and neurological deficit in stroke patients. *PLoS ONE.* (2015) 10:e0122615. doi: 10.1371/journal.pone.0122615
66. Bertolucci F, Chisari C, Fregni F. The potential dual role of transcallosal inhibition in post-stroke motor recovery. *Restor Neurol Neurosci.* (2018) 36:83–97. doi: 10.3233/RNN-170778
67. Borich MR, Wheaton LA, Brodie SM, Lakhani B, Boyd LA. Evaluating interhemispheric cortical responses to transcranial magnetic stimulation in chronic stroke: a TMS-EEG investigation. *Neurosci Lett.* (2016) 618:25–30. doi: 10.1016/j.neulet.2016.02.047
68. Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. *Stroke.* (2003) 34:2653–8. doi: 10.1161/01.STR.0000092122.96722.72
69. Qü M, Buchkremer-Ratzmann I, Schiene K, Schroeter M, Witte OW, Zilles K. Bihemispheric reduction of GABAA receptor binding following focal cortical photothrombotic lesions in the rat brain. *Brain Res.* (1998) 813:374–80. doi: 10.1016/S0006-8993(98)01063-4
70. Hara Y. Brain plasticity and rehabilitation in stroke patients. *J Nippon Med Sch.* (2015) 81:4–13. doi: 10.1272/jnms.82.4
71. Jung DH, Ahn SM, Pak ME, Lee HJ, Jung YJ, Kim KB, et al. Therapeutic effects of anodal transcranial direct current stimulation in a rat model of ADHD. *Elife.* (2020) 9:e56359. doi: 10.7554/eLife.56359
72. Wang HY, Crupi D, Liu J, Stucky A, Cruciata G, Di Rocco A, et al. Repetitive transcranial magnetic stimulation enhances BDNF-TrkB signaling in both brain and lymphocyte. *J Neurosci.* (2011) 31:11044–54. doi: 10.1523/JNEUROSCI.2125-11.2011
73. Soundara Rajan T, Ghilardi MFM, Wang HY, Mazzon E, Bramanti P, Restivo D, et al. Mechanism of action for rTMS: a working hypothesis based on animal studies. *Front Physiol.* (2017) 8:457. doi: 10.3389/fphys.2017.00457
74. Paquette C, Sidel M, Radinska BA, Soucy JP, Thiel A. Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement. *J Cereb Blood Flow Metab.* (2011) 31:2086–95. doi: 10.1038/jcbfm.2011.72
75. Thiel A, Schumacher B, Wienhard K, Gairing S, Kracht LW, Wagner R, et al. Direct demonstration of transcallosal disinhibition in language networks. *J Cereb Blood Flow Metab.* (2006) 26:1122–7. doi: 10.1038/sj.jcbfm.9600350
76. Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.* (2010) 3:95–118. doi: 10.1016/j.brs.2009.10.005
77. Kim HK, Blumberger DM, Downar J, Daskalakis ZJ. Systematic review of biological markers of therapeutic repetitive transcranial magnetic stimulation in neurological and psychiatric disorders. *Clin Neurophysiol.* (2021) 132:429–48. doi: 10.1016/j.clinph.2020.11.025
78. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive

transcranial magnetic stimulation (rTMS). *Clin Neurophysiol.* (2014) 125:2150–206. doi: 10.1016/j.clinph.2014.05.021
79. Weiler M, Moreno-Castilla P, Starnes HM, Melendez ELR, Stieger KC, Long JM, et al. Effects of repetitive transcranial magnetic stimulation in aged rats depend on pre-treatment cognitive status: toward individualized intervention for successful cognitive aging. *Brain Stimul.* (2021) 14:1219–25. doi: 10.1016/j.brs.2021.08.008
80. Geyh S, Kurt T, Brockow T, Cieza A, Ewert T, Omar Z, et al. Identifying the concepts contained in outcome measures of clinical trials on stroke using the international classification of functioning, disability and health as a reference. *J Rehabil Med.* (2004) 44:56–62. doi: 10.1080/16501960410015399
81. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. *Neurorehabil Neural Repair.* (2017) 31:784–92. doi: 10.1177/1545968317732662
82. Starkey ML, Schwab ME. Anti-nogo-A and training: can one plus one equal three? *Exp Neurol.* (2012) 235:53–61. doi: 10.1016/j.expneurol.2011.04.008
83. Kwakkel G, Van Wegen E, Burridge JH, Winstein CJ, van Dokkum L, Alt Murphy M, et al. Standardized measurement of quality of upper limb movement after stroke: consensus-based core recommendations from the second stroke recovery and rehabilitation roundtable. *Int J Stroke.* (2019) 14:783–91. doi: 10.1177/1747493019873519
84. Caglayan AB, Beker MC, Caglayan B, Yalcin E, Caglayan A, Yulug B, et al. Acute and post-acute neuromodulation induces stroke recovery by promoting survival signaling, neurogenesis, and pyramidal tract plasticity. *Front Cell Neurosci.* (2019) 13:144. doi: 10.3389/fncel.2019.00144
85. Cote SL, Hamadjida A, Quessy S, Dancause N. Contrasting modulatory effects from the dorsal and ventral premotor cortex on primary motor cortex outputs. *J Neurosci.* (2017) 37:5960–73. doi: 10.1523/JNEUROSCI.0462-17.2017
86. Cote SL, Elgbeili G, Quessy S, Dancause N. Modulatory effects of the supplementary motor area (SMA) on primary motor cortex outputs. *J Neurophysiol.* (2020) 123:407–19. doi: 10.1152/jn.00391.2019
87. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol.* (2017) 4:811–20. doi: 10.1002/acn3.488

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 28 February 2022
doi: 10.3389/fresc.2022.824684

Treatment of the Linguistic and Temporal Components of Lexical Activation to Improve Word Retrieval in Aphasia

Nadine Martin [1†], Jessica Obermeyer [2†], Julie Schlesinger [1†] and Robert W. Wiley [3†]*

[1] Department of Communication Sciences and Disorders, Temple University, Philadelphia, PA, United States, [2] Department of Communication Sciences and Disorders, University of North Carolina at Greensboro, Greensboro, NC, United States, [3] Department of Psychology, University of North Carolina at Greensboro, Greensboro, NC, United States

Current approaches to treatments for word processing impairments in aphasia emphasize two components to target, the linguistic content, semantic or phonological representations of words, and the processing component, access to and retrieval of those representations. In this study, we explore these two components of a treatment to improve lexical activation that supports access and retrieval of word representations. Five people with aphasia participated. The treatment task was repetition of concrete word pairs after a 5-s response delay which was intended to provide practice in maintaining activation of the words for that 5-s period before reproducing them. Two of the five participants demonstrated a difficulty in maintaining activation of single words in repetition, with accuracy decreasing significantly after the 5-s interval. The treatment was applied to all participants, however, to determine if its benefit was specific to those with the activation maintenance impairment. Results confirmed that the activation maintenance treatment in the context of this repetition task led to more treatment gains for the two participants who demonstrated this specific impairment. They made gains on four of the nine measures compared to improvements on one to two measures for the other participants. A second question addressed in this study was the relative importance of the item component (linguistic content) of the treatment and the processing component, maintenance of activation. To that end, there were two conditions of treatment probes, (1) repeated content for all treatment, immediate post-treatment and 3-month maintenance probes and (2) novel content for probes in these three phases of treatment. Only one participant showed significant improvement in treatment when items were novel for all probes. We discuss the possibility that this outcome reflects a more specific deficit in the temporal processing component of lexical activation compared to the two other participants who showed better performance on probes with repeated items in treatment and post-treatment phases. Clinical implications of this study and directions of future research are discussed.

Keywords: impaired lexical activation, verbal short-term memory, temporal processing of words, aphasia treatment, word processing treatment

OPEN ACCESS

Edited by:
Elizabeth Rochon,
University of Toronto, Canada

Reviewed by:
Julia Schuchard,
Children's Hospital of Philadelphia, United States
Ljubica Konstantinovic,
University of Belgrade, Serbia

***Correspondence:**
Nadine Martin
nmartin@temple.edu

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *29 November 2021*
Accepted: *19 January 2022*
Published: *28 February 2022*

Citation:
Martin N, Obermeyer J, Schlesinger J and Wiley RW (2022) Treatment of the Linguistic and Temporal Components of Lexical Activation to Improve Word Retrieval in Aphasia. Front. Rehabilit. Sci. 3:824684. doi: 10.3389/fresc.2022.824684

INTRODUCTION

Some current theories of language and aphasia incorporate a central role of short-term memory (STM) in lexical (word) processing, which is realized as short-term maintenance of semantic (meaning) and phonological (sound) representations of words over the course of word retrieval. The interactive activation (IA) model of word retrieval (1) postulates two components of lexical activation that support word processing: rate of activation spread (connection rate) and its maintenance (activation decay rate). Dell and colleagues (2–4) have hypothesized that word retrieval difficulties in aphasia are due to impairment of these activation components. Reduced connection strength slows the speed of activation transmission and the need for more time to access a word's representation. Increased rate of activation decay impairs the short-term maintenance of an activated word representation. The activation impairment can affect primarily transmission or maintenance or a combination of the two parameters. Martin and Dell (5) showed that the nature of impairment is most readily apparent when a response delay is added to a task. In picture naming or word repetition, for example, adding a 5-s response delay will result in three patterns of response compared to a 1-s response delay: increased accuracy (slow transmission benefits from more time to respond), reduced accuracy (poor maintenance leads to too-fast decay of activation), or no change in accuracy (combination of impairments to maintenance and transmission parameters). This account is supported by behavioral and computational studies linking the IA model with picture naming and word repetition data from people with aphasia (3–5). In this study, we use the IA model as a framework for a treatment that targets one of the processing components of word retrieval, activation maintenance. Below, we discuss several features of this model that are relevant to this endeavor.

Directional Flow of Activation in the IA Model

We have targeted activation maintenance processes in the contexts of repetition [[5]; (6)] and naming tasks (7), both commonly used tasks in treatments of word retrieval disorders in aphasia. Thus, it is useful to consider how the flow of activation across levels of representation in the IA model of word processing differs for these two tasks. **Figure 1** shows a depiction of the semantic-lexical-phonological network for word processing in the IA model. Also in this figure are two abstracted depictions of the pathways of activation spread through this network in word repetition and word production (e.g., picture naming). Apart from the overlap of pathways for these two tasks at the output stage (between the lexical and phonological networks), they differ in the type of information that initiates the activation flow and subsequent stages of activation. Repetition begins with auditory input that activates phonological representations of words. Though it gains support through feedforward - feedback activation of lexical and semantic representations as well, it can proceed directly to phonological output stages of production (as in the repetition of non-words). Word production (as in picture naming or self-initiated utterances) follows a path that begins with the concept to be named, moving first through activation of item specific semantic features, which converge on the target lexical (word form) representation, and activate other words to a lesser degree. Activation from each of these activated nodes in the lexicon spreads forward to corresponding sound representations in the phonological network. This activation feeds back to the lexical network, reinforcing word representations that are activated by semantic-lexical activation and activating anew other words that share the sounds activated in the phonological network.

The directional flow of activation is important to designing treatment tasks that target particular connections that are impaired. For example, if input pathways between the lexical and semantic levels of representation are impaired, repetition might not be effective unless it includes stimuli that strongly promote access to semantic representations (e.g., categorically related items). In addition to stimuli considerations, the prominence of activation from one level to another differs depending on the task. In repetition, it is the phonological-to-lexical connections that dominate, while in naming it is the semantic-lexical connections that dominate. The strengths of these connections in relation to levels of impairment (semantic or phonological) should be considered when designing treatment tasks to promote better access to and maintenance of words.

Why Should We Treat Processing Components of Word Access and Retrieval?

Treating lexical activation processes (e.g., activation maintenance) provides a complement to treatments that target the psycholinguistic content of words (e.g., semantic or phonological). Psycholinguistic approaches add greater precision to treatments compared to early approaches that focused on language abilities (e.g., naming or repetition). And yet, there remains an ongoing challenge of accounting for inconsistent responses to such treatments despite efforts to match the semantic or phonological content to the semantic or phonological impairment [e.g., (8)]. This has been successfully addressed in a recent treatment approach to improve naming that uses two treatment tasks, retrieval practice that addresses semantic-lexical connections and repetition practice that addresses the lexical-phonological connections in naming (9).

In keeping with the theme of this special issue, this study evaluates effects of two components of a treatment that combines lexical priming with activation maintenance. Using a repetition task, the treatment targets the ability to maintain activation of word representations directly, *via* a response delay manipulation and in a second treatment condition, combines this response delay with repetition priming of the words to be repeated. The results suggest that both the linguistic content and processing components of treatment impact the access and retrieval of words for participants, but that these two components may not have equal impact depending on the participant's profile. This will be discussed further in the General Discussion, but we emphasize here, that a deeper understanding of the processes that support access to and retrieval of words (activation transmission

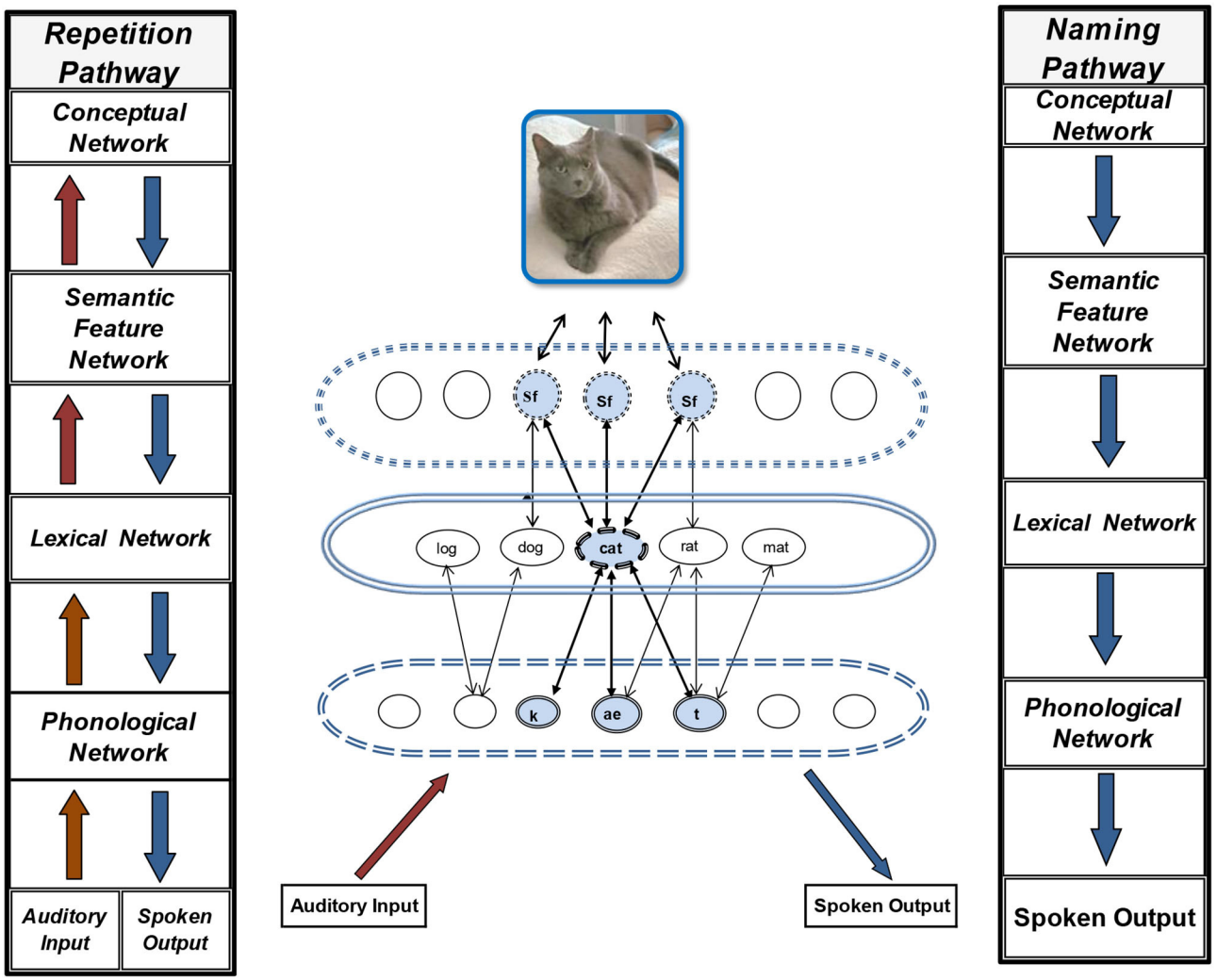


FIGURE 1 | Depiction of the interactive activation semantic-lexical-phonological network for word processing plus two abstracted depictions of the directional flow of activation spread through this network in word repetition and word production.

vs. maintenance) and their impairment will lead to more refined treatments that target both the linguistic and processing components of language ability and more precise matching of impairment to treatment. Below, we discuss some background empirical studies leading to the current study.

Treatments Targeting Impairment of Activation Maintenance Processes in Aphasia

The hypothesis that the ability to maintain activation of word representations is impaired in aphasia has motivated clinical applications including diagnostic tools that address effects of increased short-term and working memory load on language processing (10–13) and a growing number of treatments that target short-term maintenance of activation directly (6, 14–17). Here, we report a modified version of a short-term activation maintenance treatment that is embedded in a repetition task, repeating single and multiple word sequences following a response delay. In a previous study (14), we used a single set of items for training, items that would not be trained and probe items. Outcomes of that treatment study were mixed. Repetition improved mostly for the treated stimuli, with limited generalization to untrained items. There was improvement on outcome measures, including single and multiple word processing tasks as well as verbal working memory tasks and verbal spans.

Martin et al. (6) noted that using a single set of items for training, generalization to untrained items and probe items, as Kalinyak-Fliszar et al. (14) did, introduced the potential influence of repeated item exposure on acquisition of trained items. This confound makes it difficult to attribute effects of the treatment exclusively to effects of the verbal short-term maintenance component of the delayed repetition task. To control for the item-exposure variable, Martin et al. (6) used unique items in all phases of the treatment (baseline, training,

within and post-treatment probes). The aim was to minimize the effects of repeated exposure and thus isolate the effects of the verbal maintenance treatment on performance of the treatment task as well as generalization to verbal tasks that were similar to the treatment task (near-transfer tasks, e.g., repetition span) and others that were less similar (far-transfer tasks, e.g., picture naming).

Additionally, in the Martin et al. (6) version of this verbal "short-term maintenance" treatment, stimuli were customized for each person based on their performance on screening tasks which involved repetition of concrete and abstract single words, word pairs and word triplets after intervals of 1-s, 5-s, and 10-s. The screener identified the "brink accuracy" of repetition, meaning the combination of variables (stimulus type, sequence length, and interval time, 1-, 5- or 10-s) where performance falters but leaves room for improvement. Based on the results of that screener, we enrolled participants who varied widely in the stimuli used for repetition training (e.g., concrete pairs at a 10-s delay, or abstract word triplets at a 5-s delay). The treatment was designed for individuals who demonstrated an impairment in the short-term activation of words, but Martin et al. (6) included both people with and without this deficit in the sample. This would help to determine whether the treatment's effect was specific to an activation maintenance deficit or was more general. The results suggested that the treatment might be specific to a maintenance impairment: Four of the eight participants who demonstrated an activation maintenance impairment before treatment showed modest acquisition effects coupled with gains in language outcome measures, near transfer tasks that were similar to the training task (e.g., repetition span) and to a lesser degree, far transfer tasks that were less similar to the training task (e.g., naming). The four participants who did not show an activation maintenance impairment before treatment did not improve on the treatment task and showed minimal or no generalization to outcome measures.

The modest acquisition effects in Martin et al. (6) were striking in comparison to those observed in the Kalinyak-Fliszar et al. (14) study using the activation maintenance treatment (repetition + response delay). As discussed above, one important difference between the two studies was that Kalinyak-Fliszar et al. did not control for repeated exposure of trained items. Following the pattern of typical single subject designs, sets of trained and untrained items were chosen and were exposed in probes and in training sessions. The modest acquisition effect when item exposure was minimized suggests that this variable played a role in the outcomes of the Kalinyak-Fliszar et al.'s (14) study. However, the treatment protocol in that study also included a cueing procedure at the start of each training trial in addition to the response delay manipulation. Therefore, we cannot rule out that this contributed to the improvements observed in that study.

The Present Study

In this study, we sought to elucidate some of the issues surrounding item exposure in treatments to improve short-term maintenance of lexical activation. Following Martin et al. (6), we used novel items for the treatment task but for the probe items, we used a combination of novel and repeated items. To highlight effects of item exposure in this treatment study, we made some adjustments to the treatment stimuli and procedures from earlier studies to bring this variable into focus. Rather than customize the stimuli for the repetition treatment to each individual's repetition and verbal span ability, we limited the stimuli for training to concrete word pairs following a 5-s response delay. This adjustment was intended to simplify the procedures somewhat, since our primary focus was on differences in the acquisition and maintenance of repeated vs. unrepeated (novel) word pairs in the probe task. Additionally, we used concrete words rather than abstract words because of their easier access to semantics (18) and their simpler phonological composition (19). By minimizing potential difficulties in retrieval of the semantic or phonological components of the words, we aimed to minimize this potential confound with effects of repeated exposure of word stimuli. We also aimed to control for span size of each participant so that repeating word pairs would be within their span size and that their span size would not be much >2 words. Concrete word repetition spans ranged from 1.2 to 3 words (details in **Table 3**).

Additionally, we aimed to provide further evidence that this repetition-based treatment to improve short term maintenance of lexical activation will be most effective for those who demonstrate the activation maintenance deficit. As in Martin et al. (6), participants demonstrated different language impairments but also showed different patterns in word repetition accuracy following a response delay. We predicted that those whose repetition was less accurate following a response delay would be most responsive to this treatment.

The following are our research questions for this treatment protocol that uses uniquely exposed words as training stimuli in a delayed word pair repetition paradigm:

1. Will effect sizes for word pairs that are repeated across all probes be greater than effect sizes for word pairs that are unique in each probe?
2. Will performance on outcome measures improve after this treatment?
3. Will improvements on outcome measures be most robust for those participants who show a maintenance deficit in repetition?

In a *post-hoc* analysis, we review accuracy scores of the participants on selected subtests of the Temple Assessment of Language and Short-term memory in Aphasia [TALSA; (10)] that assess the effects of time interval on performance, including naming, repetition of words and non-words. The tasks that include a time interval between stimulus and response are similar to the training task and therefore might indicate some pattern of performance that is consistent with the participants' responses to the treatment.

METHODS AND MATERIALS

Research Design

We used a single subject treatment design including the following phases: baseline assessment, treatment, post-treatment assessment, and a 3-month post-treatment follow-up.

TABLE 1 | Biographical information.

ID	Sex	Age	MPO[a]	Education in years	Etiology	WAB-R[b] aphasia quotient	WAB-R aphasia classification
CN39	M	53	63	10	Left MCA[c] CVA[d]	76.3	Transcortical Motor
KC3	M	57	192	14	Left MCA CVA	77.4	Transcortical Sensory
KG62	M	54	111	14	Left MCA CVA	66.3	Broca's
KK55	M	61	126	17	Left MCA CVA	78.7	Anomic
XH46	M	50	45	7	Left MCA CVA	73.1	Conduction

[a]*MPO, months post-onset.*
[b]*WAB-R, Western Aphasia Battery-Revised (20).*
[c]*MCA, middle cerebral artery.*
[d]*CVA, cerebral vascular accident.*

TABLE 2 | Effects of response delay and memory load word processing: proportion correct by participants on subtests of the Temple Assessment of Language and Short-term Memory in Aphasia (TALSA).

	TALSA subtest									
Participant	**Naming**		**Word repetition**		**Non-word repetition**		**Rhyming triplets**		**Synonymy triplets**	
Participant ID	**1-s delay**	**5-s delay**	**1-s delay**	**5-s delay**	**1-s delay**	**5-s delay**	**Low memory load**	**High memory load**	**Low memory load**	**High memory load**
CN39	0.71	0.77	0.91	0.91	0.38	0.47	0.97	0.90	0.90	0.90
KC3	0.72	0.79	0.89	0.89	0.24	0.29	0.87	0.70	0.83	0.58
KG62	0.50	0.59	0.56	0.67	0.13	0.11	0.90	0.77	0.80	0.68
KK55	0.81	0.82	0.98	0.84	0.53	0.27	0.93	0.73	0.90	0.83
XH46	0.43	0.56	0.91	0.71	0.56	0.38	0.83	0.70	0.70	0.60

Participants

Biographical Information

Five participants with aphasia were enrolled in the treatment study after meeting criteria on a screener. All five participants were male and at least 1 year post-onset a left hemisphere stroke. Ages ranged from 50 to 61 (Mean = 55, SD = 4.18), time post onset ranged from 45 to 192 months (Mean = 107.4, SD = 57.84), and education level ranged from 7 to 17 years (Mean = 12.4, SD = 3.91). WAB-R (20) Aphasia Quotients ranged from 66.3 to 78.7 (Mean = 74.36, SD = 4.96). Biographical information for these participants is presented in **Table 1** and includes the individual Aphasia Quotients.

Subjects voluntarily enrolled in this study by signing a consent form approved by the Institutional Review Board at Temple University. All testing and treatment took place from 2017 to 2018 at the Eleanor M. Saffran Center for Cognitive Neuroscience at Temple University.

Screening Procedures

Evidence of a Repetition Impairment

To identify people that would be appropriate for this study, we adapted one of the Auditory Processing subtests from the Psycholinguistic Assessments of Language Processing in Aphasia [PALPA, (21)] to create a repetition screener. Stimuli for the screener were a mix of 1-, 2-, and 3-syllable words arranged so that each string included two words, was four syllables in length and all strings were balanced for low or high frequency. Scores were determined by string accuracy and then a percentage was derived. Anyone with a score of 80% accuracy or greater on the word pairs after a 5-s delay was considered at ceiling and did not continue with the treatment. To ensure a participant was able to complete the task of repetition of word pairs, they were required to get at least one pair correct to move forward with the treatment (see **Supplementary Figure 1**).

Word Processing Abilities With Response Delay and Memory Load Manipulations

Table 2 shows performance on five subtests from the Temple Assessment of Language and Short-term memory in Aphasia [TALSA; (10)] including picture naming, word and non-word repetition and two working memory tests involving judgment of synonymy and rhyming. Details of the stimuli can be found in Martin et al. (10). We will focus first on the word and non-word repetition subtests that will determine whether participants demonstrated an activation maintenance impairment in repetition. Recall that worse performance after a delay signals difficulty in maintaining activation long enough to achieve or sustain access to semantic and phonological representations of a word. Better performance on a task after a response delay indicates that activation is slow to rise and a time delay benefits performance. The treatment task is repetition of word pairs after a 5-s response delay. Two participants, KK55 and XH46, show a decline in repetition accuracy after a 5-s interval for both words and non-words. The other participants, CN39, KC3, and KG62, show similar accuracy rates on the

1- and 5-s delay conditions or in one case, greater accuracy on the 5-s condition. By this measure, KK55 and XH46 represent the repetition profile that is well-suited to this treatment using repetition after a response delay. If treatment gains are limited to these two individuals, this will provide additional evidence that the activation maintenance treatment is most effective when applied to individuals who demonstrate the activation maintenance impairment.

There are a few other noteworthy observations regarding the performances of KK55 and XH46 (**Table 2**). KK55's performance on all of the naming, repetition and working memory tests is higher or amongst the highest of the group at the 1-s interval. It is at 5-s that his performance falters. In naming, XH46 improves after 5 s, a hallmark of an activation transmission deficit. This suggests that his word processing deficit includes both activation maintenance and transmission components, with the latter impacting naming more than repetition. Consistent with this he achieved higher scores on tests that tap into phonological ability (repetition and rhyming judgments) compared to those that probe semantic abilities (naming and synonymy judgments). Finally, the Rhyming Triplets and Synonymy Triplets investigate the ability to judge similarity of meaning and sound under high and low working memory conditions. All five participants' scores decline in the high working memory load condition (with one exception, CN39 on the synonymy triplets). This is a common pattern on these two judgment tasks for people with aphasia and to a lesser extent, neurotypicals (22). KK55, one of the two participants who demonstrated the activation maintenance deficit profile for repetition, scored at a high level for both rhyming and synonymy triplets in the low memory load condition. However, in the high memory load condition, his performance declines considerably and more so for the rhyming triplets, which tap into phonological processing. XH46's performance on these two judgment tasks is lower than KK55 and at the low end for all participants in both memory load conditions and in both rhyming and synonymy triplets.

Stimuli Development

Stimuli for all baselines, probes, post-treatment probes, and other lab-developed assessments discussed further in this paper were derived from Brysbaert et al. "Concreteness ratings for 40 thousand generally known English word lemmas" (23). We selected only nouns and further reduced the list to include only 1-, 2-, and 3-syllable words. We excluded homophones and other words that the research team felt were inappropriate for our purposes (e.g., "slang" words). To identify concrete and abstract words, we set a criterion of 0.75 standard deviation from the mean of concreteness ratings. Words with ratings of 4.03–5 were considered concrete and words with ratings 1.44–2.77 were considered abstract. We used ∼1,900 concrete and 200 abstract 1–4 syllable words.

Baselines and Probes

All words were further controlled for frequency using $SUBTLEX_{WF}$ (Subtitle frequency: word form frequency) (24) with ratings limited to between 1 and 25 per million. Once we identified a corpus of words, we developed baselines and probes. The following criteria were set: repeated pairs remained consistent across each probe. The words in a pair could not be semantically related or strongly associated. Additionally, the words in a pair could not share the same initial phoneme, final phoneme, or stressed vowel. We attempted to follow the criteria for phonological similarity as closely as possible for all probes.

We also controlled as much as possible other shared features of words within a probe list, such as balancing for number of animals or food items in each probe and considered phonological features as well by attempting to balance for words ending with /o/, /r/, and /l/ within a single probe. All words were then controlled for phonotactic probability. For baselines, probes and post-treatment probes, concrete word pairs were always 5- or 6-syllables in total, with the 5-syllable strings being combinations of 2- + 3-syllable and 3- + 2-syllable words. For each probe list of 20 pairs, 15 of the strings were repeated and five strings were novel for each of the three (or four) baselines, eight probes, three immediate post-treatment probes, and two maintenance probes for a total of 16 probes throughout the treatment.

Treatment

All words chosen for the treatment lists were not used in any of the other lab-developed tests. Since the words developed for the treatment were not used for scoring purposes, criteria for word choice were less strict. $SUBTLEX_{WF}$ ratings for treatment stimuli did not have an upper limit. There was a wider range of frequencies that allowed for anything >25. To increase the number of concrete 3-syllable words, we included some compound words and some pseudo-repetition (kayak/kayaker, balloon/balloonist).

For treatment lists, all concrete word pairs were made of 5- and 6-syllable strings, with the 5-syllable strings balanced in 2- + 3-syllable and 3- + 2-syllable word combinations. Words were not semantically related within a line. It was more difficult to control for shared initial or final consonant or stressed vowel in each line, but since these were treatment lists, this was not considered to be as essential as with the probe lists.

Pre- and Post-treatment Assessments and Outcome Measures

The language and short-term memory assessments described below were administered immediately before treatment, immediately after treatment and 3 months following the completion of treatment to assess maintenance (except for the discourse task which is only reported for pre- and post-treatment). These assessments are described below.

Concrete and Abstract Word and Word Sequences Repetition Test

This laboratory-developed assessment (6) was used to evaluate improvement of word repetition ability. This version included eight repetition conditions that varied the number (pairs, triplets) and concreteness (concrete/abstract) of words and the response delay time (1-s or 5-s) resulting in eight combinations: Concrete Pairs 1-s, Concrete Pairs 5-s, Concrete Triplets 1-s, Concrete Triplets 5-s, Abstract Pairs 1-s, Abstract Pairs 5-s, Abstract Triplets 1-s, and Abstract Triplets 5-s.

For each condition, we administered 20 pairs of words (used only in that condition) that were balanced for syllable length within the pair or triplet and within the condition. Pairs were made up of five syllable strings that were balanced into 2- + 3-syllable combinations and 3- + 2-syllable combinations. Triplets were made of 7- and 8-syllable strings. The 7-syllable strings were balanced into combinations of 2- +2- +3-syllables, 2- + 3- + 2-syllables, or 3- + 2- + 2-syllables. Finally, the 8-syllable strings were balanced into combinations of 2- + 3- +3-syllables, 3- + 2- + 3-syllables or 3- + 3- + 2-syllables. Administration of these forms was pseudo-randomized so that duplicated conditions were not given on the same day (e.g., concrete pairs with a 1-s response delay was not given on the same day as concrete pairs after a 5-s response delay). All stimuli criteria listed above for lab-developed tests also applied in the development of these test forms.

Concrete Immediate Serial Recall Span Test

This laboratory-developed test was adapted from the span test we used in the first version of this treatment study (6), using most of the same words but in rearranged order. For this version, we had word strings ranging from one to six words with 10 trials for each list length. Words within a string appeared only once. All stimuli criteria listed previously were also used for developing this test.

Word Pointing Span

Each participant received a Word Pointing Span task that was developed as part of the Temple Assessment of Language and Short-term Memory in Aphasia (TALSA) (10). This was included to determine if the treatment improved the ability to maintain activation of verbal representations. Using the pointing span paradigm allows assessment of this ability in the context of a comprehension (word-to-picture-matching) task, without a verbal response.

Corsi Block Span Task

We administered this spatial span task as a measure of non-verbal span (25, 26). If the effect of our treatment is on verbal processing and short-term memory only, there should be little or no change in non-verbal span.

Comprehensive Aphasia Test (CAT)

The following subtests of the CAT (27) were administered: Comprehension of Spoken Language (Spoken Words, Spoken Sentences, and Spoken Paragraphs) as well as the Naming Objects subtest under Spoken Language Production.

Discourse

We administered the Nicholas and Brookshire (N&B) (28) elicitation protocol as this is shown to be a reliable pre-/post-measure of discourse.

Protocol

Testing was administered by three individuals; a licensed clinical and research speech-language pathologist and two post-doctoral fellows with a Ph.D. in speech and language pathology, one of whom also was a licensed clinical speech-language pathologist. The treatment schedule was prepared a priori on a calendar to ensure administration uniformity among testers. One of the research speech-language pathologists who was involved in administering the first version of this treatment (JS) provided training to the other two testers (JO, IM) before the start of administration.

Pre-treatment Assessment Battery

All language tests listed above were given over 5–6 sessions concurrent to administering baselines.

Probes

Baseline probe administration began during the pre-treatment assessment battery. Probe trials consisted of 20 word pairs of concrete nouns, 15 repeated across probe trials and five pairs that were unique to each probe trial. On a probe trial, the participant listened to a word pair and when cued after 5 s, repeated the word pair in the order that it was presented. The probe task was administered at the beginning of each session. At least three baseline probes were administered with an optional 4th baseline probe for any participant who demonstrated a change of $>$15 percentage points on any of the first three administrations. During the treatment phase, probes were administered at the start of eight out of nine treatment sessions, with the exception of the first session, in which no probe was administered. There were also three immediate post-treatment probes (these probes occurred within 1 to 2 weeks following the completion of treatment) and two maintenance probes administered 3 months after treatment.

Control Task

A linguistic and non-linguistic control task was administered following each probe during baseline, treatment, post-treatment, and maintenance phases. The linguistic control was the 24-item non-word reading list from the PALPA (21). Because this treatment is intended to promote a verbal-STM process that is fundamental to all language tasks, it was difficult to choose a linguistic control task that we would expect to not improve following this treatment. However, we also expect that the benefits of this treatment will vary depending on the degree of overlap between processes and representations engaged in the training task (repetition with a response delay) and those engaged in a task targeted for generalization. Generalization of positive effects to other tasks can be classified as near transfer or far transfer (6, 29). The non-word reading task would be considered a far transfer task relative to the repetition training task, though we submit that this does not preclude the possibility of performance on this task improving following this treatment.

For a non-linguistic control we used the Five-Point Test (5PT) (30). This test requires participants to generate designs using different combinations of dots and lines. We used this measure to test the hypothesis that improved performance on the outcome measures could be attributed to improved maintenance of lexical activation and not to a more domain general cognitive processing ability.

Timing of Response Delays and Periodic Rest Breaks

E-Prime 2.0 software (31) was used to present stimuli electronically to facilitate the clinician's monitoring of the timing of stimulus presentation rate (words within sequences) and the

timing of response delays (1-s and 5-s). Natural transitions served as breaks between each task. In addition, breaks were offered if clinical judgment determined it was needed or the participant requested a break.

Treatment

Treatment took place over nine sessions, three sessions per week for 3 weeks. The treatment protocol was repetition of 40-word concrete pairs after a 5-s delay. Participants listened to a word pair and waited for a beep cue, which occurred when 5 s had passed. They would then repeat the words in the same order they were presented. Timing and beep cues were programmed into E-prime for accuracy. Treatment stimuli consisted of balanced 2- and 3-syllable words in pairs all of which were novel.

Each session began with a 20-item list probe of concrete pairs (15 repeated strings and 5 novel) followed by a linguistic and non-linguistic control task, the order of which was alternated each session. An example of a probe form is included in the **Supplementary Materials**.

Treatment began after the treatment probe and two control probes were administered. The treatment and probe tasks were the same: the participant listened to a concrete word pair, waited 5-s until a cue to respond, and then repeated the word pair as accurately as possible. Again, an E-Prime program was used to control for the clinician's presentation rate of the word pairs and the 5-s response delay condition. Each day's treatment was broken into two cycles. Each cycle consisted of two sets—Set A and Set B. Each set consisted of 10 pairs.

Scoring

Accuracy of Word Production

The criteria for accuracy of word production in all probes and all outcome measures was 100% phoneme accuracy. We accepted distortions of phoneme production as long as the phoneme was recognizable. We also accepted regionalisms. For example, it is common in the Philadelphia area to pronounce "ambulance" as /æmb?læns/ so this was considered correct.

Scoring of the Probe Tasks

Sessions were audio recorded and following each session, the examiner listened to the sound file to score the responses. Four scores were calculated from the word pair probe data, all expressed as percentages correct:

1. Strings correct in serial order (String ISO). This occurred when the participant produced both words in the pair correctly and in the same order they were presented. The score for each trial could be 0 or 1 out of 1.
2. Strings correct in any order (String IAO). This occurred when the participant produced both words in the pair without regard to order. Score for each trial could be 0 or 1 out of 1.
3. Words correct in serial order (Words ISO). This was a measure of the total items in the word pair produced correctly. Score for each trial could be 0, 1, or 2 out of 2.
4. Words correct in any order (Words IAO). This was a measure of the total items in the word pair produced correctly without regard to order. Score for each trial could be 0, 1, or 2 out of 2.

So, if the target is *recipe, arcade* and the response after the beep is "recipe, arcade," that word pair would be scored as 1 out of 1 for String ISO/String IAO and 2 out of 2 for total Words ISO/IAO. In another example, if the target is *thunder, coconut* and the response after the beep is "thunder, /kodɛkɛnɛt/, coconut" that would be considered 0 out of 1 for String ISO as it was not completely correct but would receive a 1 out of 1 for string IAO, 1 out of 2 for total words ISO and 2 out of 2 for total words IAO. See **Supplementary Materials** for a probe that is filled in using this scoring method.

Reliability

For the probe task, reliability was evaluated by having a trained undergraduate volunteer serve as a second scorer. For probes, each participant had one baseline, one immediate post-test, and one maintenance probe randomly selected for rescoring, which was ∼17.65% of the total amount of probes administered to each person. Substantial agreement was seen for strings ISO (kappa = 0.688) scoring for probe responses (32).

Statistical Analyses

To address Research Question 1, we calculated effect sizes across word pair types and time points using linear mixed-effects regression. Specifically, binomial regression was used to regress accuracy on the two predictors of interest as well as their interaction. The regression models were fit in R with the package *lme4* [version 1.1-26; (33)]. A separate model was fit to each individual participant's data, with fixed effects for Time Point (Baseline, Immediate post-treatment, 3 months post-treatment, simple coded with Baseline as the reference level), Word Pair Type (Repeated and Novel, coded +1/-1), the interaction between Time Point and Word Pair Type, and a random intercept by-items. Accuracy on the two control tasks (PALPA Non-words and 5-Point Test) were analyzed in the same way, except the regression was fixed-effects only, with the only regressor being Time Point (and so the models were fit in the base R package *stats* [v. 4.0.5, (34)]. Effect sizes are all reported as odds ratios (OR).

To address Research Question 2, the various outcome measures were either scored and compared against established benchmarks, as described in the Results, or else were analyzed with regression similar to the approach described for Research Question 1. Specifically, the laboratory-developed Concrete and Abstract Word and Word Sequences Repetition Test was analyzed with (binomial) fixed effects regression, with regressors for Time Point, Delay (1-s vs. 5-s), String Size (Pairs vs. Triplets), and Word Type (Concrete vs. Abstract; each of these categorical variables had their levels coded as +1/-1. The interactions between Time Point and each of the other regressors were also included. Therefore, a single regression model (per participant) provided estimates and *p*-values for the "main effect" of Time Point, as well as whether that effect differed under the various conditions. For example, the interaction of Time Point X Delay tested whether any changes from pre-treatment to immediate-post treatment (or from pre- treatment to 3-months post-treatment) were different for words tested at 1-s vs. 5-s. Only significant interactions with Time Point were followed-up with

comparisons to report condition-specific changes in accuracy across time (e.g., a significant interaction of Time Point X Delay was followed up with a test of Time Point at 1-s delay and Time Point at 5-s delay), using the R package emmeans [v. 1.5.5-1; (35)].

Discourse was evaluated pre-treatment and post-treatment. The Discourse elicitation protocol described by Nicholas and Brookshire (28) was used to evaluate the connected speech of each participant. All 10 samples from the Nicholas and Brookshire (28) protocol were used and included single picture descriptions (4), sequential picture descriptions (2), procedural discourse samples (2), and personal narratives (2). Results of the 10 samples were totaled for each participant. The primary discourse outcome was the proportion of correct information units (CIUs). CIUs are words that are accurate and relevant to the stimuli and not repeated (28). The proportion of CIUs was calculated by totaling the number of CIUs across all 10 discourse samples divided by the total number of words produced in all 10 discourse samples for each participant. Additionally, number of words, number of CIUs and mazes (false starts and filled pauses in discourse) were evaluated for each participant. Discourse transcription was completed by trained research assistants. Point-to-point reliability was evaluated for 17% of transcripts with 93.5% agreement. Transcription reliability was determined by dividing total agreed upon words, utterances, false starts, filled pauses, and silent pauses (pauses >2 s) over the total number possible. Point-to-point coding reliability was also evaluated for 48% of transcripts. Agreement for words was 99.4% (total agreed upon words over total words) and agreement for CIUs was 89.9% (total agreed upon CIUs over total CIUs). The primary discourse outcome (%CIUs) was evaluated using the benchmark of change greater than twice the standard error of the mean (4.2%) established by Nicholas and Brookshire (28) and used to evaluate change in %CIUs after treatment (36, 37).

To evaluate Research Question 3, we examined the performances of all five participants on the treatment probes as well as outcome measures, to determine whether those participants who demonstrated a maintenance deficit in repetition benefited from the treatment more so than those who did not.

RESULTS

Research Question 1

Figures 2–6 show the results of baseline, treatment, post-treatment, and follow-up probe trials for each participant. The results are expressed as proportions of strings correct ISO and IAO (2a-6a) and proportions of words correct ISO and IAO (2b-6b).

The first research question asked whether treatment effect sizes for word pairs repeated across all probes would be greater than effect sizes for word pairs that are unique in each probe? "Overall" effects refer to collapsing across pair Type (Repeated and Novel). An odds ratio (OR) < 1 indicates a decrease in accuracy, whereas an OR > 1 indicates improvement. An OR equal to exact 1 indicates no change whatsoever. Strings ISO refers to the proportion of word strings recalled accurately in serial order. Words ISO refers to the proportion of words recalled within strings and in serial order.

Effect Sizes for Changes on Probes From Pre-treatment to Immediate Post-treatment and to 3 Months Post-treatment

Summaries of the results for each participant on the treatment measures are provided below.

CN39

For baseline to immediate post-treatment, across the two outcome measures (Strings ISO, Words ISO), Overall ORs ranged from 1.6 to 2.2, canonical small effects (38). Of those, only Words ISO (OR = 2.20) was marginally significant ($p \approx 0.06$); all other effects were not significant, p's > 0.10. The ORs for Novel pairs, ranging from 1.8 to 2.7, were numerically larger than those for Repeated pairs, ranging from 1.3 to 1.8. However, there were no significant differences between Novel and Repeated pairs, p's > 0.10.

For baseline to maintenance (3 months post-treatment), Overall ORs ranged from 1.3 to 2.1. None of the effects, however, were significant (p's > 0.10). The ORs for Novel pairs, ranging from 1.6 to 5.1, were numerically larger than those for Repeated pairs, ranging from 0.8 to 1.4. However, there were no significant differences between Novel and Repeated pairs, p's > 0.10.

KC3

For baseline to immediate post-treatment, Overall ORs ranged from 0.5 to 1.1, none of which were significant (p's > 0.10). However, large and significant differences emerged between Novel and Repeated pairs. The ORs for Novel pairs ranged from 0.04 to 0.5, with String ISO (OR = 0.04) showing a marginally significant *decrease* in the odds of a correct response ($p \approx 0.06$). The ORs for Repeated pairs ranged from 2.4 to 6.9. Results for Repeated pairs indicated significant improvements with a medium effect for Words ISO and a large effect for String ISO. The differences between Novel and Repeated pairs were significant for both of these outcome measures (p's < 0.05).

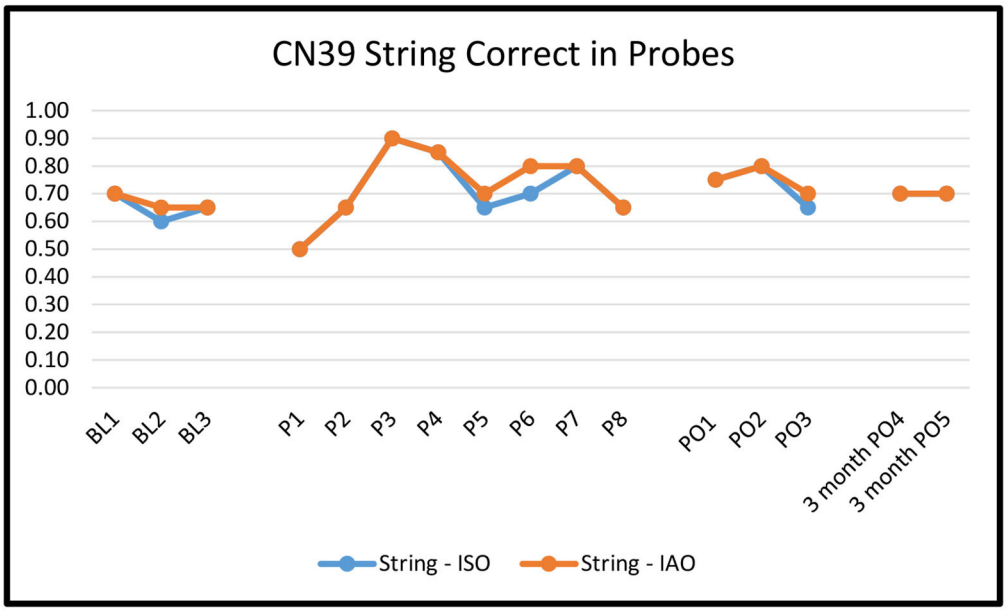
For baseline to maintenance, the pattern was largely the same, with non-significant *decreases* in accuracy on Novel pairs (ORs 0.07–0.5, p's > 0.10), but significant maintenance of improvement on Repeated pairs with large effect sizes (ORs 3.5–17.4, p's < 0.01). The differences between Novel and Repeated pairs were significant for Strings ISO and Words ISO.

KG62

For baseline to immediate post-treatment, overall ORs ranged from 0.8 to 1.6, none of which were significant (p's > 0.10). The effects were numerically more positive for Novel pairs (ranging from 1.0 to 2.2) than Repeated pairs (ranging from 0.6 to 1.2). However, none of the effects or differences between Novel and Repeated pairs were significant (p's > 0.10).

For baseline to maintenance, the pattern was largely the same: no significant changes on either Novel or Repeated pairs (ORs 0.5–1.0, p's > 0.10) and no significant differences between the two.

A



B

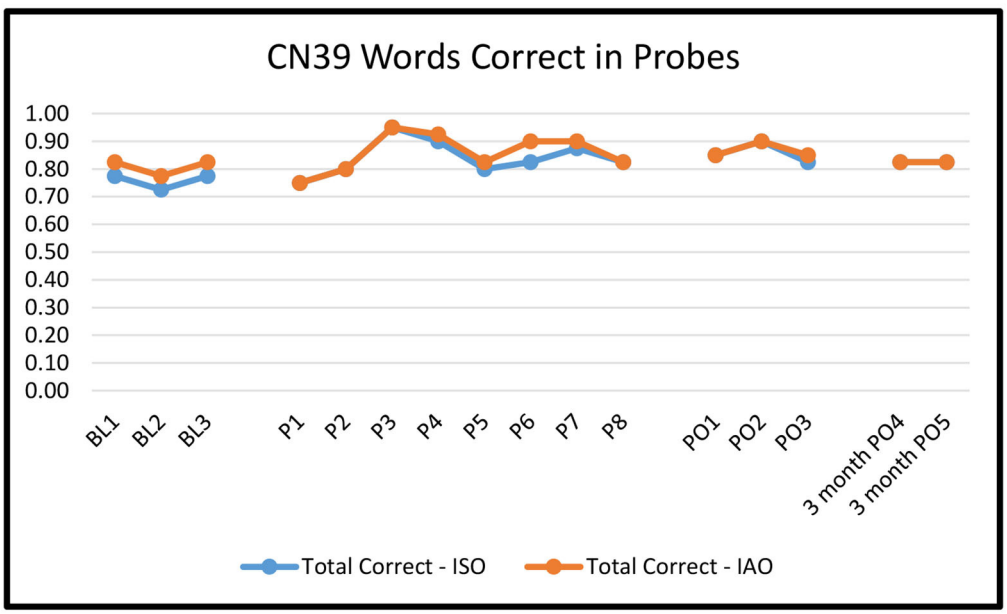
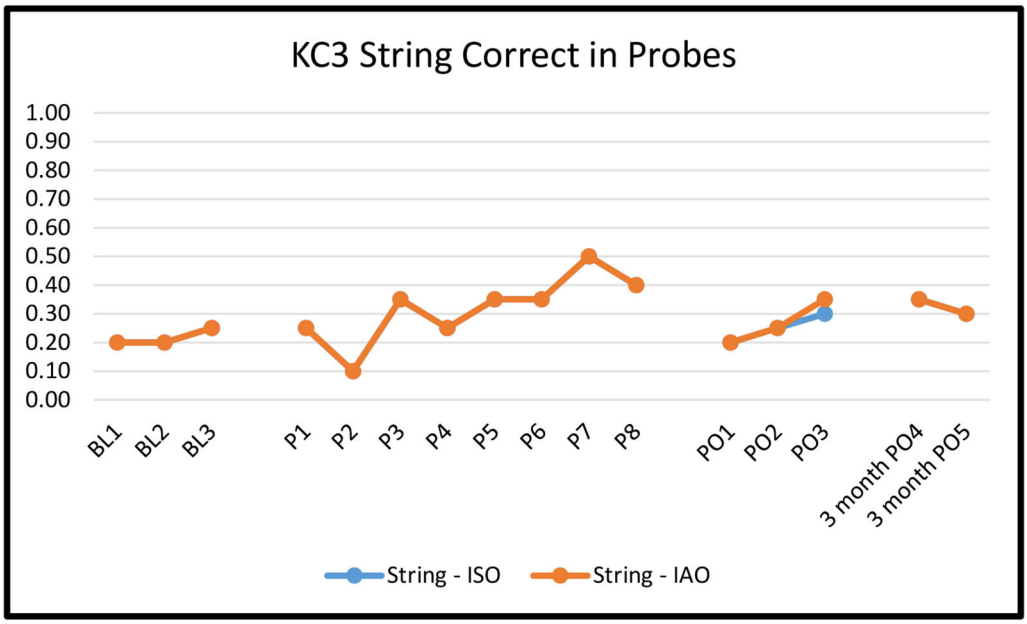


FIGURE 2 | CN39: Proportion of word strings **(A)** and words **(B)** correct in baseline, treatment, post-treatment, and 3 months follow-up probes.

A_



B

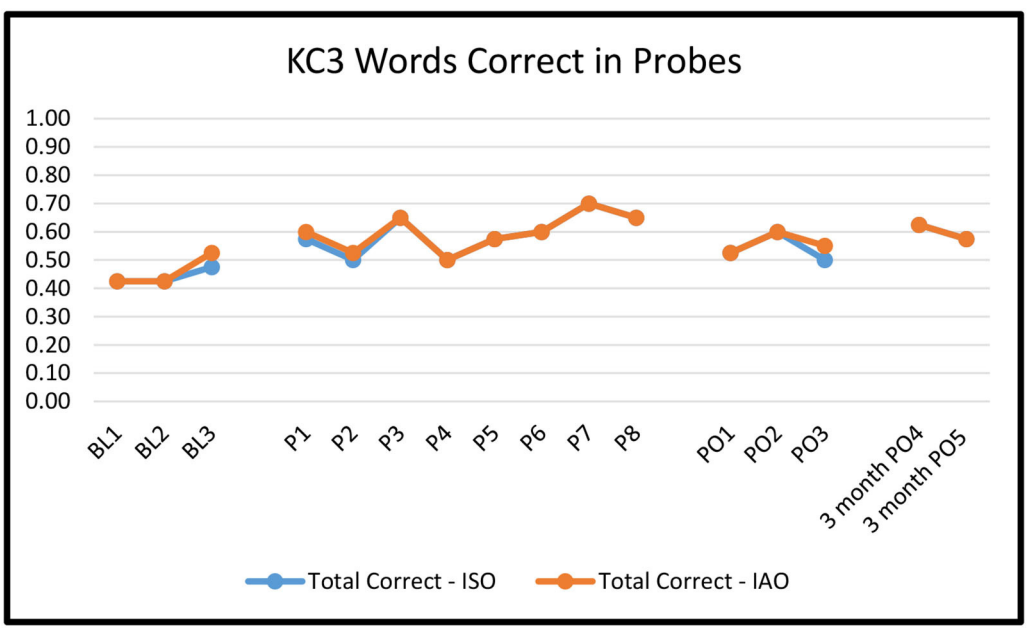
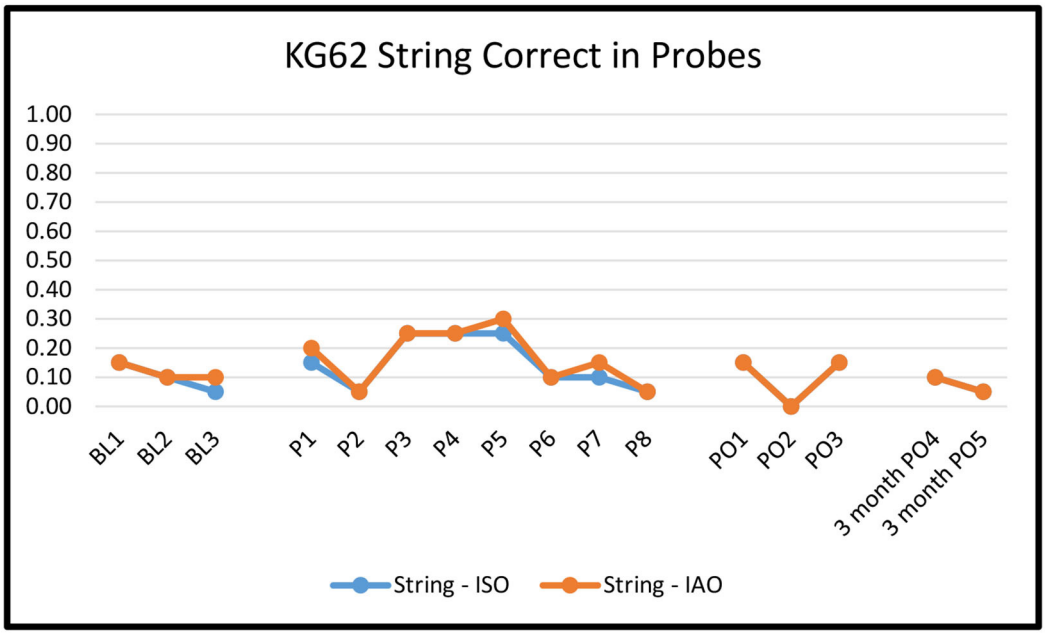


FIGURE 3 | KC3: Proportion of word strings **(A)** and words **(B)** correct in baseline, treatment, post-treatment, and 3 months follow-up probes.

A



B

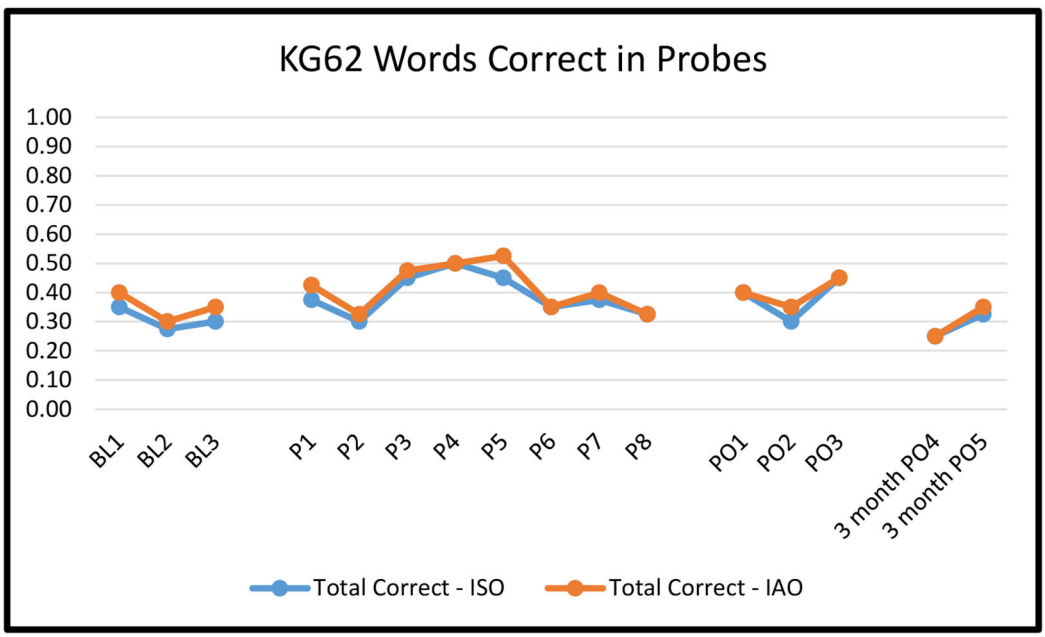
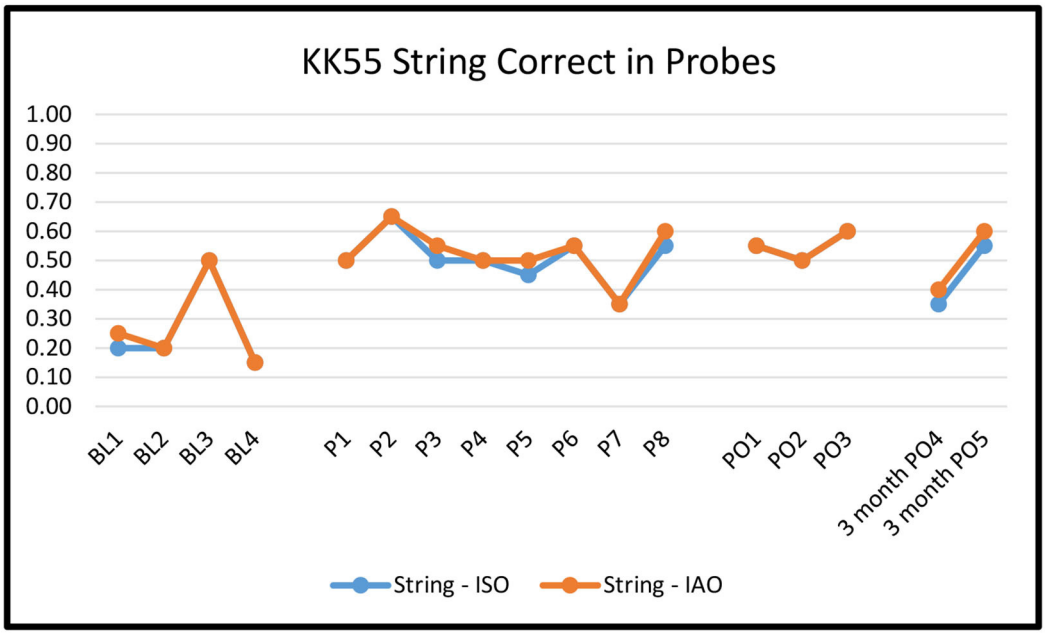


FIGURE 4 | KG62: Proportion of word strings **(A)** and words **(B)** correct in baseline, treatment, post-treatment, and 3 months follow-up probes.

A



B

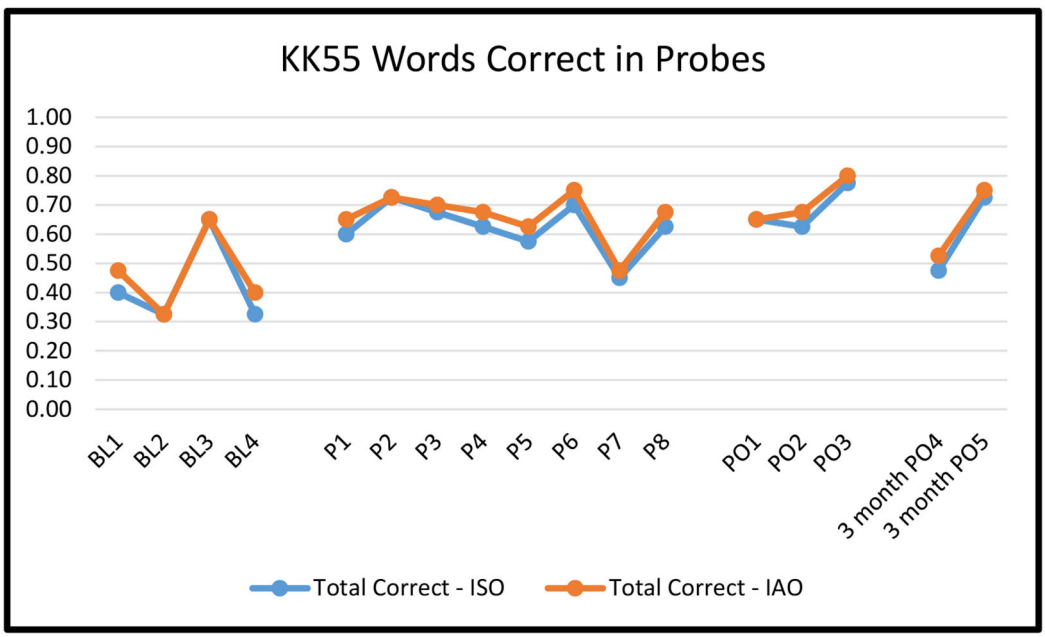
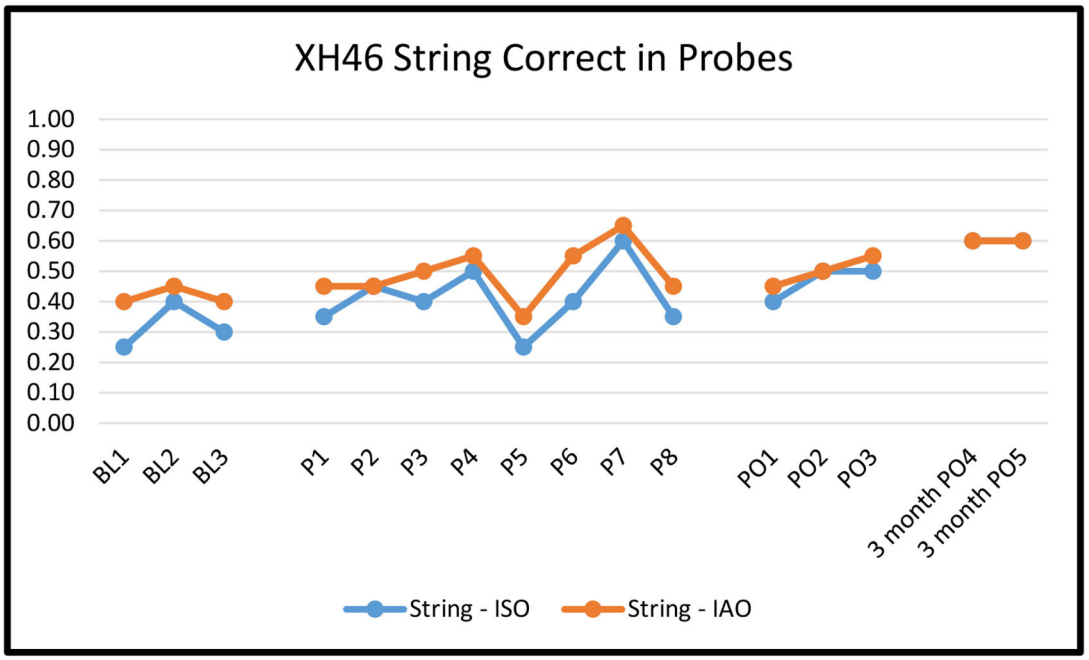


FIGURE 5 | KK55: Proportion of word strings **(A)** and words **(B)** correct in baseline, treatment, post-treatment, and 3 months follow-up probes.

A



B

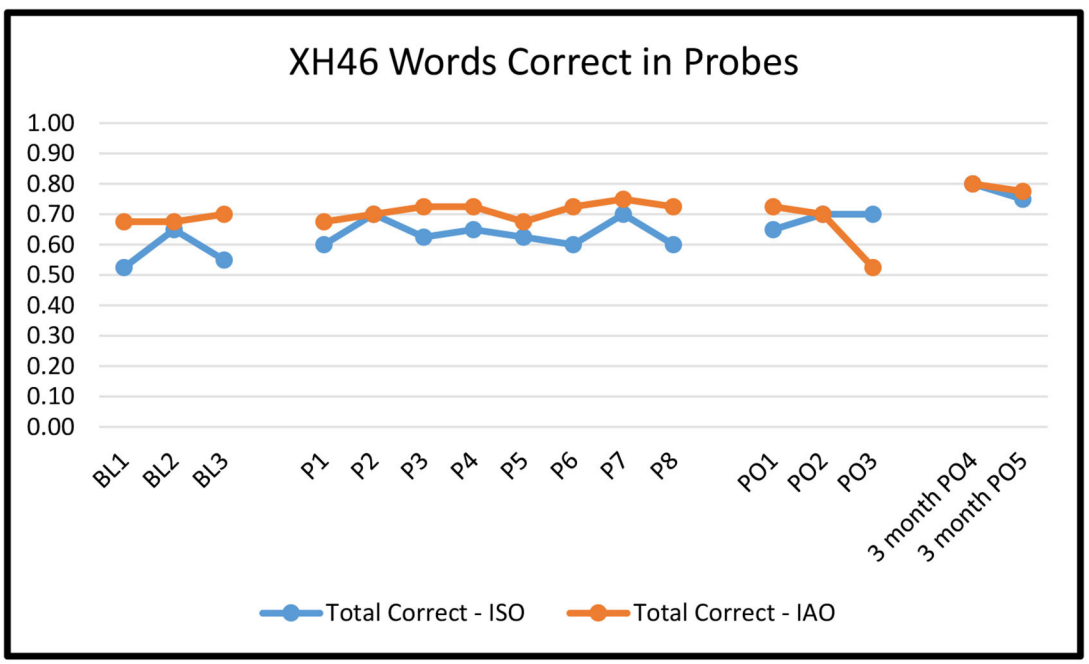


FIGURE 6 | KK55: Proportion of word strings **(A)** and words **(B)** correct in baseline, treatment, post-treatment, and 3 months follow-up probes.

KK55

For baseline to immediate post-treatment, Overall ORs ranged from 3.2 to 3.9, medium effects, all of which were significant (p's < 0.01). The effects were of very similar magnitude for Novel pairs (ranging from 2.8 to 4.0) and Repeated pairs (ranging from 3.2 to 3.9), with no significant differences between the two (p's > 0.10).

For baseline to maintenance, Overall ORs ranged from 1.3 to 1.9, small effects, none of which were significant (p's > 0.10). The effects were numerically larger for Novel pairs (ranging from 1.2 to 2.9) than for Repeated pairs (ranging from 1.2 to 1.7), however none of the effects were significant nor were they different from each other (p's > 0.10).

XH46

For baseline to immediate post-treatment, overall ORs ranged from 1.3 to 1.6, none of which were significant (p's > 0.10). Effects for Novel pairs ranged from 0.7 to 1.1, none of which were significant (p's > 0.10). However, effects for Repeated pairs ranged from 1.5 to 3.5, with significant improvement for Strings ISO and Words ISO (p's < 0.01). The difference between Novel and Repeated pairs was marginally significant for String ISO ($p \approx 0.8$), driven by significant improvement for Repeated pairs but (non-significant) declines for Novel pairs.

For baseline to maintenance, overall ORs ranged from 1.2 to 2.2, none of which were significant (p's > 0.10). Effects for Novel pairs showed non-significant declines (ORs 0.6–0.7), whereas effects for Repeated pairs (ORs 2.4–6.6) showed improvements that were significant for Strings ISO and Words ISO (p's < 0.05). The difference between Novel and Repeated pairs for Words ISO was marginally significant ($p \approx 0.06$), driven by significant improvement on Repeated pairs and (non-significant) declines on Novel pairs.

Summary

Participants CN39 and KG62 showed no significant changes from baseline, at either immediate post-treatment or maintenance.

KC3 showed significant improvement on Repeated pairs, with large effect sizes for Strings ISO (ORs 6.7 and above) and small-to-medium effects for Words ISO. KC3's improvements on Repeated items were significantly greater than on Novel pairs (which showed no significant changes). These improvements were maintained 3 months after finishing treatment.

KK55 showed significant improvements on both Novel and Repeated items immediately post-treatment, with medium effect sizes (ORs 2.8–3.9). However, improvements were not significantly maintained 3 months after treatment.

Finally, XH46 showed significant improvement only for Repeated items, for Strings ISO or Words ISO; the effect sizes were small-to-medium immediately post-treatment (ORs 2.3–3.5) but were medium-to-large 3 months after treatment (ORs 3.6–6.6).

Research Question 2

Will this treatment that combines repeated and novel stimuli in the probe stimuli lead to improvements in outcome measures? Results of an analysis of outcome measures before and after treatment and at 3 months post-treatment are reported below.

Concrete and Abstract Word and Word Sequences Repetition Test

No significant changes were observed on the String ISO outcome measure; the following results all reflect changes in Words ISO.

CN39

There was a significant interaction between Time Point (baseline vs. 3 months) and String Size (OR $= 0.73$, $p < 0.05$). Follow-up comparisons revealed that this interaction was driven by a significant decrease from baseline to 3 months post-treatment for pairs (65 to 53%; OR $= 0.60$, $p < 0.05$) contrasting with a trend toward an increase for triplets (41 to 43%; OR $= 1.09$, $p \approx 0.64$).

KC3

There was a marginal interaction between Time Point (baseline vs. 3 months) and String Size (OR $= 0.76$, $p \approx 0.08$). Follow-up comparisons revealed a similar pattern of results as observed for CN: the interaction was driven by a marginally significant increase for triplets (19 to 26%; OR $= 1.47$, $p \approx 0.08$) contrasting with a trend toward a decrease in accuracy for pairs (46 to 42%; OR $= 0.84$, $p \approx 0.43$).

KG62

There was a significant main effect of Time Point (baseline vs. immediate post-treatment), reflecting an overall improvement from 12 to 16% (OR $= 1.74$, $p < 0.05$). There was also a significant interaction between Time Point (baseline vs. 3 months) and Word Type (OR $= 1.78$, $p < 0.05$). Follow-up comparisons revealed the interaction was driven by a marginally significant increase for abstract words (4 to 7%, OR $= 2.25$, $p \approx 0.11$) contrasting with a trend toward a decrease for concrete words (21 to 16%, OR $= 0.73$, $p \approx 0.24$).

KK55

There was a marginal interaction between Time Point (baseline vs. 3 months) and String Size (OR $= 1.41$, $p \approx 0.07$). Follow-up comparisons revealed the interaction was driven by a marginally significant decrease in accuracy for triplets (15 to 9%; OR $= 0.59$, $p \approx 0.07$) contrasting with a trend toward an increase in accuracy for pairs (31 to 35%; OR $= 1.18$, $p \approx 0.48$).

XH46

There was a significant interaction between Time Point (baseline vs. 3 months) and Delay (OR $= 1.49$, $p < 0.01$), and marginally significant interactions between Time Point (baseline vs. immediate post-treatment) and Duration (OR $= 1.29$, $p \approx 0.09$) and Time Point (baseline vs. 3 months) and Word Type (OR $= 0.77$, $p \approx 0.09$). Because of the presence of interactions between Time Point and both Delay and Word Type, we tested for the presence of a 3-way interaction; this was found to be significant, OR $= 1.32$, $p \approx 0.014$. Follow-up comparisons revealed the interaction was driven by significant decreases particular to abstract words tested at the 5-s delay, contrasting with no change or improvements at 1-s and for concrete words. The specific pattern was: at 1-s delay, there were no significant changes for

TABLE 3 | Spans in serial order (ISO) and in any order (IAO) at pre-treatment, immediate post-treatment, and 3 months maintenance.

		Participant ID									
		CN39		KC3		KG62		KK55		XH46	
Span task	**Time Point**	**ISO**	**IAO**	**ISO**	**IAO**	**ISO**	**IAO**	**ISO**	**IAO**	**ISO**	**IAO**
Concrete word repetition span	Pre-tx	3	3	2	2	1.2	1.2	2.2	2.2	2	2.8
	Immediate post-tx	3	3	2	2	1.8	1.8	2	2	2.4	2.6
	3 mo post-tx	3.4	3.4	2	2	1.2	1.2	2.2	2.2	3.0*	3.2
Word pointing span	Pre-tx	4.2	4.2	2	2.2	3	3	2.4	2.6	2.4	3
	Immediate post-tx	3.8	3.8	2	2	2.6	2.8	2.6	2.8	3	3
	3 mo post-tx	4.4	4.4	2	2.2	3.4	3.4	2.4	2.4	3	3
Corsi block span	Pre-tx	5.7	6	5	5.3	4.7	7	4	4	5	6
	Immediate post-tx	5.7	6.7	4.3	5.7	4.7	5.7	4	4.7	5	5.3
	3 mo post-tx	5.3	6	4	4.7	5.3	5.7	4.3	4.3	4.7	6

**Increase of 1.0 in span is considered to be noteworthy improvement.*

abstract words (p's > 0.10), but at 5-s, abstract words decreased significantly from baseline to immediately post-treatment (44 to 27%, OR = 0.45, $p < 0.05$) and remained near significantly below baseline at 3 months (28%, OR = 0.55, $p \approx 0.053$). This contrasts with concrete words, which showed no effects of duration but rather numerical improvement from baseline to immediate post-treatment (38–39%) and marginally significant improvement from baseline to 3 months (38 to 47%, OR = 1.42, $p \approx 0.08$).

Summary

In terms of improvements on this task, one participant (KG62) showed significant gains overall, while two individuals (KC3 and XH46) showed marginally significant gains specific to certain conditions. Specifically, KC3 marginally improved on Triplets at 3 months post-treatment, and XH46 marginally improved on Concrete words at 3 months post-treatment. KG62, who improved significantly in general from baseline to immediate post-treatment, remained marginally significantly better at Abstract words 3 months post-treatment. Neither CN39 nor KK55 showed any improvements (p's > 0.10); instead, they showed some declines (CN39 performed significantly worse on Pairs at 3 months post-treatment; KK55 performed marginally worse on Triplets 3 months post-treatment).

Verbal and non-verbal span tasks. The results of three span measures are reported in **Table 3**.

Concrete Immediate Serial Recall Span Test

Using Log Odds ratios, we looked at pre- and post-spans to determine improvement. One person, XH, showed an improvement from 2.0 ISO span before treatment to a span of 3.0 ISO at maintenance (trend: $p = 0.0655$). As a participant in the version of this treatment reported by Martin et al. (6), XH46's performance on the Concrete Immediate Serial Recall Span Test improved from 1.4 ISO pre-treatment to 2.4 ISO post-treatment. Thus, his concrete word span, as measured in this study, shows continued improvement.

Word Pointing Span Task

No significant gains in word pointing span were observed for any participant from baseline to immediate post-treatment and maintenance testing at 3 months.

Corsi Block Span Task

No significant gains were observed on this measure of non-verbal span for any participant from baseline to immediate post-treatment and maintenance testing at 3 months.

Comprehensive Aphasia Test (CAT)

Results of the Comprehensive Aphasia Test (27) are shown in **Table 4**. All subtests of the Comprehension of Spoken Language (Spoken Words, Spoken Sentences, and Spoken Paragraphs) as well as the Naming Objects subtest under Spoken Language Production were compared pre-treatment and post-treatment using t-scores to determine change. Benchmarks varied for significant improvement and were taken from the CAT manual. Two of the five participants showed some significant improvement. For Comprehension of Spoken Language, KK55 went from a t-score of 43 at baseline, to 57 at immediate post-treatment, and 55 at maintenance. XH46 improved in Spoken Language Production (naming objects) with a t-score of 51 at baseline to 59 at maintenance. These results are shown in **Table 4**. It is worth noting here that XH46 also showed improvement in naming [on the Philadelphia Naming Test, (39)] in the version of this therapy reported by Martin et al. (6).

Discourse Samples

One of the five participants demonstrated evidence of improvement on the primary discourse outcome (%CIUs), while one participant demonstrated a decline. At pre-treatment, KK55 produced 49% CIUs which increased to 60% at post-treatment. His total number of words at pre-treatment were 670 and 486 at post-treatment. Total number of CIUs produced were 327 at pre-treatment and 290 at post-treatment. This combination of higher %CIUs and lower total words indicates an increase in his efficiency of relevant content production. CN39 produced a smaller proportion of mazes when comparing

TABLE 4 | Comprehensive Aphasia Test (CAT) subtest T-scores at pre-treatment (pre-tx), immediate post-treatment (imm post), and 3 months maintenance (3 mo post).

		CN39			KC3			KG62			KK55			XH46		
Language domain	**Subtest**	**Pre-tx**	**Imm post**	**3 mo post**	**Pre-tx**	**Imm post**	**3 mo post**	**Pre-tx**	**Imm post**	**3 mo post**	**Pre-tx**	**Imm post**	**3 mo post**	**Pre-tx**	**Imm post**	**3 mo post**
Comprehension of spoken language	Spoken words	58	53	58	49	45	55	60	51	58	46	53	53	58	65	65
	Spoken sentences	65	60	57	41	43	44	53	52	54	43	57	55*	65	67	65
	Spoken paragraphs	49	49	43	43	49	43	49	49	49	49	43	49	60	60	60
	Total score	61	56	55	43	43	46	53	50	53	43	53*	52*	62	67	65
Spoken language production	Naming objects	64	60	61	53	54	54	53	50	50	62	66	61	51	52	59*

*Significant T-score changes (indicated by an *) vary by subtest and are taken from Table 4.3 in the CAT manual. For Spoken Words and Spoken Sentences the change is 9, for Spoken Paragraphs the change is 10, for Total Comprehension of Spoken Language the change is 7, and for Naming Objects the change is 7.*

pre-treatment to post-treatment performance. At pre-treatment he produced 22% mazes which were determined by dividing the total number of mazes (false starts and filled pauses) over the total words produced. At post-treatment, %mazes decreased to 14% which could indicate improved efficiency of lexical retrieval since false starts and filled pauses are often considered behavioral indicators of lexical retrieval difficulty (40). KG62 demonstrated a decline in %CIUs when comparing pre-treatment and post-treatment performance. At pre-treatment he produced 50% CIUs and at post-treatment 40% CIUs. Total words (pre-treatment = 291, post-treatment = 324) and total CIUs (pre-treatment = 146, post-treatment = 130) were consistent with this decline and indicated a reduction in efficiency and relevant content which was evidenced by the production of more words and fewer CIUs.

Performance on Control Tasks Before and After Treatment and at 3 Months Post-treatment

Individual performance on the control tasks is detailed below.

CN39

The PALPA non-word reading accuracy increased significantly from 11% at baseline to 26% immediately post-treatment, OR = 2.87, $p < 0.05$. At 3 months post, the score remained marginally significant above baseline at 23%, OR = 2.38, $p \approx 0.09$. The 5-point drawing test (5PT) decreased significantly from 61% at baseline to 39% immediately post-treatment, OR = 0.42, $p < 0.01$, but there was no significant difference between baseline and 3 months post-treatment (53%, OR = 0.75, $p \approx 0.39$).

KC3

The PALPA score increased significantly from 5% at baseline to 20% immediately post-treatment, OR = 4.10, $p < 0.05$. At 3 months post, the score remained significantly above baseline at 19%, OR = 3.92, $p < 0.05$. The 5PT increased significantly from 68% at baseline to 85% immediately post-treatment, OR = 2.67, $p < 0.05$, but there was no significant difference between baseline and 3 months post-treatment (78%, OR = 1.75, $p \approx 0.23$).

KG62

The PALPA score showed no significant changes, neither from baseline (5%) to immediately post-treatment (4%, OR = 0.74, $p \approx 0.70$), nor to 3 months post (6%, OR = 1.13, $p \approx 0.87$). The 5PT decreased significantly from 43% at baseline to 23% immediately post-treatment, OR = 0.38, $p < 0.01$, and remained significantly below baseline to 3 months post-treatment (24%, OR = 0.41, $p < 0.01$).

KK55

The PALPA score increased significantly from 25% at baseline to 53% immediately post-treatment, OR = 3.35, $p < 0.001$. At 3 months post, the score remained significantly above baseline at 46%, OR = 2.54, $p < 0.5$. The 5PT showed no significant changes from baseline to immediate post-treatment (unchanged at 61%, OR = 0.98, $p \approx 0.96$) or 3 months post-treatment (57%, OR = 0.82, $p \approx 0.60$).

XH46

The PALPA score showed no significant changes, neither from baseline (0%) to immediately post-treatment (0%) nor to 3 months post (0%). The 5PT likewise showed no significant changes, from 37% at baseline to 31% immediately post-treatment (OR = 0.78, $p \approx 0.50$), and 38% at 3 months post-treatment (OR = 1.06, $p \approx 0.88$).

Summary of Performance on Control Tasks

Linguistic Control, Non-word Reading

CN39, KC3, and KK55 showed significant improvements immediately post-treatment and this improvement was maintained at 3 months (significant for KC3 and KK55 and marginally significant for CN39).

Non-linguistic Control, the Five-Point Test

KC3 increased significantly immediately following treatment, but this was not maintained at follow-up. Other participants did not show any significant improvement on this test immediately following treatment or at follow-up.

Research Question 3

Will improvements in outcome measures be most robust for those participants who show a maintenance deficit in repetition?

Two participants, KK55 and XH46, demonstrated the activation maintenance impairment with accuracy of word and non-word repetition declining after a 5-s response delay (**Table 2**). KK55 demonstrated significant improvement on the treatment task for both repeated and unrepeated items from baseline to post-treatment and baseline to maintenance (3 months post treatment). XH46 showed significant improvement for repeated items at post-treatment and at maintenance. Of those who did not show the maintenance impairment in repetition, only KC3 showed improvement in word repetition after this treatment for repeated items immediately post-treatment and at 3 months maintenance.

On outcome measures, KK55 showed significant improvement on the comprehension of spoken sentences subtests of the CAT and XH46 improved significantly on the naming subtest of the CAT. On the span tasks, XH46's span for concrete words increased from 2 to 3. On Discourse measures, KK55 improved significantly on the rate of CIUs produced. On the repetition of concrete-abstract sequences test, KG62 showed an overall main effect from baseline to immediate post-test, and XH46 showed a significant decrease in accuracy specific to abstract words at a 5-s delay.

In summary, three participants showed significant effects sizes for the treatment, KK55, XH46, and KC3, but only KK55 showed these effects for repeated and novel probes. KK55 and XH46, who demonstrated the activation maintenance deficit in repetition, also made gains on outcome measures as detailed above.

These findings indicate that this treatment is most effective with individuals who show an activation maintenance deficit in repetition, KK55 and XH46. To illustrate the improvement by the two participants relative to other participants in this treatment study, **Table 5** shows nine language and verbal span measures where evidence can be found for improvement. KK55 and XH46 made gains on four of the nine measures, followed by KC3 who improved on two and then CN39 and KG62 who each improved on one of the nine measures.

DISCUSSION

The treatment described here is a follow-up from the treatment reported by Martin et al. (6) in which item exposure in a word sequence repetition treatment was minimized to reveal effects of a 5-s response delay, which invokes short-term maintenance of activated word representations. By tackling the difficulty in maintaining activation of representations directly, we aimed to improve this ability that supports access to and retrieval of words in repetition, naming and other language tasks. The results of that study were different from our prior studies [e.g., (14, 41)] that combined the response delay manipulation with a set of treated, untreated and probe items used in all phases of treatment (baseline through maintenance). In this study, we investigated more closely the effect of response delay with and without the added influence of repeated item exposure. As in the Martin et al. (6) study, some participants improved following this treatment while others did not. Some possible reasons for this outcome are offered below.

Starting with our initial aim, we first wanted to know if an effect of repeated exposure would be evident for items repeated in the probe trials compared to those items that were unique on each probe trial. Two participants, CN39 and KG62, showed no improvement on repeated or novel probes. For those individuals who benefited from the treatment, KC3 and XH46 showed significant improvement on the repeated probe items compared to the novel probe items. KK55 showed comparable levels of improvement on both repeated and novel probe item conditions.

In Martin et al. (6), effects of the maintenance treatment with minimal repetition of stimuli were modest overall, but still, improvements in outcome measures were observed for four of the eight participants. A similar pattern was observed in this study with two of the participants who demonstrated the activation maintenance impairment showing gains in several outcome measures. KK55 improved on the CAT sentence comprehension test and the primary discourse measure, % CIUs. XH46 improved in naming on the CAT test and showed a span increase from 2 to 3. This increase demonstrates continued improvement from the change in his span that was observed when he participated in the Martin et al. (6) study (span increased from 1.4 to 2.4).

XH46's continued gains in span abilities in this second round of a version of the activation maintenance treatment raises the question of effectiveness of multiple treatments distributed over time. KC3 and CN39, whose gains were more limited, also participated in the Martin et al. (6) activation maintenance treatment study. Although evidence favors the benefit of multiple treatment periods distributed over time [e.g., (42)], the span of time between participation in these two studies ranged from 15 to 24 months. With this amount of time and the likelihood of participation in numerous communication activities in the interim, we considered this to be a new treatment for these

TABLE 5 | Summary of gains made on the outcome measures.

	Measure	CN39	KC3	KG32	KK55	XH46
1	Treatment effect sizes - repeated probes		+		+	+
2	Treatment effect sizes - novel probes				+	
3	Concrete and abstract word sequence repetition		+*	+		+*
4	Concrete words immediate serial recall					+
5	Word Pointing span					
6	CAT Spoken Language Comprehension				+	
7	CAT Spoken Word production (Naming)					+
8	Discourse: Increased CIUs				+	
9	Discourse: Decreased % Mazes	+				
	Total of measures showing some improvement	**1**	**2**	**1**	**4**	**4**

+ *signifies an effect significant at* $p < 0.05$.
+* *signifies a marginally significant effect.*

three individuals rather than a continuation of their previous participation in a similar treatment. Nonetheless, it is worth noting that XH46 showed continued improvement in this second round of the activation maintenance treatment.

We also observed changes in the two control tasks following therapy, especially the linguistic control, non-word reading. Three participants improved on this measure, CN39, KC3, and KK55. In hindsight, this outcome is not completely surprising given the nature of the treatment—practice in maintaining access to words (their activation) sufficiently for longer periods of time. This ability is fundamental to language processing, and improvements in this ability could result in improvements on other language tasks besides the treatment task. Non-word reading is considered a distant measure, meaning there is not much overlap with the repetition task used for treatment. However, non-words are potential words and reading does share output production processes with repetition. Thus, some extension of improvements to this task may be expected. Of greater concern is the improvement seen for participant KC3 on the 5-point test, the non-linguistic control task. However, this improvement was observed in the immediate post-treatment testing but was not sustained in the 3 months maintenance testing period. This finding could also be indicative of the potency of repeated trials in acquisition, similar to the repeated probe items.

Understanding the Linguistic and Processing Components of This Treatment and Word Processing Impairments in Aphasia

The activation maintenance treatment combines repetition with a response delay. Here, we disentangled influences of the linguistic component (the words to be repeated) and the activation maintenance component (the response delay) by varying the exposure of items in the probes, with some repeated across all probe trials and others novel across probe trials. The results indicate that the treatment was successful for some but not all the participants, and more successful when items in probes were repeated. As we develop and refine this treatment approach toward its eventual use in the clinic, it is worth addressing a few questions about the approach and its potential as a clinical tool.

Why Do Some People Respond to This Treatment and Not Others?

One of the most important issues to be addressed in aphasia rehabilitation is why some people with aphasia respond well to an impairment-based treatment while others do not. An obvious first thought is that the treatment does not match up with the impairment. With broad diagnoses such as Broca's aphasia or fluent aphasia, it is likely that there will be enough variability in symptoms within a diagnostic category that some people with that diagnosis would not respond well to a treatment designed for its cardinal symptoms. A related concern is that other cognitive abilities (e.g., attention) may be impaired and are somehow compounding the language impairment. As diagnostic tools become more detailed in their descriptions of an impairment, the matches between treatment and impairment type should fit more closely. Psycholinguistic models and linguistic theory, for example, have guided development of tests that probe access to linguistic elements of words and sentences [e.g., (21, 43)], providing more precise measurements of impairments to language function.

The activation maintenance treatment is an outgrowth of another variable of impairment to language ability, the processing component. Our knowledge of the components of activation processes that support language is increasing [e.g., (1, 44, 45)]. Studies also have revealed how impairment to processing components impacts language performance (2–5, 46). Martin and Dell (5) provide evidence for two processing parameters, activation transmission and activation maintenance, that regulate access and retrieval of words. This study provides further evidence that the activation maintenance component of language processing is a viable treatment target for certain participants. Similar to Martin et al. (6), we found that participants with poor maintenance of activated word representations in repetition, KK55 and XH46, made the most gains on the treatment task and outcome measures (see **Table 5**).

What Is the Nature of the Separate and Combined Linguistic and Activation Maintenance Components of This Treatment?

KK55 was the only participant who improved on both novel and repeated probe items. Further, KK55 demonstrated improvement on several outcome measures including the CAT and the primary discourse outcome (%CIUs). At pre-treatment, KK55's scores on word and non-word repetition were higher than the other participants in the 1-s condition (see **Table 2**) and his scores dropped after 5 s. Thus, KK55's pre-treatment profile suggests that access to linguistic information (the activation transmission component of language processing) is less problematic for him than maintaining access to those representations. XH46 also presents with a maintenance deficit, but when comparing his pre-treatment assessment results and his response to this treatment, the pattern is quite different than KK55. XH46's language performance is more impaired than KK55's in the 1-s condition of the repetition and two working memory tasks, synonymy and rhyming triplets, and it becomes even more impaired in the 5-second condition.

Additionally, XH46's accuracy on the TALSA naming subtests (**Table 2**) improves after a 5-s response delay, which is the signature of an activation transmission deficit. How can we account for the XH46's task specific activation impairments, transmission in naming and maintenance in repetition? We suggest that XH46's lexical activation impairment includes both transmission and maintenance components and that the manifestation of these deficits differs depending on the task and the locus of impairment. As described in the Introduction, in word production, activation spreads from activated semantic representations to an arbitrarily related word form. In repetition, activation spreads from an input sequence of phonemes to a phonological word form. It is conceivable that the spread of activation from semantics to the lexical form is more vulnerable to a transmission impairment than the input phonological activation to a phonological word form. Regarding the locus of impairment, XH46's performance on all subtests reported in **Table 2** was impaired, but it was less accurate on those subtests with a substantial semantic component (naming and synonymy triplets). In treatment, XH46's improvement on the repeated probe items suggests that this condition provided priming of the semantic-lexical representations needed to facilitate the transmission between these levels of representation. A broader message of this finding is that both lexical priming (i.e., repeated exposure of training items) and processing (activation transmission or maintenance) treatments may be needed for more severely impaired language abilities or when there are different severity levels of impairment to semantic vs. phonological processes.

How Do the Activation Maintenance and Transmission Treatments Fit With Current Taxonomies of Treatment Approaches?

Recent developments in rehabilitation science provide a framework for evaluating principles and components of treatment approaches, the Rehabilitation Treatment Specification System [RTSS, (47, 48)], that can be applied to various rehabilitation practices (e.g., physical therapy, occupational therapy). Turkstra et al. (49) propose the application of this system to practice in speech and language pathology and in a recent series of papers (50–53), a group of researchers in aphasia rehabilitation considered the value of the RTSS framework for evaluating rehabilitation approaches in aphasia. RTSS evaluates three aspects of a treatment: the target (behavior that the treatment will change), the treatment ingredients (essential elements of the treatment) and the mechanism(s) of action (how a treatment works). Within this framework, the characterization of the treatment reported here and its variants (6, 14) could be the following: The target is improved access to words in the context of various language tasks and the endurance of that activation. There are three ingredients in this treatment: the task (repetition, but could be another language task, e.g., naming), a response delay and repetition priming *via* repeated exposure of probes and/or training items (6). Martin et al. (10) demonstrated adverse or beneficial effects of a response delay on performance of many language tasks, allowing for flexibility in the choice of therapy target and task. Logically speaking, the response delay should be essential to a treatment that aims to improve maintenance of activation, simply because it targets the deficit directly. It could also be a sufficient ingredient for some [e.g., KK55 in this study and four of the participants in the Martin et al. (6) study]. For others, though, lexical priming may be needed in combination with a response delay to improve performance after a 5-s response delay. It is not certain whether lexical priming alone (through repeated practice on probe items in this study) could be sufficient to improve the ability to maintain activation of a word to the extent that repetition accuracy increases after a response delay. This possibility would be difficult to test because the definition of an activation maintenance impairment is accurate repetition with no delay in response and impaired repetition after a response delay. The evidence thus far suggests that lexical priming in combination with a response delay is effective for some participants and for others, targeting the response delay alone (with the novel lexical items) improves accuracy after the delay, suggesting improvement in activation maintenance ability. Further studies are needed to learn how to detect impairments that involve each component of repetition—lexical activation and maintenance of that activation, or some combination of these. As we investigate variations of this paradigm in future studies, we note that RTSS characterization of task components has served as a useful starting point to understanding the cognitive-linguistic mechanisms that underlie this treatment.

Limitations

One limitation of this study is the method used to evaluate item repetition. In hindsight, it might have been beneficial to include repeated probe items and repeated treatment items to further evaluate how item repetition was related to acquisition. In future studies, we will investigate effects of varying repeated and novel training items as well as probe items.

Clinical Implications and Future Directions

The results of this study illuminate three clinically relevant findings: (1) The verbal STM component of word processing (activation maintenance) is a potential target for intervention

and for some participants, addressing this ability directly by adding a response delay, can improve overall language performance. (2) Item repetition plays a role in improvement potentially through practice effects and/or priming effects. (3) These two variables, item repetition and activation maintenance, may be differentially affected in someone's overall profile of input and output word processing abilities. The results of this study provide greater insight into the nature of the treatment task itself, including its lexical component (words to be repeated) and processing component (the response delay). Both components are important to the success of the therapy, but there is an indication that some may need the temporal processing component of the treatment more than the lexical component.

Future testing is needed to determine how these two components contribute to the success of the treatment and whether those contributions vary depending on the nature of the lexical impairment (semantic and/or phonological), its severity or other factors. Additionally, to better understand the mechanism of this improvement more studies are needed that evaluate the contributions of these two components of lexical processing in different tasks and in the context of various lexical processing profiles (i.e., semantic or phonological input and output impairments). To that end, we are currently investigating the effectiveness of a naming treatment that follows the same principles as the repetition plus response delay treatment (7).

CONCLUSION

This study of a treatment for word processing impairment in aphasia focuses on improving one of two parameters of activation that support access to and retrieval of words. The treatment task is repetition and a critical addition to that task is a response delay that for some people with aphasia, challenges their ability to maintain activation of the words that are to be repeated. The results of this study showed that this treatment led to gains in the treatment task (repetition of concrete word pairs after a 5-s delay) for three of our five participants when items in probes were repeated and for one person when the probes used novel items on each probe trial. On the outcome measures, we found evidence indicating that this treatment is specific to those who demonstrate an impairment of activation maintenance in repetition; two participants that demonstrated this deficit made gains on more outcome measures than the other participants in this study.

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 Temple University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NM, JO, JS, and RW contributed equally to the content of this research and to the written document. JO and JS provided the treatment and analysis of the data. RW provided statistical analyses and interpretation of the treatment results and outcome measures. NM provided her expertise on theories of lexical processing theories of language and aphasia that postulate a role of verbal STM in language processing. All authors contributed equally to writing as well as to the discussion and interpretation of the results of this study. All authors contributed to the article and approved the submitted version.

FUNDING

Research reported in this publication was supported by National Institute on Deafness and other Communication Disorders Center of the National Institutes of Health under award numbers R01DC013196 and R01DC016094.

ACKNOWLEDGMENTS

We are grateful to the five individuals with aphasia who participated in this study. Their time and interest in this work is much appreciated. We would also like to thank undergraduate volunteers Moira Mckniff for her help with reliability scoring and Brenna Rapone for her assistance with data compilation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fresc.2022.824684/full#supplementary-material

REFERENCES

1. Foygel D, Dell GS. Models of impaired lexical access in speech production. *J Mem Lang.* (2000) 43:182–216. doi: 10.1006/jmla.2000.2716
2. Dell GS, Schwartz MF, Martin N, Saffran EM, Gagnon DA. Lexical access in aphasic and non-aphasic speakers. *Psychol Rev.* (1997) 104:801–38. doi: 10.1037/0033-295X.104.4.801
3. Schwartz MF, Dell GS, Martin N, Gahl S, Sobel P. A case series test of the two-step interactive model of lexical access: evidence from picture naming. *J Mem Lang.* (2006) 54:228–64. doi: 10.1016/j.jml.2005.10.001
4. Dell GS, O'Seaghdha PG. Stages of lexical access in language production. *Cognition.* (1992) 42:287–314. doi: 10.1016/0010-0277(92)90046-K
5. Martin N, Dell GS. Maintenance versus transmission deficits: the effect of delay on naming performance in aphasia. *Front Hum Neurosci.* (2019) 2019:406. doi: 10.3389/fnhum.2019.00406

6. Martin N, Schlesinger J, Obermeyer J, Minkina I, Rosenberg S. Treatment of verbal short-term memory abilities to improve language function in aphasia: a case series treatment study. *Neuropsychol Rehabil.* (2020) 48:199–22. doi: 10.1080/09602011.2020.1731554
7. Martin N, Schlesinger J, Obermeyer J, Wiley R, Dell GS. A computational account of naming impairments in aphasia, including model-based diagnosis, treatment, and post-treatment assessment. *Soc Neurobiol Lang.* (2021) 5:2021. doi: 10.1017/S1366728912000533
8. van Hees S, Angwin A, McMahon K, Copland D. A comparison of semantic feature analysis and phonological components analysis for the treatment of naming impairments in aphasia. *Neuropsychol Rehabil.* (2013) 23:102–32. doi: 10.1080/09602011.2012.726201
9. Schuchard J, Middleton EL. Word repetition and retrieval practice effects in aphasia: evidence for use-dependent learning in lexical access. *Cogn Neuropsychol.* (2018) 35:271–87. doi: 10.1080/02643294.2018.1461615
10. Martin N, Minkina I, Kalinyak-Fliszar M, Kohen FP. Assessment of linguistic and verbal short-term memory components of language abilities in aphasia. *J Neurolinguist Res.* (2018) 48:199–225. doi: 10.1016/j.jneuroling.2018.02.006
11. Obermeyer J, Reinert L, Kamen RM, Pritchard-Laval D, Park H, Martin N. Effects of memory load and typicality of semantic category on semantic processing in aphasia. *Am J Speech Lang Pathol.* (2021) 20:283. doi: 10.1044/2021_AJSLP-20-00283
12. Minkina I, Rosenberg S, Kalinyak-Fliszar M, Martin N. Short-term memory and aphasia: from theory to treatment. *Semin Speech Lang.* (2017) 38:17–28. doi: 10.1055/s-0036-1597261
13. Salis C, Kelly H, Code C. Assessment and treatment of short-term and working memory impairments in stroke aphasia: a practical tutorial. *Int J Lang Commun Disord.* (2015) 50:721–36. doi: 10.1111/1460-6984.12172
14. Kalinyak-Fliszar M, Kohen F, Martin N. Remediation of language processing in aphasia: improving activation and maintenance of linguistic representations in (verbal) short-term memory. *Aphasiology.* (2011) 25:1095–131. doi: 10.1080/02687038.2011.577284
15. Koenig-Bruhin M, Studer-Eichenberger F. Therapy of short-term memory disorders in fluent aphasia: a single case study. *Aphasiology.* (2007) 21:448–58. doi: 10.1080/02687030600670593
16. Majerus S, Van Der Kaa MA, Renard C, Van der Linden M, Poncelet M. Treating verbal short-term memory deficits by increasing the duration of temporary phonological representations: a case study. *Brain Lang.* (2005) 95:174–5. doi: 10.1016/j.bandl.2005.07.094
17. Salis C. Short-term memory treatment: patterns of learning and generalization to sentence comprehension in a person with aphasia. *Neuropsychol Rehabil.* (2012) 22:428–48. doi: 10.1080/09602011.2012.656460
18. Walker I, Hulme C. Concrete words are easier to recall than abstract words: evidence for a semantic contribution to short-term serial recall. *J Exp. Psychol. Learn Mem Cogn.* (1999) 25:1256–71. doi: 10.1037/0278-7393.25.5.1256
19. Reilly J, Kean J. Formal distinctiveness of high- and low-imageability nouns: analyses and theoretical implications. *Cogn Sci.* (2010) 41:1071–89. doi: 10.1080/03640210709336988
20. Kertesz A. *Western Aphasia Battery-Revised (WAB-R).* Austin, TX: Pro-Ed (2006). doi: 10.1037/t15168-000
21. Kay J, Lesser R, Coltheart M. Psycholinguistic assessments of language processing in aphasia (PALPA): An introduction. *Aphasiology.* (1996) 10:159–80. doi: 10.1080/02687039608248403
22. Martin N, Kohen FP, Kalinyak-Fliszar M, Soveri A, Laine M. Effects of increased working memory load on processing of sounds and words in aphasia. *Aphasiology.* (2012) 26:462–93. doi: 10.1080/02687038.2011.619516
23. Brysbaert M, Warriner AB, Kuperman V. Concreteness ratings for 40 thousand generally known English word lemmas. *Behav Res Methods.* (2014) 46:904–11. doi: 10.3758/s13428-013-0403-5
24. Brysbaert M, New B. Moving beyond Kucera and Francis: a critical evaluation of current word frequency norms and the introduction of a new and improved word frequency measure for American English. *Behav Res Methods.* (2009) 41:977–90. doi: 10.3758/BRM.41.4.977
25. Corsi PM. *Human Memory and the Medial Temporal Region of the Brain*. (Doctoral Thesis), McGill University, Montreal, QC, Canada (1972).
26. Kessels RPC, van Zandvoort MJE, Postma A, Kappelle LJ, de Haan EHF. The corsi block-tapping task: standardization and normative data. *Appl Neuropsychol.* (2000) 7:252–8. doi: 10.1207/S15324826AN0704_8
27. Swinburn K, Porter G, Howard D. *The Comprehensive Aphasia Test*. Hove: Psychology Press (2005). doi: 10.1037/t13733-000
28. Nicholas LE, Brookshire RH. A system for quantifying the informativeness and efficiency of the connected speech of adults with aphasia. *J Speech Lang Hear Res.* (1993) 36:338–50. doi: 10.1044/jshr.3602.338
29. Zakariás L, Salis C, Wartenburger I. Transfer effects on spoken sentence comprehension and functional communication after working memory training in stroke aphasia. *J Neurolinguistics.* (2018) 48:47–63. doi: 10.1016/j.jneuroling.2017.12.002
30. Goebel S, Fischer R, Ferstl R, Mehdorn HM. Normative data and psychometric properties for qualitative and quantitative scoring criteria of the Five-point Test. *Clin Neuropsychol.* (2009) 23:675–90. doi: 10.1080/13854040802389185
31. Psychology Software Tools, Inc. *E.-Prime, 2.0*. Pittsburgh, PA. (2012). Available online at: https://pstnet.com/ (accessed January 31, 2022).
32. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* (1977) 33:159–74. doi: 10.2307/2529310
33. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw.* (2015) 67:1–48. doi: 10.18637/jss.v067.i01
34. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria (2021). Available online at: https://www.R-project.org/
35. Lenth RV. *Emmeans: Estimated Marginal Means, aka Least-Squares Means. R Package Version 1.5.5–1*. (2021).
36. Edmonds LA, Nadeau SE, Kiran S. Effect of verb network strengthening treatment (VNeST) on lexical retrieval of content words in sentences in persons with aphasia. *Aphasiology* (2009) 23:402–24. doi: 10.1080/02687030802291339
37. Wambaugh JL, Ferguson M. Application of semantic feature analysis to retrieval of action names in aphasia. *J Rehabil Res Dev.* (2007) 44:381–94. doi: 10.1682/jrrd.2006.05.0038
38. Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odd rations in epidemiological studies. *Commun Statist.* (2010) 39:860–4. doi: 10.1080/03610911003650383
39. Roach A, Schwartz MF, Martin N, Grewal RS, Brecher A. The Philadelphia naming test: scoring and rationale. *Clin Aphasiol.* (1996) 24:121–33. doi: 10.1037/t56477-000
40. Obermeyer JA, Leaman MC, Edmonds LA. Evaluating change in the conversation of a person with mild aphasia after attentive reading with constrained summarization-written treatment. *Am J Speech Lang Pathol.* (2020) 29:1618–28. doi: 10.1044/2020_AJSLP-19-00078
41. Martin N, Kohen FP, McCluskey M, Kalinyak-Fliszar M, Gruberg N. Treatment of a language activation maintenance deficit in Wernicke's Aphasia. In: *Clinical Aphasiology Conference*. Keystone, Colorado (2009).
42. Schuchard J, Rawson KA, Middleton EL. Effects of distributed practice and criterion level on word retrieval in aphasia. *Cognition.* (2020) 198:104216. doi: 10.1016/j.cognition.2020.104216
43. Thompson CK. *Northwestern Assessment of Verbs and Sentences*. Evanston, IL: NU Live Techonology (2011).
44. Rapp B, Goldrick M. Discreteness and interactivity in spoken word production. *Psychol Rev.* (2000) 107:460–99. doi: 10.1037/0033-295X.107.3.460
45. Walker GM, Hickok G. Bridging computational approaches to speech production: the semantic–lexical–auditory–motor model (SLAM). *Psychon Bullet Rev.* (2016) 23:229–352. doi: 10.3758/s13423-015-0903-7
46. Martin N, Saffran EM, Dell GS. Recovery in deep dysphasia: evidence for a relation between auditory-verbal STM and lexical errors in repetition. *Brain Lang.* (1996) 52:83–113. doi: 10.1006/brln.1996.0005
47. Van Stan JH, Dijkers MP, Whyte J, Hart T, Turkstra LS, Zanca JM, et al. The Rehabilitation Treatment Specification System: implications for improvements in research design, reporting, replication, and synthesis.

Archiv Phys Med Rehabil. (2019) 100:146–55. doi: 10.1016/j.apmr.2018.09.112
48. Hart T, Dijkers MP, Whyte J, Turkstra L, Zanca JM, Packel A, et al. A theory-driven system for the specification of rehabilitation treatments. *Arch Phys Med Rehabil.* (2019) 100:172–80. doi: 10.1016/j.apmr.2018.09.109
49. Turkstra LS, Norman R, Whyte J, Dijkers MP, Hart T. Knowing what we're doing: why specification of treatment methods is critical for evidence-based practice in speech-language pathology. *Am J Speech Lang Pathol.* (2016) 25:164–71. doi: 10.1044/2015_AJSLP-15-0060
50. Boyle M, Gordon JK, Harnish SM, Kiran S, Martin N, Rose LM, et al. Evaluating cognitive-linguistic approaches to interventions for aphasia within the rehabilitation treatment specification system (RTSS). *Archiv Phys Med Rehabil*. (2021) 7:816. doi: 10.1016/j.apmr.2021.07.816
51. Cherney LR, DeDe G, Hoover EL, Murray L, Obermeyer J, Hunting Pompon R. Applying functional communication treatment approaches for aphasia to the rehabilitation treatment specification system (RTSS). *Archiv Phys Med Rehabil*. (2021). doi: 10.1016/j.apmr.2021.10.016
52. Fridriksson J, Basilakos A, Boyle M, Cherney LR, DeDe G, Gordon JK, et al. Demystifying the complexity of aphasia treatment: Application of the Rehabilitation Treatment Specification System (RTSS). *Archiv Phys Med Rehabil*. (2021) 8:25. doi: 10.1016/j.apmr.2021.08.025
53. Johnson L, Basilakos A, Hula WD, Kiran S, Walker GM, Fridriksson J. Defining the neurobiological mechanisms of action in aphasia therapies: applying the RTSS framework to research and practice in aphasia. *Archiv Phys Med Rehabil*. (2021) 10:17. doi: 10.1016/j.apmr.2021.10.017

Author Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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.

frontiers | Frontiers in Rehabilitation Sciences

ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fresc.2022.815780

Cognitive Training to Enhance Aphasia Therapy (Co-TrEAT): A Feasibility Study

Tijana Simic[1,2], Laura Laird[3,4], Nadia Brisson[5], Kathy Moretti[5], Jean-Luc Théorêt[5], Sandra E. Black[2,4,6,7], Gail A. Eskes[2,8†], Carol Leonard[2,3,5†] and Elizabeth Rochon[2,3,4,7†]*

[1] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), Montreal, QC, Canada, [2] Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Ottawa, ON, Canada, [3] Department of Speech-Language Pathology, University of Toronto, Toronto, ON, Canada, [4] Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada, [5] School of Rehabilitation Sciences, University of Ottawa, Ottawa, ON, Canada, [6] Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [7] KITE Research Institute, Toronto Rehab, University Health Network, Toronto, ON, Canada, [8] Departments of Psychiatry and Psychology and Neuroscience, Dalhousie University, Halifax, NS, Canada

OPEN ACCESS

Edited by:
Erin L. Meier, Northeastern University, United States

Reviewed by:
Evy Visch-Brink, Erasmus University Rotterdam, Netherlands
Rossella Muò, Azienda Sanitaria Locale "Città di Torino", Italy

***Correspondence:**
Tijana Simic
tijana.simic@umontreal.ca

† These authors share senior authorship

Specialty section:
This article was submitted to Interventions for Rehabilitation, a section of the journal Frontiers in Rehabilitation Sciences

Received: *15 November 2021*
Accepted: *03 March 2022*
Published: *05 April 2022*

Citation:
Simic T, Laird L, Brisson N, Moretti K, Théorêt J-L, Black SE, Eskes GA, Leonard C and Rochon E (2022) Cognitive Training to Enhance Aphasia Therapy (Co-TrEAT): A Feasibility Study. Front. Rehabilit. Sci. 3:815780. doi: 10.3389/fresc.2022.815780

Persons with aphasia (PWA) often have deficits in cognitive domains such as working memory (WM), which are negatively correlated with recovery, and studies have targeted WM deficits in aphasia therapy. To our knowledge, however, no study has examined the efficacy of multi-modal training which includes both WM training and targeted language therapy. This pilot project examined the feasibility and preliminary efficacy of combining WM training and naming therapy to treat post-stroke PWA. Chronic PWA were randomly assigned to either the a) Phonological Components Analysis (PCA) and WM intervention (WMI) condition (i.e., a computerized adaptive dual n-back task), or b) PCA and active control condition (WMC). Participants received face-to-face PCA therapy 3 times/week for 5 weeks, and simultaneously engaged in WM training or the active control condition five times/week, independently at home. Six PWA were enrolled, 3 in each condition. Feasibility metrics were excellent for protocol compliance, retention rate and lack of adverse events. Recruitment was less successful, with insufficient participants for group analyses. Participants in the WMI (but not the WMC) condition demonstrated a clinically significant (i.e., > 5 points) improvement on the Western Aphasia Battery- Aphasia Quotient (WAB-R AQ) and Boston Naming Test after therapy. Given the small sample size, the performance of two individuals, matched on age, education, naming accuracy pre-treatment, WAB-R AQ and WM abilities was compared. Participant WMI-3 demonstrated a notable increase in WM training performance over the course of therapy; WMC-2 was the matched control. After therapy, WMI-3's naming accuracy for the treated words improved from 30 to 90% (compared to 30–50% for WMC-2) with a 7-point WAB-R AQ increase (compared to 3 for WMC-2). Improvements were also found for WMI-3 but not for WMC-2 on ratings of communicative effectiveness, confidence and some conversation parameters in discourse. This feasibility study demonstrated excellent results for most aspects of Co-TrEAT. Recruitment rate, hampered by limited resources,

must be addressed in future trials; remotely delivered aphasia therapy may be a possible solution. Although no firm conclusions can be drawn, the case studies suggest that WM training has the potential to improve language and communication outcomes when combined with aphasia therapy.

Keywords: aphasia, working memory, rehabilitation, multi-modal therapy, anomia

INTRODUCTION

Approximately 40% of individuals who survive a stroke will present with aphasia—the inability to produce and/or understand language (1). Aphasia is a "complex clinical entity" (2) that can manifest in a variety of communication impairments, including difficulty producing words and sentences and in understanding spoken and/or written language. A study by Lam and Wodchis (3) found that, out of 60 medical diagnoses and 15 health conditions, aphasia has the largest negative effect on health-related quality of life (QoL), ahead of diagnoses such as cancer and Alzheimer's disease. Indeed, even when physical abilities, well-being and social support are comparable to stroke patients without aphasia, individuals with aphasia engage in fewer extended activities of daily living and report diminished QoL (4). Thus, there is a clear imperative for aphasia to be a focus of investigation for improved optimization of care and improved outcomes in stroke.

There is a large and growing body of literature demonstrating the efficacy of treatments for communication impairments associated with aphasia in the acute and chronic stages post-stroke [e.g., (2, 5–11)]. Brady et al.'s (6) Cochrane review demonstrates that speech therapy induces greater language improvements compared to no therapy, and that group, one-on-one, computer- and volunteer-facilitated treatments appear to be equally effective in improving language outcomes. However, Brady et al. (6) caution that although speech-language therapy improves functional communication (i.e., communication in day-to-day contexts), the benefits do not necessarily hold over time and further research on long-term efficacy is required. In addition, treatment-related benefits are not always seen for specific language deficits (such as naming difficulties). These apparently nonspecific benefits may be due to the lack of targeted treatments in their review. For example, several of the negative studies [e.g., (12, 13)] which had naming as an outcome did not specifically treat naming. Of the studies that did treat naming [e.g., (14)], the outcome measure did not include the treated words. Importantly, studies evaluating the efficacy of therapy specifically aimed at the treatment of naming deficits show robust short- and long-term improvements in naming of the treated words, for most (but not all) individuals who are treated [e.g., (10, 15–18)].

Phonological Components Analysis Naming Therapy

A well-known targeted treatment for naming is the Phonological Components Analysis (PCA) protocol which uses guided phonological and orthographic cueing to stimulate naming (19, 20). PCA has been shown to be efficacious, significantly improving the short- and long-term naming accuracy of treated words (19, 21–23), as well as the long-term naming accuracy of untreated words (23, 24). Studies have considered the mechanisms of PCA treatment efficacy within the context of the Interactive Activation (IA) model of word retrieval (25–27). Namely, the IA model proposes that word retrieval occurs through feedforward and feedback spreading activation across a network of nodes, organized into three layers of representations: semantic, lexical and phonological. Evidence suggests that PCA therapy may strengthen lexical-phonological connections (23), and/or increase access to semantic network nodes via spreading activation across all levels of representation in the word retrieval network (22, 28). Importantly, despite the overall efficacy of PCA therapy, individual recovery patterns vary and not all who undergo therapy show significant improvements (as is generally the case for most anomia treatments; (15)).

Non-linguistic Cognitive Abilities in Aphasia Rehabilitation

Increasingly, studies are demonstrating that residual non-linguistic cognitive abilities may play an important role in rehabilitation after acquired brain injury in general (29–31) and can be key predictors of successful language recovery in particular [e.g., (32–35)]. This supports the notion, proposed in reviews of the literature (36, 37), that aphasia rehabilitation must focus not only on content (language representations) but also on process (non-linguistic cognitive structures that support the use of these language representations). Working memory (WM) is one such cognitive process, which is of primary interest in the present study.

WM has been conceptualized by Baddeley (38, 39) as a multi-component system, containing domain-specific buffers for maintenance of verbal (phonological loop) and visuo-spatial (visual sketchpad) representations, together with an episodic buffer for access to long-term storage; the model also includes a domain-general central executive for updating and controlling the contents and efficiency of active buffers (38). Individuals with aphasia have been found to have both verbal [e.g., (40)] and nonverbal [e.g., (36, 41, 42)] WM deficits [e.g., (43)]. In addition, studies have found that WM capacity is significantly associated with naming therapy outcomes, predicting the extent of recovery or response to rehabilitation (34, 44–46). Within the context of the IA model of word retrieval, there is evidence supporting the importance of WM in maintaining linguistic representations at the lexical and phonological access stages of word retrieval, in order for correct naming to occur [(47); see also (48)].

WM Training in Aphasia

The evidence suggests that treating WM deficits in aphasia may benefit language and/or communication outcomes. For example, one study (49) compared the effects of a WM training program vs. routine speech-language therapy, on memory and language functioning in individuals with post-stroke Broca's aphasia. WM training consisted of category and digit memory span tasks (backwards and forwards) of varying difficulty levels, as well as a paced auditory serial addition task (i.e., adding the last two numbers heard in a continuous list). Compared to routine speech-language therapy (i.e., the control group), individuals in the WM training group showed significant improvements in both trained and untrained WM tasks, as well as the speech fluency, auditory comprehension, naming and repetition subtests of the Persian version of the Western Aphasia Battery (P-WAB-1; (50)). In another study, combined intermittent theta-burst stimulation and computerized WM training were administered to an individual with post-stroke nonfluent aphasia over 10 consecutive daily sessions (51). WM training consisted of computerized span- and mental manipulation tasks of increasing difficulty. Significant improvements were seen on a measure of nonverbal intelligence, and a trend toward improvement was noted on receptive and expressive language tasks (auditory comprehension, following commands, naming, reading). In addition, studies have shown improvements after WM training (Attention Process Training, delayed repetition) on measures of reading comprehension (52) and repetition (53), respectively.

Recently, Zakariás et al. (54) conducted a systematic review of short-term memory (STM)/WM treatments in aphasia. In this study, STM was defined as the temporary maintenance and retrieval of information, whereas WM was defined as the maintenance and mental manipulation of information. Of 17 eligible studies, nine trained STM using repetition and/or recognition tasks, whereas eight trained WM (using e.g., n-back and mental arithmetic tasks). Improvements in STM were noted in 85% of studies training STM, and improvements in WM were noted in 82% of studies training WM. Additionally, improvements in sentence comprehension after training were reported in seven out of nine studies that included this outcome measure. However, the authors caution that the current evidence base remains unclear on the mechanisms underlying the relationship between WM training and language outcomes. In addition, the studies in this review did not administer combined WM training and language therapy; to date, there is limited evidence on the efficacy of such a combined, multi-modal treatment approach.

The N-Back Task

While a number of tasks can be used to measure and train WM, the n-back task has many positive features for persons with aphasia (55). In the n-back task, a stream of information is monitored with the goal of deciding whether the current item matches an item that was "n" number of trials ago in the sequence. Thus, this task requires both maintenance and updating of information with each trial. Neuroimaging studies indicate this task activates a bilateral fronto-parietal network that overlaps with language networks (56, 57). In addition, the task can be varied parametrically, depending upon the "n" involved and thus difficulty can be individually adjusted. Finally, the task requires a simple recognition response and can present a variety of stimuli, from letters, words, pictures to spatial locations, making it easier to differentiate linguistic and non-linguistic deficits. In addition, Mayer and Murray (55) tested the n-back across different stimuli and WM loads (from 0 to 2-back) and found the n-back was reliable and sensitive to WM deficits in people with aphasia compared to controls.

Adaptive WM training using the n-back has also been found to improve trained and untrained WM tasks and, in at least some studies, generalize to other cognitive functions (e.g., Raven's Progressive Matrices, which measures general non-verbal intelligence and abstract reasoning) in both young and older healthy individuals and patient populations [(58–63)]. Importantly, in a multiple-baseline study (64), three participants with post-stroke aphasia received computerized WM training, which consisted of practice on an n-back task (either with pictures or spoken words) four times per week, for 4 weeks. Post-training, all participants showed some improvement in sentence comprehension and everyday memory activities; two participants additionally demonstrated improvements in functional communication (i.e., assessor ratings of understandability and intelligibility of spoken messages on familiar everyday topics). As such, the n-back task provides a promising method for WM training in aphasia to combine with naming therapy in a multi-modal approach to aphasia therapy.

Summary and Objectives

In sum, although treatments for post-stroke naming deficits, such as the PCA therapy, have been shown to be efficacious, individual patterns of recovery can be highly variable, and the mechanisms underlying treatment-induced recovery remain somewhat unclear. It has been suggested that non-linguistic cognitive functions, and specifically WM, may play an important role in supporting language recovery. Indeed, WM has been identified as an important factor in supporting lexical retrieval and treatment success for anomia specifically, and studies that have administered WM training to individuals with post-stroke aphasia have reported improved language outcomes, particularly in auditory comprehension and functional communication measures. To our knowledge, however, no study to date has examined the efficacy of multi-modal rehabilitation which includes simultaneous administration of both WM training and a targeted anomia treatment protocol. The present investigation aimed to explore the feasibility and added benefit in communication outcomes, of combining WM training with the PCA naming therapy.

The primary objective of this pilot study was to examine the feasibility (i.e., practicality and acceptability) of combining two established and manualized treatment protocols—one targeting naming deficits in aphasia (i.e., PCA; (19)) and the other targeting WM (i.e., the *N-Igma* WM training task, described below; (65)). In addition, we aimed to examine the added benefit (i.e., preliminary efficacy) of combining naming therapy with WM training to treat individuals with post-stroke aphasia.

METHODS

Participants

Ethical approval for the present study was granted by the Research Ethics Boards (REBs) of the University of Toronto and the Aphasia Institute, and ethical approval was also obtained from the March of Dimes Aphasia and Communication Disabilities Program REB. Participants were recruited from these referral sites in the Greater Toronto Area. Informed consent was obtained using both written and pictorial materials and supported communication strategies (66, 67). The following inclusion criteria applied to all participants: (a) history of a single left-hemisphere unilateral stroke, (b) in the chronic stage of recovery (i.e., at least 6 months post-onset), (c) presence of aphasia with anomia (i.e., 10–75% accuracy on the Boston Naming Test-BNT; (68)), (d) normal or corrected-to-normal vision and hearing, (e) right-handed, (f) primarily English-speaking, and (g) with computer and Internet access. Participants were excluded from the study if they: (a) were actively engaged in speech therapy at the time of recruitment, (b) presented with severe comprehension deficits (based on WAB-R auditory comprehension scores), (c) had a known history of drug and/or alcohol abuse, and (d) had a known history of major psychiatric and/or neurological illness.

Using guidelines proposed by Bowen et al. (69), the present study measured the feasibility of a combined WM and anomia intervention according to the following areas of focus: practicality (i.e., the extent to which an intervention can be delivered when resources are constrained), acceptability (i.e., how participants react to the intervention), and limited- or preliminary-efficacy testing (i.e., testing the intervention in a convenience sample, with limited statistical power). Thus, a convenience sample was recruited: with consent, participants' files were reviewed, and participants were screened for eligibility according to the inclusion criteria stated above. Eligible participants were enrolled, and randomly assigned to one of two conditions: PCA and WM control (WMC) or PCA and WM intervention (WMI). Participants were blind to condition. In the WMC condition, participants were administered the PCA treatment for anomia, in combination with an active control task (i.e., a matched computer activity that did not require working memory since the task remained stable at span size 1; described below). In the WMI condition, participants were administered PCA treatment in combination with WM training using the computerized adapted dual n-back *N-Igma* task (to be described in detail below).

PCA Treatment for Anomia

Prior to therapy, participants underwent baseline testing, whereby naming performance on a battery of 198 colored photographs of nouns was assessed on three separate occasions (presentation order was randomized at each administration). Words named incorrectly on at least two of the baseline sessions were pooled and considered to be potential treatment targets. Two lists (30 words each) were created from this pool of words: the treated list, which was targeted in therapy, and the untreated list, which served as a within-participant control. Treated and untreated lists were matched as closely as possible on the variables of semantic category, word frequency and number of syllables. The list of 30 words was then treated using the PCA therapy approach, approximately 1.5 h per day, 3 days a week for 5 weeks. Therapy was administered by a trained research assistant either at the University of Toronto, or in the participants' homes. Briefly, in PCA naming therapy, participants are presented with a picture of the target word and asked to name it. They are given feedback, and regardless of their ability to name the target, they are asked to identify five phonological components related to the target word (e.g., rhymes with? number of syllables?), guided by the use of a chart (for a detailed protocol description please see (19)).

WM Training

We trained WM in individuals with aphasia using a computerized adaptive dual n-back task called *N-Igma* (65). Briefly, the *N-Igma* task requires participants to monitor two streams of auditory stimuli (e.g., aurally presented letters, numbers or animal sounds) and visual stimuli (e.g., pictures that varied in location of stimuli, or different landscapes) to indicate whether the current stimulus matches the one presented "n" trials ago. The "n" started at 1 and increased adaptively as performance for both streams reached 90% correct over a block. Accuracy and reaction time were collected for each trial and stored on a secure, university-based server. Stimuli were changed and training level reset to $n = 1$ after every 5 days of training to increase interest and prevent development of stimulus-specific strategies.

In the WMI condition, the n-back task was adaptive, and increased (e.g., from 1- to 2-back, etc.) as participants progressed through the task. In the WMC condition, we employed a non-adaptive dual n-back task as the active control, to match all other aspects of the training program, without the working memory component. Thus, participants remained at 1-back (a simple short term recognition task) and also were encouraged to improve speed and accuracy throughout the training. After an initial practice week in which single stream n-back tasks were practiced, participants engaged with the dual stream *N-Igma* task (in either the WMI or WMC active control conditions) 30 min a day, 5 days a week, for 5 weeks (i.e., simultaneously with, and throughout the duration of the PCA therapy). WM training (or active control) was completed on the participants' personal computers, independently at home. Weekly check-ins were conducted with participants to maintain motivation, and to problem-solve any issues in WM training and active control conditions.

Feasibility: Practicality and Acceptability

We collected data on the practicality and acceptability (69) of administering anomia and WM treatments simultaneously. To assess practicality, the following metrics were tracked, in line with previously published work in individuals with post-stroke aphasia (70): (a) ease of recruitment (success in reaching recruitment targets, number of eligible patients enrolled); (b) compliance (number of participants who completed at least 80% of each of the PCA and WM training sessions); (c) retention rate (number of participants engaged in combined therapy at

discharge/total number of participants enrolled); (d) protocol deviations (unforeseen changes from the combined therapy protocol) which were noted weekly by the project coordinator. For the purposes of this pilot study, our initial recruitment target was set at 20 participants (ten in each condition). To assess acceptability, participants completed the System Usability Scale (SUS; (71, 72)), evaluating the usability of the *N-Igma* computerized WM training platform. The SUS comprises ten items evaluating usability characteristics (e.g., satisfaction, ease of use), and rated on a 5-point Likert rating scale, which generates a usability score out of 100 (for scoring procedures, see (71)). The SUS has been used in previous work with the stroke population (65) and has been adapted for use with individuals with aphasia by our group (73). Given the small sample size, descriptive statistics were used to analyze feasibility metrics.

Feasibility: Preliminary Efficacy and Communication Outcomes

Outcomes related to treatment efficacy were collected pre- and post-training and at 1-month follow-up and included: (a) naming accuracy of the treated and matched untreated words, (b) performance on the Western Aphasia Battery-Revised (WAB-R; (74)), (c) performance on the BNT (68); (d) ratings of functional communication ability and communication confidence, measured, respectively, by the Communication Effectiveness Index (CETI; (75)), and Communication Confidence Rating Scale for Aphasia (CCRSA; (76)), and (e) discourse, using the Discourse Comprehension Test (DCT; (77)). In addition, a 10-min conversation sample with a family member or friend was obtained. Speech samples were examined for changes that have been linked to WM function in discourse, such as coherence and topic maintenance (78). Although improvements in language were of primary interest in the present study, we also tracked changes in WM capacity on both the Wechsler Memory Scale digit span task (79) and the Corsi-block tapping visual span task (80, 81), with a focus on the backward span in each task, given its close association with WM capacity. Statistical analyses for each outcome measure are described below. Post-treatment outcomes were collected and scored by a research associate who did not administer treatment.

Naming of the treated and untreated words was scored as follows: words named correctly within 10 s of stimulus presentation (including self-corrections) were given a score of 1, and words named incorrectly (including paraphasias of all types), or words named beyond the 10 s time limit, were given a score of 0. Treatment-induced changes in naming accuracy of the treated and untreated words (outcome a above) were analyzed using the Weighted Statistics (WEST) approach (82). This approach overcomes problems of autocorrelation and is suitable for evaluating repeated measurements of an item. Each assessment timepoint is weighted in order to account for underlying linear trends in the data (i.e., the WEST-Trend), and to ensure that the rate of change (ROC) post-treatment is significantly greater than the null ROC expected at baseline (i.e., the WEST-ROC). Weighted scores for a given item are summed and analyzed using one-sample *t*-tests (one-tailed). Results were corrected for multiple comparisons using the Bonferroni procedure (i.e., alpha was set at $0.05/4 = 0.013$). For detailed descriptions of this analysis approach, please see Simic et al. (23) for a comparable study design using PCA therapy, and Howard et al. (82). Following Howard et al.'s (82) recommendations, treatment effects were considered significant only when both the WEST-Trend and WEST-ROC analyses showed significant results.

Due to the small sample size, changes in performance on the WAB, BNT, CETI and CCRSA (outcomes b, c, and d above) were analyzed using descriptive statistics. In addition, we evaluated whether changes on the WAB and BNT represented a clinically significant difference, according to published benchmarks (83). Similarly, descriptive statistics were used to track WM performance on digit and visual span tasks over time.

Descriptive statistics are also presented for the DCT (outcome e above), and conversational speech samples were analyzed using the Profile of Word Errors and Retrieval in Speech (POWERS) approach (84). Briefly, an independent rater blind to treatment condition and assessment time coded speech samples according to the following conversation parameters: substantive turns (i.e., a turn which contains at least one content word), minimal turns (i.e., a turn which does not contribute meaningfully to the conversation), content words (i.e., nouns, proper nouns, adjectives, adverbs, verbs and numerals), nouns (i.e., proper and common nouns), and word errors (i.e., circumlocutions, semantic paraphasias, phonological errors, neologisms, pauses greater than 2 s and filled pauses). Once coded, the following ratios were calculated (85): (a) minimal turns/total turns, (b) word errors/content words, (c) word errors/turns, (d) number of content words/substantive turns, and (e) nouns/substantive turns.

RESULTS

Six participants were recruited for the present study, and three each were randomly assigned to either the WMC or WMI conditions. Overall, participants had a mean age of 59.2 years (SD = 8.6 years), an average of 16 years of education (SD = 2.9 years), and were 2.83 years post-onset of stroke, on average (SD = 2.1). Individual participant details, as well as means for the WMC and WMI conditions can be seen in **Table 1**.

Feasibility: Practicality and Acceptability

Overall, 37 participants introduced to the study from information sessions expressed an interest in participating. After an initial review of each participant's file, 25 did not meet inclusion criteria (e.g., due to a history of bilateral or right hemisphere strokes, no stroke etiology, or pre-existing psychological disorders). The remaining 12 were screened for eligibility. Of those, one presented with a pre-existing cognitive impairment, one with mild anomia, exceeding our cut-off of 75% naming accuracy on the BNT, and three with moderate-severe apraxia of speech (AOS). One participant also presented with AOS and comprehension difficulties and did not have computer nor Internet access. The resulting final sample size was six. Thus,

TABLE 1 | Individual participant characteristics.

Code	WM Condition	Sex	Age	Education (yrs)	Yrs Post Stroke	Aphasia Type
WMI-1	Intervention	M	59	14	1.25	Anomic
WMI-2	Intervention	M	59	18	4	Anomic
WMI-3	Intervention	F	53	21	0.75	Conduction
WMC-1	Control	M	75	14	6	Broca's
WMC-2	Control	M	59	16	3.5	Anomic
WMC-3	Control	M	50	14	1	Broca's
	Total Mean (SD)	59.2 (8.6)	16 (2.9)	2.83 (2.1)		
	WMI Mean (SD)	57 (3.5)	17.7 (3.5)	2 (1.8)		
	WMC Mean (SD)	61.3 (12.7)	14.7 (1.2)	3.5 (2.5)		

All participants had a single left-hemisphere cerebrovascular accident and were premorbidly right-handed.

our initial recruitment target of 20 participants (i.e., 10 in each condition) was not met.

However, the six participants who were enrolled in the study completed it, and feasibility metrics were excellent for protocol compliance, retention rate and lack of adverse events. All participants completed 100% of PCA therapy sessions, and 100% of WM training sessions. In addition, only one deviation from the protocol was noted: two participants in the WMC condition (WMC-1 and WMC-3) engaged in the active control task more than 5 days a week. Finally, with respect to the usability of the WM training task, results from the SUS indicate an average score of 69.2/100 for the WMI condition (i.e., WMI-1 = 65.0, WMI-2 = 57.5, and WMI-3 = 85.0), and an average score of 47.5/100 for the WMC condition (i.e., WMC-1 = 40.0, WMC-2 = 60.0, and WMC-3 = 42.5).

Feasibility: Preliminary Efficacy and Communication Outcomes

Naming Accuracy of Treated and Untreated Words

Overall, all participants in both conditions showed improvements in naming accuracy for the treated words with a mean change of 45.6% (SD = 21.9%) from baseline- to post-treatment, and 42.2% (SD = 22.78%) from baseline- to 1-month follow-up. Individual participant WEST analyses indicate significantly improved naming accuracy in four participants (WMI-2, WMI-3, WMC-1 and WMC-3), two in each condition. Three of these participants showed significant improvements in naming accuracy at the 1-month follow-up stage as well (WMI-3, WMC-1 and WMC-3). For the untreated words, naming accuracy improved by a mean of 16.5% (SD = 11.7%) from baseline to post-treatment, and by a mean of 23.2% (SD = 14.8%) from baseline to 1-month follow-up. According to WEST analyses, two participants showed significant improvements in naming of the untreated words at post-treatment (WMC-2) and at 1-month follow-up (WMC-3), respectively (individual participant scores are presented in **Table 2**).

Aphasia and Anomia Severity

Individual participant WAB-AQ and BNT scores at each assessment time are presented in **Table 3**. Individuals in the WMI condition showed an average improvement on the WAB-AQ of 5.4 points pre- to post-treatment, and of 8.6 points from pre- to 1-month follow-up. This change indicates a clinically significant difference (i.e., a change of greater than five points, or 5%). In comparison, individuals in the WMC condition did not attain this benchmark, showing an average WAB-AQ improvement of 3.7 points pre- to post-treatment, and 3.8 points pre- to 1-month follow-up. It is important to note, however, that individuals in the WMC condition presented with overall lower WAB-AQ scores.

With respect to anomia severity, participants in the WMI condition demonstrated an average of 10% improvement in naming accuracy on the BNT pre- to post-treatment, and 11.7% pre- to 1-month follow-up. This corresponds to an improvement in naming on six and seven items on the BNT, respectively. As with the WAB-AQ, a change of greater than three points out of 60 (or 5%) indicates a clinically significant difference. In comparison, individuals in the WMC condition showed an improvement in BNT naming accuracy of 2.2% pre- to post-treatment, and a slight decrease (0.6%) pre- to 1-month follow-up.

Communication Effectiveness and Confidence

According to self-ratings on the CETI, communicative effectiveness for participants in the WMI condition improved by an average of 7.9% pre- to post-treatment, and 7.8% pre- to 1-month follow-up. Participants in the WMC condition made a comparable improvement of 7.5% pre- to post-treatment, but communicative effectiveness largely returned to pre-treatment levels at the 1-month follow-up stage. According to partner ratings of communicative effectiveness, the participants in the WMI condition were rated 5.9% higher from pre to post treatment, and 10.4% higher from pre- to 1-month follow-up. Post-treatment CETI partner ratings were not available for two participants in the control condition (WMC-1 and WMC-2), and minimal (0.7%) change was seen in those in the WMC condition from pre- to 1-month follow-up.

Ratings of communication confidence based on the CCRSA show a similar pattern: participants in the WMI condition rated themselves 10.8% higher from pre- to post-treatment, and 4.2% higher pre- to 1-month follow-up. In comparison, those in the WMC condition rated themselves 2.5% higher pre- to post-treatment, which largely returned to pre-treatment levels at

TABLE 2 | Percent naming accuracy of treated and untreated words for each individual participant, across the three baseline periods, and at post-treatment and follow-up.

		B1	B2	B3	Mean (B1–B3)	Post	4WFU	
Treated words (%)								
Intervention	WMI-1	0.00	6.67	16.67	7.78	26.67	30.00
	WMI-2	16.67	6.67	20.00	14.44	**66.67***	46.67
	WMI-3	10.00	10.00	16.67	12.22	**86.67***	**90.00***
Control	WMC-1	10.00	26.67	6.67	14.44	**80.00***	**76.67***
	WMC-2	33.33	13.33	3.33	16.67	46.67	53.33
	WMC-3	3.33	0.00	0.00	1.11	**33.33***	**23.33***
	Mean	**12.22**	**10.56**	**10.56**	**11.11**	**56.67**	**53.33**
	SD	*11.86*	*9.05*	*8.28*	*9.73*	*24.86*	*25.99*
Untreated Words (%)								
Intervention	WMI-1	3.33	0.00	10.00	4.44	10.00	13.33
	WMI-2	16.67	6.67	13.33	12.22	16.67	30.00
	WMI-3	0.00	6.67	26.67	11.11	30.00	60.00
Control	WMC-1	13.33	16.67	6.67	12.22	30.00	23.33
	WMC-2	20.00	3.33	26.67	16.67	**53.33***	46.67
	WMC-3	0.00	0.00	3.33	1.11	16.67	**23.33***
	Mean	**8.89**	**5.56**	**14.44**	**9.63**	**26.11**	**32.78**
	SD	*8.86*	*6.21*	*10.04*	*8.37*	*15.55*	*17.31*

**Significant WEST-ROC and WEST-Trend result, based on one-sample t-tests (one-tailed). Bonferroni-corrected for multiple comparisons (i.e., alpha = 0.05/4 = 0.013). Note. WEST weighting factors are based on three baseline measures and one post-therapy measure (i.e., either post-treatment, or 4r-week follow-up). B1, Baseline 1; B2, Baseline 2; B3, Baseline 3; 4WFU, 4-week follow-up.*

1-month follow-up. Please see **Table 3** for individual participant scores on the CETI and CCRSA.

WM Span Tasks

Although not the primary aim of the present study, results from WM tasks suggest impairments in WM digit span in our sample of participants with post-stroke aphasia. Overall better performance was observed in the visual span task for participants in both conditions. In addition, WMC-2 demonstrated improvements in the forward visual span task over time, whereas participants WMC-1 and WMI-3 demonstrated improvements in the backward visual span task over time. All other participants remained relatively stable in their performance on the WM span tasks. Please see **Table 3** for details.

Discourse

Performance on the DCT did not notably change across assessment times (**Table 3**). Discourse analysis of conversational speech using the POWERS reveals variable performance across participants and assessment times (see **Table 4**). Smaller ratios of minimal turns/total turns, word errors/content words and word errors/turn indicate better performance (ratios 1–3 in **Table 4**). In the WMI condition, participant WMI-1 showed a decrease in these ratios pre- to post-treatment and maintained a small ratio of minimal turns/total turns at 1-month follow-up. Participants WMI-2 and WMI-3 demonstrated stable or increasing performance for these ratios. In the WMC condition, all participants show decreasing ratios of word errors/content words and word errors/turn across assessment times. The ratio of minimal turns/total turns remained stable or increased in the WMC condition, across assessment times.

A larger ratio of content words/substantive turns, and nouns/substantive turns indicates better performance (ratios 4 and 5 in **Table 4**). In the WMI condition, participants WMI-1 and WMI-3 show increases in these ratios across assessment times; WMI-2 shows relatively stable performance across assessment times. In the WMC condition, minimal change and/or a slight decrease in these ratios is noted across assessment times.

Interim Summary of Findings

The findings suggest trends toward greater improvement for individuals in the WMI condition (e.g., WAB-R AQ; BNT; patient reported CETI; CCSRA; conversational speech analysis). However, other results do not distinguish performance of individuals in the two conditions (e.g., performance on treated and untreated words; DCT). Since the number of individuals in each condition was too small to be analyzed separately as two conditions, we chose to compare in detail the performance of two well-matched patients from each condition, as described below.

Case Comparison

Given the small number of participants, and the variability of findings summarized above, it is difficult to extract clear patterns in the data between the participants in the WMI and WMC conditions. Thus, in order to investigate the potential benefits of combining WM training with anomia therapy, we present here the case of participant WMI-3, who demonstrated a notable increase in WM training performance over the course of therapy (i.e., WMI-3 was

TABLE 3 | Individual participant scores on measures of anomia and aphasia severity, communicative effectiveness and confidence, WM and discourse comprehension across assessment times.

	WM Intervention				WM Control			
	WMI-1	**WMI-2**	**WMI-3**	***Mean***	**WMC-1**	**WMC-2**	**WMC-3**	***Mean***
Western Aphasia Battery-Revised-Aphasia Quotient (WAB-R-AQ)								
Pre	76.8	81.1	79.4	*79.1*	66.2	77.6	43.6	*62.5*
Post	85.2	82.5	85.7	*84.5*	72.2	77.2	49.0	*66.1*
1-month	84.6	92.9	85.7	*87.7*	76.6	81.3	40.9	*66.3*
Boston Naming Test (BNT)-Naming Accuracy (%)								
Pre	13.3	38.3	40.0	*30.6*	65.0	55.0	15.0	*45.0*
Post	15.0	46.7	60.0	*40.6*	63.3	53.3	25.0	*47.2*
1-month	11.7	46.7	68.3	*42.2*	60.0	56.7	16.7	*44.4*
Communication Effectiveness Index (CETI)-Patient (%)								
Pre	52.4	82.4	46.4	*60.4*	47.5	65.3	54.3	*55.7*
Post	57.4	64.0	83.5	*68.3*	49.2	63.5	76.6	*63.1*
1-month	41.5	83.8	79.5	*68.3*	53.4	73.1	43.2	*56.5*
Communication Effectiveness Index (CETI)-Partner (%)								
Pre	47.8	71.0	61.6	*60.1*	46.1	60.9	77.6	*61.5*
Post	52.7	64.7	80.5	*66.0*	n/a*	n/a*	69.4	-
1-month	57.1	63.1	91.2	*70.5*	53.1	n/a*	71.3	*62.2*
Communication Confidence Rating Scale for Aphasia (CCRSA; %)								
Pre	57.5	72.5	65.0	*65.0*	60.0	75.0	60.0	*65.0*
Post	60.0	77.5	90.0	*75.8*	60.0	75.0	67.5	*67.5*
1-month	52.5	82.5	72.5	*69.2*	65.0	72.5	60.0	*65.8*
Wechsler Memory Scale (WMS) Digit Span - Forward (max score = 12)								
Pre	8	7	0	*5.0*	4	8	0	*4.0*
Post	5	7	3	*5.0*	4	8	0	*4.0*
1-month	8	8	2	*6.0*	5	7	1	*4.3*
Wechsler Memory Scale (WMS) Digit Span-Backward (max score = 12)								
Pre	4	3	2	*3.0*	2	3	1	*2.0*
Post	5	3	4	*4.0*	3	3	0	*2.0*
1-month	4	3	4	*3.7*	2	4	3	*3.0*
Corsi Block Tapping Visual Span-Forward (max score = 14)								
Pre	10	5	8	*7.7*	6	5	5	*5.3*
Post	9	7	8	*8.0*	7	9	7	*7.7*
1-month	11	7	9	*9.0*	6	10	4	*6.7*
Corsi Block Tapping Visual Span-Backward (max score = 12)								
Pre	7	7	6	*6.7*	7	7	7	*7.0*
Post	8	5	9	*7.3*	6	7	6	*6.3*
1-month	8	6	10	*8.0*	10	8	6	*8.0*
Discourse Comprehension Test (DCT)-Auditory (%)								
Pre	92.5	92.5	77.5	*87.5*	75.0	77.5	65.0	*72.5*
Post	70.0	95.0	82.5	*82.5*	82.5	90.0	60.0	*77.5*
1-month	90.0	90.0	87.5	*89.2*	72.5	75.0	52.5	*66.7*

**CETI score not available (not completed accurately).*

performing the dual WM task at the 3-back level by the end of treatment). We compare the performance of WMI-3 to a participant in the control condition, WMC-2, who was well-matched in terms of age, education, years post-stroke (see **Table 1**), as well as pre-treatment WAB-AQ, naming performance and WM capacity (particularly for backward span tasks; see **Tables 2**, **3**).

After therapy, WMI-3's naming accuracy for the treated words improved from 30 to 90% (compared to an increase from 30 to 50% for WMC-2). WEST analyses indicate significantly improved naming of the treated words post-treatment and at 1-month follow-up for WMI-3, but not for WMC-2. Interestingly, however, WMC-2 showed significant improvements in naming of the untreated words post-therapy.

TABLE 4 | Conversational speech analysis using POWERS parameters and associated ratios across participants and assessment times.

	Intervention			Control		
	WMI-1	**WMI-2**	**MWI-3**	**WMC-1**	**WMC-2**	**WMC-3**
1. Minimal Turns/Total Turns						
Pre	0.27	0.24	0.19	0.4	0.13	0.44
Post	0.15	0.33	0.19	0.57	-	0.4
1-month	0.08	0.29	0.2	0.61	0.31	0.52
2. Word Errors/Content Words						
Pre	0.22	0.06	0.12	2	0.39	0.19
Post	0.05	0.17	0.26	1.47	-	0.07
1-month	0.23	0.15	0.28	0.89	0.28	0.1
3. Word Errors/Turn						
Pre	0.67	0.15	0.76	1.59	0.89	0.31
Post	0.2	0.49	3.33	0.49	-	0.08
1-month	1.34	0.44	4.48	0.21	0.52	0.12
4. Number Content Words/Substantive Turns						
Pre	4.31	4.19	8.2	1.97	3.2	3.22
Post	5.45	4.54	19.82	1.3	-	1.95
1-month	7.13	4.43	19.9	1.13	4.32	2.77
5. Nouns/Substantive Turns						
Pre	1.11	1.33	1.4	1.41	1.92	0.7
Post	1.26	0.98	2.24	0.87	-	0.64
1-month	2.06	1.62	4.1	0.92	1.26	1

Post-treatment speech sample not available for WMC-2. All scores represent ratios based on POWERS conversational parameters [as per (84, 85)].

In addition, WMI-3 demonstrated a mean increase of 7-points on the WAB-AQ (compared to a mean increase of 3-points for WMC-2). Similarly, mean percent change on the BNT was 24.2% for WMI-3, whereas WMC-2 showed no mean change on the BNT across assessment times. Interestingly, WMC-2 showed the greatest improvement on the forward visual span task over time (mean change of 32.2%), whereas WMI-3 showed the greatest improvement on the backward visual span task (mean change of 25.2%), which, much like the n-back task, places greater demands on WM updating capacity. Finally, WMI-3 but not WMC-2 showed improved ratings of communicative effectiveness, and communicative confidence.

On the DCT, WMI-3's performance improved by an average of 7.5% and demonstrated the greatest amount of improvement at 1-month follow-up. In comparison, WMC-2 showed an average improvement of 5% on the DCT, but this involved a return to baseline performance at 1-month follow-up. Conversational analyses using the POWERS indicate that although WMI-3 showed increased ratios of word errors/content words and word errors/turn, she also demonstrated improvements on the number of content words per substantive turn and nouns per substantive turn at post-treatment and at 1-month follow-up. In comparison, these same improvements were not observed for WMC-2 (see **Table 4**).

DISCUSSION

The aim of this pilot study was to evaluate the feasibility of a combined treatment approach which involved self-administered computerized adaptive dual n-back WM training, and clinician-administered PCA treatment for anomia in post-stroke aphasia. To assess feasibility, we also conducted an exploratory investigation into the preliminary efficacy of a combined therapy approach through detailed descriptions of trends in the data, as well as a case comparison.

Feasibility: Practicality and Acceptability

Overall, our findings suggest that a self-paced, individualized WM program, in combination with targeted face-to-face naming therapy is feasible for individuals with post-stroke aphasia. Compliance and retention rates were excellent: participants followed through with both training protocols at the required schedule. Only a single protocol deviation was noted, whereby two participants in the WMC condition engaged with the active control task more than expected. However, there was no evidence that this influenced WM performance; the active control condition remained at the 1-back level, and as such did not increase in difficulty. The primary challenge in the present study was recruitment. Our initial recruitment target of 20 participants was not met, due to various barriers, including strict inclusion criteria and limited resources for face-to-face treatment. A potential solution to the latter may be to offer virtual (see (73)) and/or self-guided PCA treatment, which could access a greater number of individuals. The excellent compliance rates for the virtual WM training in this study suggest that virtually delivered therapy may indeed be an acceptable option for individuals with post-stroke aphasia. Although not eligible for other reasons, one participant who was screened for the study did not have computer or Internet access. Equipping individuals with the technology needed for virtual therapy, or connecting them with local telerehabilitation centers, may be necessary to remove accessibility barriers and implement virtual treatment approaches more broadly.

Results from the SUS indicate acceptable, but not excellent usability scores for the WMI condition. Usability ratings may have been impacted by difficulty with the n-back task (e.g., discriminating visual and auditory stimuli) or by the dual nature of the task, which may have been too challenging for some participants. A single n-back paradigm may be more appropriate for the post-stroke aphasia population, although this requires further investigation. It is important to continue to solicit feedback from individuals with aphasia, in order to gain valuable insights for additional aphasia-friendly modifications that can be made in future iterations of this WM training approach. As expected, those in the WMC condition found the active control task somewhat repetitive, which could explain the lower usability scores for the WMC condition. Despite these difficulties, all participants persisted and completed the WM training, which suggests that challenging tasks can be motivating in therapy.

Feasibility: Preliminary Efficacy and Communication Outcomes

In the present study, preliminary efficacy was assessed using a variety of outcome measures, with a focus on exploring the added benefit in communication outcomes among individuals who received a combined WM training and anomia therapy approach (i.e., the WMI condition). Individual by-item analyses of naming accuracy for the treated and untreated words indicate significantly improved naming of the treated words for four participants overall—two in each condition. In addition, two participants demonstrated significant improvements in naming of the untreated words following therapy. These findings are in line with previous work demonstrating that PCA induces significant changes in naming in approximately 70% of participants (19, 23). Although the small sample precluded statistical analysis, naming improvements were also noted on the BNT (i.e., an untrained naming task). Interestingly, participants in the WMI condition made clinically significant improvements on the BNT, whereas those in the WMC condition demonstrated limited change.

This pattern is echoed in the participants' WAB-R performance over time. While participants in both the WMI and WMC conditions demonstrated improvements in the WAB-R AQ following intervention, only those in the WMI condition demonstrated a clinically significant change of greater than 5 points (83). These results suggest a trend toward treatment-induced changes in anomia and aphasia severity (i.e., becoming milder) for those in the WMI condition. The comparison of two well-matched cases provides further support for this trend. Participants WMI-3 and WMC-2 presented with comparable demographics, naming performance and aphasia severity (i.e., WAB-R AQ) prior to treatment. Importantly, they also demonstrated comparable pre-treatment WM capacity. Participant WMI-3 showed great improvements during WM training. Following therapy, WMI-3 demonstrated significant improvements in naming accuracy for the treated words, and clinically meaningful improvement on the BNT and WAB-AQ. WMC-2 did not show improvements in these areas. A similar pattern was seen when comparing WMI-3 and WMC-2 on communicative effectiveness, and communicative confidence. In fact, participants in the WMI condition showed overall greater and/or longer-lasting improvements in ratings of communicative effectiveness and confidence, compared to those in the WMC condition.

Although not a primary aim of this study, we also tracked changes in WM performance over time, with a particular interest in performance on the backward visual and digit span tasks, which are more closely associated with WM (as opposed to STM) capacity. Of note, all participants demonstrated some WM deficits on the digit span task, corroborating previous work (36, 40–43). Performance on the visual span task was generally better than performance on the digit span task, suggesting that the former may be a more appropriate measure of WM in individuals with aphasia, as it may remove some of the confounds associated with the language impairments in question. No discernible differences in WM performance were noted between individuals in the WMI and WMC conditions.

Interestingly however, participant WMI-3, who showed great progress during WM training, also demonstrated a large improvement in performance on the backward visual span task (i.e., a measure of WM that more closely resembles the updating demands of the n-back task). In comparison, WMC-2, who was in the active control condition, demonstrated a large improvement in performance on the forward visual span task (i.e., a measure of STM). In line with previous work [e.g., (54)], this finding encourages more research on the potential for WM training programs (such as *N-Igma*) to improve WM capacity in people with aphasia.

Finally, participants in both conditions demonstrated some improvement in their conversational discourse, tending to contribute more meaningfully and accurately to conversations following therapy (i.e., reducing minimal turns and word errors). However, participants in the WMI condition also demonstrated an increased proportion of content words and nouns following therapy. As above, this is underlined in the comparison of WMI-3 and WMC-2, whereby the former (but not the latter) demonstrated improvements in the proportion of content words and nouns used in conversational speech. This finding may suggest that treatment at the single-word level can transfer to a discourse task, possibly by increasing the availability and use of content words and nouns. The added benefit of WM training may be to support the active maintenance of, and access to, the words needed in a conversational task, as has been suggested in previous work (45).

Although improvements were noted in discourse production, limited change was observed in discourse comprehension on the DCT. This result may be due to higher levels of comprehension at baseline across the participants, or otherwise, because the DCT is not an appropriate outcome measure for the PCA treatment approach (i.e., which primarily targets production abilities). Previous work has shown that WM training in individuals with aphasia can lead to improvements in sentence comprehension [e.g., (54)]. Thus, perhaps a sentence (rather than discourse) comprehension task may be a more appropriate outcome measure to include in future studies.

Limitations

The primary limitation of the present study is the small sample size, which only allowed for a descriptive analysis of the data. Given the numerous factors that can impact treatment outcomes in individuals with post-stroke aphasia, replication in a larger and more homogeneous sample is imperative. Also, it is notable that while participants in the WMI condition presented with somewhat milder aphasia (based on the WAB-R AQ), they also presented with a more severe anomia (based on the BNT). As such, pre-therapy status between individuals in the intervention and control conditions was not matched which may have influenced the results.

CONCLUSION

Further research is needed to better understand the efficacy of combined WM training and language therapy for the treatment of aphasia (54). As well, further investigation of the different cognitive abilities that potentially underpin treatment response at different stages of recovery is warranted (45). Nevertheless, the present findings suggest that a combined treatment for both WM and naming deficits in individuals with post-stroke aphasia is not only feasible but may have the potential to augment treatment efficacy and support generalization to broader communication contexts.

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 Toronto Research Ethics Board (#25523), Aphasia Institute (no REB #), March of Dimes Aphasia and Communication Disabilities Program (no REB #). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ER, CL, GE, and SB contributed to conception and design of the study. LL managed patient recruitment and data collection. NB, KM, and J-LT performed discourse analyses. TS analyzed and interpreted data and wrote the manuscript. ER, CL, GE, and LL contributed to manuscript writing and revision. All authors approved the submitted version.

FUNDING

This work was supported by a catalyst grant from the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery (CPSR), awarded to ER, CL, GE, and SB.

ACKNOWLEDGMENTS

The authors wish to acknowledge all study participants and their families for generously devoting their time and efforts to participate in our study, as well as the Aphasia Institute, and the March of Dimes Aphasia and Communication Disabilities Programs across Ontario, for their assistance with participant recruitment. The authors would also like to extend their gratitude to Anna Huynh, Natalie Le, Alex Pachete, Katie McKearney, and Arthur MacDonald for their invaluable assistance with participant recruitment, data collection, and coding.

REFERENCES

1. National Aphasia Association. *Aphasia Statistics, National Aphasia Association*. Available online at: https://www.aphasia.org/aphasia-resources/aphasia-statistics/.
2. Bhogal SK, Teasell RW, Foley NC, Speechley MR. Rehabilitation of aphasia: More is better. *Top Stroke Rehabil.* (2003) 10:66–76. doi: 10.1310/RCM8-5TUL-NC5D-BX58
3. Lam JM, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related qualiy of life in Ontario hospital-based long-term care residents. *Med Care.* (2010) 380–7. doi: 10.1097/MLR.0b013e3181ca2647
4. Hilari K. The impact of stroke: Are people with aphasia different to those without? *Disabil Rehabil.* (2011) 33:211–8. doi: 10.3109/09638288.2010.508829
5. Breitenstein C, Grewe T, Flöel A, Ziegler W, Springer L, Martus P, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet.* (2017) 389:1528–38. doi: 10.1016/S0140-6736(17)30067-3
6. Brady MC, Godwin J, Enderby P, Kelly H, Campbell P. Speech and language therapy for aphasia after stroke: An updated systematic review and meta-analyses. *Stroke.* (2016) 47:e236–7. doi: 10.1161/STROKEAHA.116.014439
7. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Arch Phys Med Rehabil.* (2011) 92:519–30. doi: 10.1016/j.apmr.2010.11.015
8. Faroqi-Shah Y, Frymark T, Mullen R, Wang B. Effect of treatment for bilingual individuals with aphasia: a systematic review of the evidence. *J Neurolinguistics.* (2010) 23:319–41. doi: 10.1016/j.jneuroling.2010.01.002
9. Simmons-Mackie N, Raymer A, Armstrong E, Holland A, Cherney LR. Communication partner training in aphasia: a systematic review. *Arch Phys Med Rehabil.* (2010) 91:1814–37. doi: 10.1016/j.apmr.2010.08.026
10. Nickels L. Therapy for naming disorders: Revisiting, revising, and reviewing. *Aphasiology.* (2002) 16:935–79. doi: 10.1080/02687030244000563
11. Robey RR. A meta-analysis of clinical outcomes in the treatment of aphasia. *J Speech Lang Hear.* (1998) 41:172–87. doi: 10.1044/jslhr.4101.172
12. Varley R, Cowell PE, Dyson L, Inglis L, Roper A, Whiteside SP. Self-administered computer therapy for apraxia of speech: two-period randomized control trial with crossover. *Stroke.* (2016) 47:822–8. doi: 10.1161/STROKEAHA.115.011939
13. Katz RC, Wertz RT. The efficacy of computer-provided reading treatment for chronic aphasic adults. *J Speech Lang Hear Res.* (1997) 40:493–507. doi: 10.1044/jslhr.4003.493
14. Doesborgh SJC, van de Sandt-Koenderman MWME, Dippel DWJ, van Harskamp F, Koudstaal PJ, Visch-Brink EG. Cues on request: The efficacy of multicue, a computer program for wordfinding therapy. *Aphasiology.* (2004) 18:213–22. doi: 10.1080/02687030344000580
15. Wisenburn B, Mahoney K. A meta-analysis of word-finding treatments for aphasia. *Aphasiology.* (2009) 23:1338–52. doi: 10.1080/02687030902732745
16. Nickels L, Best W. Therapy for naming disorders (part I): Principles, puzzles and progress. *Aphasiology.* (1996) 10:21–47. doi: 10.1080/02687039608248397
17. Nickels L, Best W. Therapy for naming disorders (part II): Specifics, surprises and suggestions. *Aphasiology.* (1996) 10:109–36. doi: 10.1080/02687039608248401
18. Best W, Nickels L. From theory to therapy in aphasia: Where are we now and where to next? *Neuropsychol Rehabil.* (2000) 10:231–47. doi: 10.1080/096020100389147
19. Leonard C, Rochon E, Laird L. Treating naming impairments in aphasia: Findings from a phonological components analysis treatment. *Aphasiology.* (2008) 22:923–47. doi: 10.1080/02687030701831474

20. Madden EB, Robinson RM, Kendall DL. Phonological treatment approaches for spoken word production in aphasia. *Semin Speech Lang.* (2017) 38:62–73. doi: 10.1055/s-0036-1597258
21. van Hees S, Angwin A, McMahon K, Copland D. A comparison of semantic feature analysis and phonological components analysis for the treatment of naming impairments in aphasia. *Neuropsychol Rehabil.* (2013) 23:102–32. doi: 10.1080/09602011.2012.726201
22. Leonard C, Laird L, Burianová H, Graham S, Grady C, Simic T, et al. Behavioural and neural changes after a "choice" therapy for naming deficits in aphasia: preliminary findings. *Aphasiology*. (2015) 29:506–25. doi: 10.1080/02687038.2014.971099
23. Simic T, Chambers C, Bitan T, Stewart S, Goldberg D, Laird L, et al. Mechanisms underlying anomia treatment outcomes. *J Commun Disord.* (2020) 88:3039–54. doi: 10.1016/j.jcomdis.2020.106048
24. Simic T, Leonard C, Laird L, Stewart S, Rochon E. The effects of intensity on a phonological treatment for anomia in post-stroke aphasia. *J Commun Disord.* (2021) 106125. doi: 10.1016/j.jcomdis.2021.106125
25. Schwartz M. Theoretical analysis of word production deficits in adult aphasia. *Phil Trans R Soc Lond B Biol Sci.* (2014) 369:1–10. doi: 10.1098/rstb.2012.0390
26. Dell GS, Schwartz MF, Martin N, Saffran EM, Gagnon DA. Lexical access in aphasic and non-aphasic speakers. *Psychol Rev.* (1997) 104:811–38.
27. Foygel D, Dell GS. Models of impaired lexical access in speech production. *J Mem Lang.* (2000) 43:182–216. doi: 10.1006/jmla.2000.2716
28. Rochon E, Leonard C, Burianova H, Laird L, Soros P, Graham S, et al. Neural changes after phonological treatment for anomia: An fMRI study. *Brain Lang.* (2010) 114:164–79. doi: 10.1016/j.bandl.2010.05.005
29. Leśniak M, Bak T, Czepiel W, Seniów J, Członkowska A. Frequency and prognostic value of cognitive disorders in stroke patients. *Dement Geriatr Cogn Disord.* (2008) 26:356–63. doi: 10.1159/000162262
30. Keil K, Kaszniak AW. Examining executive function in individuals with brain injury: a review. *Aphasiology*. (2002) 16:305–35. doi: 10.1080/02687030143000654
31. Robertson IH, Murre JM. Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol Bull.* (1999) 125:544. doi: 10.1037/0033-2909.125.5.544
32. Lambon Ralph MA, Snell C, Fillingham JK, Conroy P, Sage K. Predicting the outcome of anomia therapy for people with aphasia post CVA: Both language and cognitive status are key predictors. *Neuropsychol Rehabil.* (2010) 20:289–305. doi: 10.1080/09602010903237875
33. Brownsett SL, Warren JE, Geranmayeh F, Woodhead Z, Leech R, Wise RJ. Cognitive control and its impact on recovery from aphasic stroke. *Brain.* (2014) 137:242–54. doi: 10.1093/brain/awt289
34. Harnish SM, Lundine JP. Nonverbal working memory as a predictor of anomia treatment success. *Am J Speech Lang Pathol.* (2015) 24:S880–94. doi: 10.1044/2015_AJSLP-14-0153
35. van de Sandt-Koenderman WM, van Harskamp F, Duivenvoorden HJ, Remerie SC, van der Voort-Klees YA, Wielaert SM, et al. MAAS (Multi-axial Aphasia System): realistic goal setting in aphasia rehabilitation. *Int J Rehabil Res.* (2008) 31:314–20. doi: 10.1097/MRR.0b013e3282fc0f23
36. Murray LL. Direct and indirect treatment approaches for addressing short-term or working memory deficits in aphasia. *Aphasiology.* (2012) 26:317–37. doi: 10.1080/02687038.2011.589894
37. Martin N, Reilly J. Short-term/working memory impairments in aphasia: Data, models, and their application to aphasia rehabilitation. *Aphasiology.* (2012) 26:253–7. doi: 10.1080/02687038.2011.648163
38. Baddeley A. Working memory: Theories, models, and controversies. *Annu Rev Psychol.* (2012) 63:1–29. doi: 10.1146/annurev-psych-120710-100422
39. Baddeley AD. Developing the concept of working memory: The role of neuropsychology. *Arch Clin Neuropsychol.* (2021) 36:861–73. doi: 10.1093/arclin/acab060
40. Potagas C, Kasselimis D, Evdokimidis I. Short-term and working memory impairments in aphasia. *Neuropsychologia.* (2011) 49:2874–8. doi: 10.1016/j.neuropsychologia.2011.06.013
41. Wright HH, Fergadiotis G. Conceptualising and measuring working memory and its relationship to aphasia. *Aphasiology.* (2012) 26:258–78. doi: 10.1080/02687038.2011.604304
42. Murray L, Salis C, Martin N, Dralle J. The use of standardised short-term and working memory tests in aphasia research: a systematic review. *Neuropsychol Rehabil.* (2018) 28:309–51. doi: 10.1080/09602011.2016.1174718
43. Wright HH, Shisler RJ. Working memory in aphasia: theory, measures, and clinical implications. *Am J Speech Lang Pathol.* (2005) 14:107–18. doi: 10.1044/1058-0360(2005/012)
44. Seniów J, Litwin M, Leśniak M. The relationship between non-linguistic cognitive deficits and language recovery in patients with aphasia. *J Neurol Sci.* (2009) 283:91–4. doi: 10.1016/j.jns.2009.02.315
45. Simic T, Bitan T, Turner G, Chambers C, Goldberg D, Leonard C, et al. The role of executive control in post-stroke aphasia treatment. *Neuropsychol Rehabil.* (2019) 30:1853–40. doi: 10.1080/09602011.2019.1611607
46. Minkina I, Rosenberg S, Kalinyak-Fliszar M, Martin N. Short-term memory and aphasia: From theory to treatment. *Semin Speech Lang.* (2017) 38:17–28. doi: 10.1055/s-0036-1597261
47. Abel S, Huber W, Dell GS. Connectionist diagnosis of lexical disorders in aphasia. *Aphasiology.* (2009) 23:1353–78. doi: 10.1080/02687030903022203
48. Hula WD, McNeil MR. Models of attention and dual-task performance as explanatory constructs in aphasia. *Semin Speech Lang.* (2008) 29:169–87. doi: 10.1055/s-0028-1082882
49. Nikravesh M, Aghajanzadeh M, Maroufizadeh S, Saffarian A, Jafari Z. Working memory training in post-stroke aphasia: Near and far transfer effects. *J Commun Disord.* (2021) 89:106077. doi: 10.1016/j.jcomdis.2020.106077
50. Nilipour R, Pourshahbaz A, Ghoreyshi ZS. Reliability and validity of bedside version of persian WAB (P-WAB-1). *Basic Clin Neurosci.* (2014) 5:253–8.
51. Kranou-Economidou D, Kambanaros M. Combining intermittent theta burst stimulation (iTBS) With computerized working memory training to improve language abilities in chronic aphasia: a pilot case study. *Aphasiology.* (2020) 1–25. doi: 10.1080/02687038.2020.1852165
52. Lee JB, Sohlberg MM. Evaluation of attention training and metacognitive facilitation to improve reading comprehension in aphasia. *Am J Speech Lang Pathol.* (2013) 22:S318–33. doi: 10.1044/1058-0360(2013/12-0099)
53. Kalinyak-Fliszar M, Kohen F, Martin N. Remediation of language processing in aphasia: Improving activation and maintenance of linguistic representations in (verbal) short-term memory. *Aphasiology.* (2011) 25:1095–131. doi: 10.1080/02687038.2011.577284
54. Zakariás L, Kelly H, Salis C, Code C. The methodological quality of short-term/ working memory treatments in poststroke aphasia: a systematic review. *J Speech Lang Hear Res.* (2019) 62:1979–2001. doi: 10.1044/2018_JSLHR-L-18-0057
55. Mayer JF, Murray LL. Measuring working memory deficits in aphasia. *J Commun Disord.* (2012) 45:325–39. doi: 10.1016/j.jcomdis.2012.06.002
56. Rottschy C, Langner R, Dogan I, Reetz K, Laird AR, Schulz JB, et al. Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage.* (2012) 60:830–46. doi: 10.1016/j.neuroimage.2011.11.050
57. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp.* (2005) 25:46–59. doi: 10.1002/hbm.20131
58. Jaeggi SM, Buschkuehl M, Jonides J, Perrig WJ. Improving fluid intelligence with training on working memory. *Proc Nat Acad Sci.* (2008) 105:6829–33. doi: 10.1073/pnas.0801268105
59. Rudebeck SR, Bor D, Ormond A, O'Reilly JX, Lee AC. A potential spatial working memory training task to improve both episodic memory and fluid intelligence. *PLoS ONE.* (2012) 7:e50431. doi: 10.1371/journal.pone.0050431
60. Bürki CN, Ludwig C, Chicherio C, de Ribaupierre A. Individual differences in cognitive plasticity: an investigation of training curves in younger and older adults. *Psychol Res.* (2014) 78:821–35. doi: 10.1007/s00426-014-0559-3
61. Li SC, Schmiedek F, Huxhold O, Röcke C, Smith J, Lindenberger U. Working memory plasticity in old age: practice gain, transfer, and maintenance. *Psychol Aging.* (2008) 23:731. doi: 10.1037/a0014343
62. Cicerone KD. Remediation of working attention in mild traumatic brain injury. *Brain injury.* (2002) 16:185–95. doi: 10.1080/02699050110103959
63. Ploughman M, Eskes GA, Kelly LP, Kirkland MC, Devasahayam AJ, Wallack EM, et al. Synergistic benefits of combined aerobic and cognitive training on fluid intelligence and the role of IGF-1 in chronic stroke. *Neurorehabil Neural Repair.* (2019) 33:199–212. doi: 10.1177/1545968319832605

64. Zakariás L, Salis C, Wartenburger I. Transfer effects on spoken sentence comprehension and functional communication after working memory training in stroke aphasia. *J Neurolinguist.* (2018) 48:47–63. doi: 10.1016/j.jneuroling.2017.12.002
65. Caughlin S, Mehta S, Corriveau H, Eng JJ, Eskes G, Kairy D, et al. Implementing telerehabilitation after stroke: lessons learned from canadian trials. *Telemed E Health*. (2019) 26–710–9. doi: 10.1089/tmj.2019.0097
66. Kagan A. Supported conversation for adults with aphasia: methods and resources for training conversation partners. *Aphasiology.* (1998) 129:816–30. doi: 10.1080/02687039808249575
67. Kagan A, Black SE, Duchan JF, Simmons-Mackie N, Square P. Training volunteers as conversation partners using "supported conversation for adults with aphasia" (SCA): a controlled trial. *J Speech Lang Hear Res.* (2001) 44:624–38. doi: 10.1044/1092-4388(2001/051)
68. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test.* 2nd ed. Philadelphia, PA: Lippincott, Williams and Wilkins (2001).
69. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. *Am J Prev Med.* (2009) 36:452–7. doi: 10.1016/j.amepre.2009.02.002
70. Mallet KH, Shamloul RM, Corbett D, Finestone HM, Hatcher S, Lumsden J, et al. (2016). Recover Now: Feasibility of a mobile tablet- based rehabilitation intervention to treat post-stroke communication deficits in the acute care setting. *PLoS ONE*. (2016) 11:e0167950. doi: 10.1371/journal.pone.0167950
71. Brooke J. *SUS: A Quick and Dirty Usability Scale*. (1986). Digital Equipment Co Ltd. Available online at: http://www.usabilitynet.org/trump/documents/Suschapt.doc.
72. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Intl J Hum Comput Interact.* (2008) 24:574–94. doi: 10.1080/10447310802205776
73. Simic T, Leonard C, Laird L, Cupit J, Höbler F, Rochon E. A usability study of internet-based therapy for naming deficits in aphasia. *Am J Speech Lang Pathol.* (2016) 25:642–53. doi: 10.1044/2016_AJSLP-15-0030
74. Kertesz A. *Western Aphasia Battery-Revised*. Harcourt Assessments (2006).
75. Lomas J, Pickard L, Bester S, Elbard H, Finlayson A, Zoghaib C. The communicative effectiveness index: Development and psychometric evaluation of a functional communication measure for adult aphasia. *J Speech Hear Disor.* (1989) 54:113–24.
76. Cherney LR, Babbitt EM, Semik PE, Heinemann AW. Psychometric properties of the communication confidence rating scale for aphasia (CCRSA): Phase 1. *Top Stroke Rehabil.* (2011) 18:352–60. doi: 10.1310/tsr1804-352
77. Brookshire RH, Nicholas LE. *The Discourse Comprehension Test*. Tucson, AZ: Communication Skill Builders/The Psychological Corporation (1993).
78. Henderson A, Kim H, Kintz S, Frisco N, Wright HH. Working memory in aphasia: Considering discourse processing and treatment implications. *Semin Speech Lang.* (2017) 38:40–51. doi: 10.1055/s-0036-1597257
79. Wechsler D. *Manual for the Wechsler Memory Scale – Revised*. New York, NY: The Psychological Corporation (1987).
80. Corsi PM. Human memory and the medial temporal region of the brain. *Diss Abstr Int.* (1972) 34:819B.
81. Lezak MD. *Neuropsychological Assessment*. 3rd ed.. New York, NY: Oxford University Press (1995).
82. Howard D, Best W, Nickels L. Optimising the design of intervention studies: critiques and ways forward. *Aphasiology.* (2015) 29:526–62. doi: 10.1080/02687038.2014.985884
83. Gilmour G, Porcelli S, Bertaina-Anglade V, Arce E, Dukart J, Hayen A, et al. Relating constructs of attention and working memory to social withdrawal in Alzheimer's disease and schizophrenia: issues regarding paradigm selection. *Neurosci Biobehav Rev.* (2019) 97:47–69. doi: 10.1016/j.neubiorev.2018.09.025
84. Herbert R, Best W, Hickin J, Howard D, Osborne F. *Profile of Word Errors and Retrieval in Speech (POWERS)*. North Guilford: JR Press. (2013).
85. Best W, Grassly J, Greenwood A, Herbert R, Hickin J, Howard D. A controlled study of changes in conversation following aphasia therapy for anomia. *Disabil. Rehabil.* (2011) 33:229–42. doi: 10.3109/09638288.2010.534230

Conflict of Interest: GE has a patent pending involving N-Igma.

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

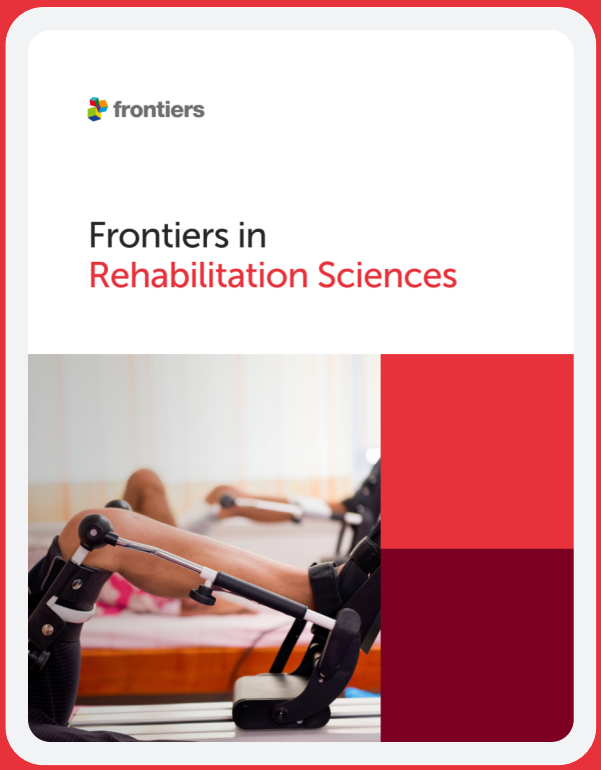
Frontiers in
Rehabilitation Sciences

Innovations in optimizing functioning for people who experience disability

An innovative journal which investigates new ways to optimize the functioning and wellbeing of people who experience disability, focusing on rehabilitation as the health strategy of the 21st century.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Swizerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact