However, comprehensive assessments of its short-term and sustained effectiveness across various cognitive and physical domains, as well as optimization of stimulation parameters are still needed. This study aims to address these gaps by evaluating the short-term and sustained effects of NIBS on cognitive and physical functions among people with MCI, Alzheimer's disease (AD), and other types of dementias, and determining the optimal stimulation parameters.

Methods

A systematic review was performed by querying eight databases including PubMed (Medline), Ovid (Medline), Web of Science, CINAHL (via EBSCO), SCOPUS, the Cochrane Library, PsycINFO (via ProQuest), and Embase from their inception until April 8, 2024. We exclusively selected randomized controlled trials implementing NIBS interventions vs sham or control for people with MCI and dementia. The assessment of methodological quality and potential bias in individual studies was conducted utilizing the Physiotherapy Evidence Database (PEDro) scale and the Cochrane Risk of Bias 2.0 (ROB 2.0) tool. The quality of evidence for each outcome was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system. Sensitivity and meta- regression analyses were performed to assess the robustness of our results under heterogeneity and to investigate the sources of heterogeneity and the impact of specific variables on effect size.

Results

Seventy-one studies involving 2895 participants were reviewed. The main findings indicate that traditional repetitive transcranial magnetic stimulation (trTMS) significantly enhances short-term global cognitive function (g ¼ 0.41, p < 0.01), verbal episodic memory (g ¼ 0.38, p < 0.01), visuospatial abilities (g ¼ 0.43, p ¼0.04), attention (g ¼ 0.64, p < 0.01), and activities of daily living (ADLs) (g ¼ 0.51, p <0.01), with sustained effects on ADLs (g ¼ 0.65, p < 0.001). Transcranial direct current stimulation (tDCS) significantly improves short-term global cognitive function (g ¼ 0.81, p < 0.01), working memory (g ¼ 0.58, p ¼ 0.01), verbal fluency (g ¼ 1.09, p < 0.01), and attention (g ¼ 0.89, p < 0.01), and induced sustained benefits for cognitive flexibility (g ¼ 4.28, p < 0.01), attention (g ¼ 1.62, p ¼ 0.02), and visuospatial abilities (g ¼ 5.60, p < 0.001). Intermittent theta-burst stimulation significantly improves short- term verbal episodic memory (g ¼ 0.55, p < 0.001), working memory (g ¼ 1.17, p ¼ 0.04), verbal fluency (g ¼ 0.49, p ¼ 0.02), naming (g ¼ 0.75, p < 0.001), and visuospatial abilities (g ¼ 0.97, p < 0.01). Other NIBS techniques significantly improve short-term verbal episodic memory (g ¼ 0.57, p < 0.01), working memory (g ¼ 0.48, p ¼ 0.03), and attention (g ¼ 0.78, p < 0.03). Effective trTMS protocols targeted the left Dorsolateral Prefrontal Cortex (DLPFC) or other areas at 10Hz or 20Hz, with 80% RMT intensity, 3-7 sessions per week, for at least two weeks, totaling over 20,000 pulses. tDCS showed significant short-term cognitive improvement by targeting the left DLPFC at 2mA for 20-30 minutes per session, with at least ten sessions over two weeks.

Discussion

This review provides a comprehensive analysis of the short-term and sustained effects of NIBS on cognitive and physical function related outcomes in patients with MCI, AD and other types of dementia. trTMS effectively improves global cognition and verbal episodic memory in both MCI and dementia, aligning with Jiang et al., who highlighted trTMS's efficacy as a non-pharmacological intervention for enhancing global cognition and memory in people with MCI [1]. However, its impact on nonverbal memory remains unclear due to limited studies. The benefits of trTMS are more pronounced in MCI than in AD, possibly due to less severe brain atrophy in MCI [2]. tDCS Enhances global cognition, working memory, and verbal fluency, consistent with Xu et al., who observed positive impacts of NIBS on global cognition, executive functions and language in people with MCI [3]. Our review clarifies that improvements in executive and language functions attributed to NIBS are primarily due to tDCS's impact on working memory and verbal fluency. iTBS significantly enhances memory, executive and language functions by mimicking endogenous theta rhythms, leading to sustained synaptic enhancement [4, 5]. Other NIBS techniques, such as transcranial photobiomodulation and transcranial alternating current stimulation, show promising cognitive enhancements, though further original studies are needed. Both trTMS and tDCS show significant cognitive improvements with high-frequency stimulation of specific brain regions. Multi-site stimulation may enhance cognitive reserve by improving interhemispheric connectivity [6]. NIBS, particularly trTMS, improves ADLs in dementia, likely due to enhanced cortical excitability and neural plasticity [7].

In conclusion, NIBS effectively improves cognitive function, ADLs and mobility in people with MCI and dementia, showing both short-term and sustained benefits. This study identifies optimal stimulation protocols for trTMS and tDCS that enhance treatment reproducibility and clinical translation. More original research is needed in the future to explore the sustained efficacy of NIBS and refine therapeutic parameters for people with MCI and other types of dementias.

Keywords: Cognitive impairment, Non-invasive brain stimulation, Cognitive function, Physical function, Meta-analysis

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Disclosures

The authors declare no conflicts of interest.

DIFFERENTIAL IMPACTS OF TASK DIFFICULTY ON USER OUTCOMES IN MOTOR REHABILITATION TRAINING

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Abstract A59: Presented at the 2024 NYC Neuromodulation Conference

Synopsis

This study examined how the complexity of virtual reality (VR) motor training tasks, guided by visual augmented sensory feedback (ASF) cues, can impact post-training motor performance. The objective was to explore the necessity and opportunities for optimizing VR-based motor rehabilitation methods between levels of training task difficulty. The study employed a customized VR rehabilitation platform for recovering upper body function through myoelectric control tasks. Five neurotypical participants performed near-isometric muscle movements, and the resultant electromyography (EMG) signals were input into a support vector machine, which commanded the movement of a VR robotic arm tasked with contacting various targets. Motor performance was assessed based on minimizing the pathlength of the robot′s end-effector and task completion time. Training difficulty was specified by the length and shape of the target trajectory that needed to be followed in contacting targets. A straight-line target trajectory represented the baseline condition, while a sinusoid trajectory represented increased difficulty, i.e., a longer trajectory with curvature. Participants achieved greater improvement in post-training motor performance when training with the baseline training condition. This outcome underscores how training complexity, based on task difficulty and ASF cues for guidance, may impact cognitive resources for improving motor performance. Such results highlight the need (and opportunity) to tailor rehabilitation training to optimize motor function outcomes with customizable interfaces like VR environments.

Background

Physical therapy remains a primary solution for recovering motor function after neurological traumas such as spinal cord injuries (SCI) [1]. Emerging approaches use advanced technologies such as virtual reality (VR) [2] and wearable devices [3] to motivate patient participation [4]. However, when the treatment dosages are similar, the advantages of VR-based methods over more traditional physical therapies are marginalized [5]. Consequently, new approaches are being sought to optimize customizable computerized interfaces for improved outcomes. Augmented sensory feedback (ASF), which involves providing additional sensory-driven cues about performance during rehabilitative training, is proven to enhance motor learning [6]. Such training feedback is not standardly used in rehabilitation but can be readily integrated with immersive computerized interfaces like virtual reality.

Previous studies have examined the impact of various modes of ASF training (i.e., providing cues through different sensory modalities) [7] and the differential effects on user motor performance and physiological responses [8], [9]. However, whether such effects observed in simple tasks can be generalized to more complex activities is uncertain [10]. Thus, this pilot study employs visual ASF cues during training, which has proven effective in generating improved post- training performance for this platform [11], with two distinct levels of training task difficulty. Results from this study should indicate the ability of participants to leverage visual ASF cues with a more complex training paradigm. Such findings are essential to elucidate necessary guardrails for more intelligent design of customizable computerized interfaces for rehabilitation.

Methods

This study recruited five neurotypical individuals to voluntarily participate in this protocol approved by the Stevens Institutional Review Board. A novel computerized platform was developed for near-isometric muscle activation training with virtual reality (Figure 1a). The platform included a position-adjustable brace designed to support the arm against gravity while exerting muscular efforts intended to aid in the recovery of upper limb function [9]. The brace support system includes 3D-printed components such as cuffs, hinges, adjustable rods, and a support structure secured to a table, ensuring the upper limb maintains a stable position. A myoelectric control task in a custom-created virtual reality environment was developed using Unity. Participants were tasked with exerting muscular activations to command a virtual robotic arm to approach and contact designated targets.

Electromyography (EMG) signals from fourteen muscle groups were recorded using skin-surface sensors (Delsys Trigno) and served as inputs to a regression support vector machine in Matlab, which inferred the commanded speed and direction to move the virtual arm along a 2-D plane [12]. During training with ASF, participants received additional visual cues for guidance in the form of an emerging semi-transparent end-effector. The end-effector amplifies error feedback to the user whereby error is position deviation from the target trajectories assigned to follow during training. Participants underwent three blocks of trials: pre-training, ASF training, and post-training, with visual ASF provided only during the ASF training block. During training, participants were instructed to follow one of two trajectory types within the VR environment while approaching designated targets. The target trajectories varied in difficulty and were either a straight-line trajectory, representing the baseline condition, or a sinusoidal trajectory, representing the testing condition of increased training difficulty. Motor performance was assessed using task completion time and path length of the end-effector. For pre-and post-training trials, participants were free to move how they wished in approaching targets with the understanding of minimizing path length and the time to complete the trial as performance measures. Performance gains under both conditions were measured by comparing changes in metrics from pre- to post-training.

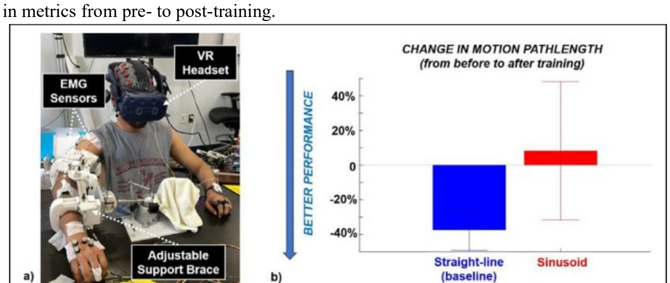

Figure 1. a) experimental setup with custom VR training platform, b) percentage change in relative pathlength after training with straight-line (baseline) versus sinusoid (increased difficulty) target trajectories.

Figure 1a) experimental setup with custom VR training platform, b) percentage change in relative pathlength after training with straight-line (baseline) versus sinusoid (increased difficulty) target trajectories.

Results

A paired t-test was conducted to verify differences between the experimental groups as each participant repeated both training conditions. Participants exhibited a significant ($p<0.05$) improvement in performance for completion time and motion pathlength under the baseline training condition (i.e., straight-line trajectory, less difficult training task). The mean pathlength was reduced by more than 30% (Figure 1b), and the completion time was reduced by 20%. Conversely, the training condition with increased difficulty (sinusoidal trajectory) indicated a slight increase in the mean pathlength metric after training. One-sample t-tests were applied for each metric and each condition to determine whether posttraining changes were significantly non-zero. Only the reduction in pathlength with baseline training was significant (p¼0.03). These results suggest that only the simpler training condition produced significant posttraining effects.

Discussion

This pilot study indicates that the post-training performance of this task depended on the difficulty level of the training task that included ASF cues. It is plausible that increasing difficulty during training may have increased cognitive loading counter-productively [13]. Furthermore, the increased difficulty may have depleted physical reserves, although participants did not report any issues of fatigue related to the training. Prior studies have indicated that increasing task difficulty with training can support greater improvements in post-training performance [14]. However, it was suggested that training outcomes are optimized if increases in training difficulty are made adaptively rather than in step increments. In this study, we only chose to examine two training difficulty levels. Tracing the sinusoidal trajectory provided a clear contrast from a baseline, with increased difficulty due to the requirement of adhering to curved paths. Participants used the same command structure (support vector machine not re-trained) for both training conditions to command the VR robot arm to adhere to target trajectories. Furthermore, the task was transparent to the participants, i.e., they clearly understood how to use myoelectric activations in a semi-fixed (near isometric) position to command the direction and speed of the VR robot arm. Thus, following curved paths should have served as an unambiguous requirement for increased difficulty in this VR training task. Beyond increased stress changes in cognitive and physical states, the reduction in performance metrics with increased training difficulty may be attributed to the lack of requirement to follow prescribed trajectories in pre- and post-training trials. Participants were allowed to follow their own paths to the targets in these trials. This experimental specification was applied to foster participant ability to develop strategy as part of demonstrating post-training skill acquisition [15]. While the training exposures in these sessions are limited and insufficient to facilitate authentic learning within single sessions, our prior work has shown such training paradigms can demonstrate short-term retention [16], [17], which in turn can indicate the potential for longer-term retention [18]. Still, in this pilot study, it is possible that the training with sinusoidal trajectories did not match the post-training task well. In post-training trials, participants would typically take more direct, straight-line trajectories in reaching targets given the incentive to maximize performance measures relying on shorter pathlengths and completion times. Given a random arrangement of targets and participants allowed to choose the order of targets, it was unclear a priori whether participants would choose or be able to command straight-line trajectories reliably in this freeform task. Yet, participants' ability to effectively control the VR arm robustly may have fostered the baseline training condition to be more aligned with the skill ideally exhibited in post-training.

In conclusion, an evident change in a presumed difficulty level with training significantly impacted the post-training performance of a motor rehabilitation task done in VR. Further work is necessary to specify contexts (e.g., motor task type, presence of neuromotor dysfunction, varying ASF cues, additional difficulty levels) in which motor rehabilitative training with ASF guidance cues can be delivered more effectively to maximize gains in motor function.

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