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New approaches for central nervous system rehabilitation

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New approaches for central nervous system rehabilitation

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Editorial: New approaches for central nervous system rehabilitation

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Editorial on the Research Topic
New approaches for central nervous system rehabilitation

Neurorehabilitation is a rapidly growing field in motor rehabilitation, which is specifically aimed at restoring neural plasticity of the central nervous system (CNS). The concept of neuroplasticity refers to the ability of the brain to reorganize itself in response to learning or exposure to enriched environments, and it is maintained for the entire human life. Thus, applying specific treatments can be beneficial for people with CNS injuries. The time frame for maximizing the benefits of neuroplasticity is critical, with the plateau observed about 12 weeks after the onset of stroke (1). Thus, it is essential to capitalize on this high level of brain reorganization by providing well-timed and well-designed treatments. A range of approaches has been developed for CNS recovery in acute, subacute, or chronic stages of injury. These approaches include priming or augmented techniques, such as end-effector robots, exoskeletons, or virtual reality, with many being confirmed as effective (2, 3). However, clinical practice still lacks specific indications for which therapy is most effective, for how long should be applied, and for which patient impairments. Therefore, this Research Topic aimed to explore new neurorehabilitative ideas and approaches, modifications of already existing techniques, and identification of research or clinical gaps, including predictive research for treatments and recovery.

There is a growing body of evidence supporting the use of innovative technologies like exoskeletons and/or orthoses (Cho et al.), virtual reality (Bian et al.) (4), and brain-computer interfaces in neurorehabilitation (Carino-Escobar et al.; de Freitas Zanona et al.). These technologies can provide a more immersive and engaging environment for therapy, and some studies have reported significant improvements in motor function and cognitive abilities in patients with CNS injuries (5). In addition to novel intervention techniques, the use of diagnostic techniques that measure cortical activity offers deeper knowledge about motor learning (6) and the changes that these techniques can cause, not only at a functional level, but also in terms of neuroplasticity. However, further research is needed to determine which technologies and interventions are most effective for different patient populations and to develop personalized treatment plans. In addition to innovative technologies, there

is a growing interest in innovative approaches to neurorehabilitation, such as peripheral electrical stimulation (Mijic et al.), Tai Chi training (Huang et al.), and audio-luminous biofeedback training for ocular motility (Misawa et al.) that have shown promise in enhancing motor function in patients with CNS injuries. However, the optimal parameters for these interventions and the patient populations that would benefit most from them are still being investigated (Paniagua-Monrobel et al.; Steendam-Oldekamp et al.).

The collection of this Research Topic included ten articles, mostly original, with a two review reports and two case reports. The original research focused on the exploration of diverse neurorehabilitative interventions and their applications across different stages of CNS injury, including acute, subacute, and chronic phases. Researchers aimed to investigate the efficacy of various neurorehabilitative interventions across different stages of CNS injury. Ten studies, spanning diverse research methodologies such as randomized controlled trials, case series, case reports, and literature reviews were, incorporated into this Research Topic.

In the study by Bian et al. authors aimed to evaluate the impact of a non-immersive virtual reality (VR)-based intervention on lower extremity movement in stroke patients, comparing its effectiveness to conventional therapies. The results suggested that the non-immersive VR-based intervention could be a valuable adjunct to conventional physical therapies, potentially augmenting overall treatment efficacy. Despite not exhibiting significant differences from conventional therapies, the intervention demonstrated noteworthy improvements in walking speed, balance, and lower extremity movement. This underscores the potential of non-immersive VR interventions as valuable complements to traditional therapies for enhanced treatment outcomes. In a study by Carino-Escobar et al. researchers explored the effectiveness of an experimental brain-computer interface (BCI) therapy in a 41-year-old COVID-19 patient who experienced a stroke. The patient, lacking traditional stroke risk factors, exhibited notable recovery in upper limb function through the BCI intervention during the chronic stroke stage. This highlights the innovative potential of BCI interventions in achieving significant motor recovery, even in COVID-19-related strokes during the chronic phase. Also, de Freitas Zanona et al. explored the effects of combining BCI with mental practice (MP) and occupational therapy (OT) on activities of daily living (ADL) performance in stroke survivors. Participants were randomized into experimental (BCI, MP, and OT) and control (OT only) groups. The experimental group showed significant improvements in various evaluations, indicating enhanced functional independence and sensorimotor recovery. Notably, the BCI group demonstrated larger effect sizes compared to the control group, suggesting the potential of BCI in promoting ADL performance and social participation in subacute post-stroke survivors. Steendam-Oldekamp et al. assessed the effectiveness of a multidisciplinary in-and-outpatient rehabilitation program for patients with advanced Parkinson's disease (PD) in stabilizing activities of daily living (ADL) and delaying nursing home admission. The intervention group, which underwent a 6-week inpatient program followed by a 2-year outpatient support program, showed significant improvements in ADL functions compared to the control group. After 2 years, 65% of the intervention group continued to live independently at home. The study emphasizes the substantial benefits of intensive rehabilitation for advanced PD patients, highlighting the potential to enhance their quality of life and delay nursing home admission. Study by Cho et al. explored the clinical effects of 3D-printed ankle-foot orthoses (3D-AFOs) on community ambulation in patients with chronic stroke. Three cases were presented, and gait assessments were conducted under various conditions. Following 4 weeks of community ambulation training with 3D-AFOs, improvements were observed in step length, stride width, ankle range of motion, and muscle efficiency during walking and stair ascent. While the training did not significantly impact patient participation, it enhanced ankle muscle strength, balance, gait symmetry, and endurance, and reduced depression. Patients expressed satisfaction with 3D-AFOs, citing their thinness, lightweight, comfort with shoes, and gait adjustability. The study by Huang et al. aimed to assess the impact of 12 weeks of Tai Chi exercise on neuromuscular responses and postural control in elderly individuals with sarcopenia. Sixty participants were randomly assigned to the Tai Chi group or the control group. After the intervention, the Tai Chi group exhibited a significant decrease in neuromuscular response times and overall stability index, indicating improved dynamic posture control and reduced fall risk. The Tai Chi group outperformed the control group in these measures. The simplified Tai Chi protocol proved feasible, safe, and effective for enhancing neuromuscular responses and postural control in elderly sarcopenic individuals, suggesting potential benefits in fall prevention. Misawa et al. conducted prospective pilot study and investigated the effectiveness of biofeedback training (BT) in individuals with homonymous hemianopsia (HH) and brain injury from various etiologies. Participants underwent five weekly BT sessions, leading to improvements in paracentral retinal sensitivity, fixation stability, contrast sensitivity, near vision visual acuity, and reading speed. Overall, the study suggests that BT resulted in encouraging enhancements in visual functions and functional vision for individuals with HH. Further confirmation through larger trials is needed, but the results indicate positive outcomes, particularly in visual ability, visual information, and mobility. Additionally, Paniagua-Monrobel et al. in their observational study, aimed to identify a "preferential patient profile" (PPP) for stroke survivors who may benefit more from early physical therapy (PT) treatment. Analyzing data from 137 individuals with stroke, they found that the PPP for early outpatient PT was a young person with left or bilateral haemorrhagic stroke. The results suggested that direct referral to PT services for this profile could lead to shorter waiting times and potentially greater recovery. The study highlights the importance of establishing a definitive profile through homogenous functional evaluations at the beginning and end of PT treatment. Further research with such evaluations is recommended to refine the PPP for efficient rehabilitation.

In the systematic review conducted by Mijic et al. researchers explored the potential role of peripheral electrical stimulation (PES) in altering somatosensory evoked potentials (SEPs) in both healthy subjects and stroke patients. Despite insufficient evidence confirming SEPs as predictors of rehabilitation prognosis after stroke, a correlation was found between sensory and

motor function assessments and changes in SEP components. Notably, PES interventions, particularly when linked to voluntary contractions for specific movements, showed positive relationships with motor function assessments. The study suggests that repetitive, task-oriented treatments enriched with PES could offer a distinct approach in stroke rehabilitation, potentially impacting motor neuroplasticity. However, further randomized controlled trials are needed to validate these findings and determine the utility of SEPs in monitoring the therapeutic effects of PES. Finally, the scoping review conducted by Favetta et al. explored the diffusion of motor control models in post-stroke rehabilitation literature. Authors analyzed 45 studies revealing a lack of clear theoretical bases in most stroke rehabilitation interventions. Only 10 studies explicitly stated the reference theoretical model. The classifications showed 21 studies referring to the robotics motor control model, 12 to self-organization, eight to neuroanatomy, and four to the ecological model. Results indicated a prevalent absence of explicit theoretical frameworks in stroke rehabilitation interventions, emphasizing the need for attention to theoretical underpinnings in designing future experimental approaches for stroke rehabilitation. The study highlights the importance of establishing solid scientific hypotheses on motor control and learning principles to advance rehabilitation as a scientifically-driven process.

The collective insights gained from the studies discussed have significantly advanced our understanding of neurorehabilitation, shedding light on the potential of various interventions informed by motor control and motor learning models. However, the scoping review by Favetta et al. underscored a notable gap in the explicit declaration and application of theoretical frameworks in many neurorehabilitative interventions. This gap highlights the need for greater attention to theoretical underpinnings in the design and reporting of interventions, emphasizing the importance of integrating scientific concepts into clinical trials. Moving forward, future research endeavors in neurorehabilitation should focus on addressing these identified gaps to further refine and expand our understanding of effective therapeutic approaches. It is crucial to explore the underlying mechanisms through which interventions impact neurorecovery, giving the basic for the development of more targeted and personalized rehabilitation strategies. One key avenue for future exploration is the integration of emerging technologies, such as virtual reality, brain-computer interfaces, and 3D printing, into rehabilitation protocols. The studies by Bian et al., Carino-Escobar et al., Cho et al., and de Freitas Zanona et al. demonstrated the potential of these technologies to enhance traditional therapeutic approaches, offering personalized, engaging, and effective interventions. Investigating the optimal ways to integrate these technologies into routine clinical practice and identifying the specific patient populations that may benefit the most will be crucial for the continued advancement of neurorehabilitation.

Additionally, research efforts should delve deeper into the mechanisms of action behind successful interventions. Understanding the neuroplastic changes, both at the structural and functional levels, induced by different therapeutic modalities will provide valuable insights. Advanced neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), could be employed to unravel the intricate processes occurring within the central nervous system during recovery. Furthermore, the emphasis should be placed on tailoring interventions to the unique needs of individuals based on the stage of injury and the nature of their impairments. Collaborative and multidisciplinary research approaches should be encouraged to address the complex nature of neurorehabilitation. Integrating expertise from neurology, rehabilitation medicine, bioengineering, and other relevant fields will foster a comprehensive understanding of the diverse factors influencing recovery. This collaborative effort can lead to the development of holistic and synergistic interventions that encompass cognitive, motor, and psychosocial aspects of rehabilitation.

In conclusion, the future of neurorehabilitation research should be guided by a commitment to refining and expanding our knowledge base. By addressing gaps in theoretical frameworks, exploring emerging technologies, unraveling the neuroplastic mechanisms, tailoring interventions, and fostering multidisciplinary collaborations, researchers can contribute to the ongoing evolution of neurorehabilitation. Ultimately, the field of neurorehabilitation is rapidly evolving, and there is a need for continued research to develop more effective and personalized treatments for patients with CNS injuries and other neurological disabilities.

Author contributions

PK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AG: Conceptualization, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. MP: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AO-P-V: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CL-M: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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A non-immersive virtual reality-based intervention to enhance lower-extremity motor function and gait in patients with subacute cerebral infarction: A pilot randomized controlled trial with 1-year follow-up

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Introduction: This study was conducted to evaluate whether a non-immersive virtual reality (VR)-based intervention can enhance lower extremity movement in patients with cerebral infarction and whether it has greater short-term and long-term effectiveness than conventional therapies (CTs).

Materials and methods: This was a single-blinded, randomized clinical controlled trial. Forty-four patients with subacute cerebral infarction were randomly allocated to the VR or CT group. All intervention sessions were delivered in the inpatient unit for 3 weeks. Outcomes were measured before (baseline) and after the interventions and at 3-month, 6-month and 1-year follow-ups. The outcomes included clinical assessments of movement and balance function using the Fugl–Meyer Assessment of Lower Extremity (FMA-LE) and Berg Balance Scale (BBS), and gait parameters in the sagittal plane.

Results: In the VR group, the walking speed after intervention, at 3-month, 6-month, and 1-year follow-ups were significantly greater than baseline ($p = 0.01$, <0.001, 0.007, and <0.001, respectively). Compared with baseline, BBS scores after intervention, at 3-month, 6-month, and 1-year follow-ups were significantly greater in both the VR group ($p = 0.006$, 0.002, <0.001, and <0.001, respectively) and CT group ($p = <0.001$, 0.002, 0.001, and <0.001, respectively), while FMA-LE scores after intervention, at 3-month, 6-month, and 1-year follow-ups were significant increased in the VR group ($p = 0.03$, <0.001, 0.003, and <0.001, respectively), and at 3-month, 6-month, and 1-year follow-ups in the CT group ($p = 0.02$, 0.004 and <0.001, respectively). In the VR group, the maximum knee joint angle in the sagittal plane enhanced significantly at 6-month follow-up from that at baseline ($p = 0.04$).

Conclusion: The effectiveness of the non-immersive VR-based intervention in our study was observed after the intervention and at the follow-ups, but it was not significantly different from that of CTs. In sum, our results suggest that non-immersive VR-based interventions may thus be a valuable addition to conventional physical therapies to enhance treatment efficacy.

Clinical trial registration: http://www.chictr.org.cn/showproj.aspx?proj=10541, ChiCTR-IOC-15006064.

KEYWORDS

virtual reality, ischemic stroke, gait analysis, motor activity, rehabilitation

Introduction

Stroke is a major health problem with a global incidence of almost 12.2 million cases each year, and has been identified as the third-leading cause of both death and disability in recent years (1). In China, stroke incidence has almost doubled over the past 30 years, posing a great burden to Chinese society, and the ischemic stroke accounted for more than 80% (2). Approximately 88% of post-stroke patients discharged from hospitals continue to suffer from impaired walking ability (3). Moreover, ∼50% of post-stroke patients who regain ambulation capability continue to experience difficulties in walking in the community (4). Limited walking ability is a major concern for stroke survivors, both physically and psychologically, as it has a negative impact on their daily function and, ultimately, their quality of life due to limited access to the community (5). The gait pattern among post-stroke survivors usually shows lower walking speed, and an abnormal hip-knee-ankle joint movement (6). Therefore, gait recovery is a major objective of stroke rehabilitation.

To improve gait function in post-stroke patients, continued physical therapy at all recovery stages is necessary. Therapeutic techniques such as virtual reality (VR) are being increasingly applied in neurorehabilitation practice, and the benefits of applying VR-based training have been widely recognized in the field of stroke rehabilitation. VR technique can be divided into non-immersive VR with different levels of immersion and immersive VR with a head-mounted display, which is closer to real-life but is easy to leave the adverse effect of dizziness (7). The effectiveness of immersive VR has been demonstrated to train motor patterns of healthy young participants, and the patterns were maintained in real-world settings (8). However, in China, the non-immersive VR is relatively not expensive and user-friendly for both therapists and patients, which is commonly applied in rehabilitation therapy. Hence this study utilized the non-immersive VR techniques to clarify the effectiveness of VR technique. VR is an advanced computer–human interface that provides artificial sensory feedback for patients while they perform real-time tasks and experience real-time events in virtual environments (9). Training with VR is considered to include the rehabilitation principles of high-intensity, repetitive and task-specific practice (10). Moreover, VR is well-recognized to improve motivation and enjoyment and consequently decrease the perception of exertion, which promotes adherence to the training activity (5). In addition, VR could reinforce the physiological basis of motor learning and descending neural pathways (11, 12), and its potential cognitive benefits to patients, including improvements in attention or memory, have been demonstrated in situations where they are required to react quickly and deal with busy environments with multiple stimuli. Therefore, thus, VR could play a beneficial role in improving balance and gait capacity among post-stroke patients (13). In clinical, VR is applied independently or in combination with the abovementioned conventional physical therapy techniques for gait rehabilitation and motor function improvement.

Recently, studies on the effectiveness of non-immersive VR among post-stroke patients have reported inconsistent findings. Some reviews have reported that the current evidence is insufficient to conclude that VR is more effective than conventional therapy (CT) (10, 14–16), while others suggested that VR enhances the lower-limb motor performance including balance and gait function of post-stroke patients more efficiently than CT (4, 17–21). Specifically, several RCTs showed no statistical differences between the effects of VR treatment and CT treatment on balance or lower extremity motor function for acute stroke patients and subacute patients (22, 23). On the other hand, one study has demonstrated that non-immersive VR as an add on to CT was more effective in balance capability than CT alone among subacute patients without long-term result reported (24). Several studies that adopted clinical measures to assess lower extremity and gait ability have also suggested VR's potential to promote functional recovery for chronic stroke patients (25), while some have shown the benefits of VR in enhancing balance capability (26, 27). Moreover, an RCT

Abbreviations: VR, virtual reality; CT, conventional therapy; FMA, fugl-meyer assessment; BBS, berg balance scale; NHISS national institute of health stroke scale; MMSE, mini mental state examination.

showed that cycling training with smartphone VR application led to significant improvements in lower extremity function, sitting balance and spatiotemporal gait performance for chronic stroke patients compared with CT (12). The controversial findings for the motor function after VR intervention possibly result from insufficient VR programs designed for impairments, and the largely varied duration before intervention (16). VR combined with conventional physiotherapy contributed to motor improvement in post-stroke patients in both subacute and chronic stages, but improvement of kinematic outcomes was confirmed for the subacute group, but not for the chronic group (28). Therefore, in our study, different VR programs with the same dosage were applied for lower-extremity motor function and gait, and subacute post-stroke patients were recruited.

Moreover, the majority of published studies followed patients for no longer than 3 months and reported contradictory follow-up outcomes. Wii-based VR intervention was found to increase Berg Balance Scale (BBS) scores both immediately after the intervention and at the 4-week follow-up, and that the scores at both time points were greater than those of the CT group (29). Nevertheless, another RCT concluded that the effectiveness of VR on balance and gait could not be maintained, and found that the CT group showed greater improvements in weight-bearing symmetry at the 3-month follow-up than the exergame group, among chronic and subacute stroke patients (30). Similarly, the effect of non-immerisve VR was shown not statistically different from that of CTs in improving balance performance or gait capability at both post-intervention and the 3-month follow-up among chronic and subacute stroke patients (23, 31, 32). Furthermore, one systematic review summarized that the evidence on the effectiveness of VR analyzed using biomechanical parameters was limited, especially for sustained effectiveness at longer than 4 weeks post-intervention (17). Additionally, the effectiveness of treatment in the follow-ups contribute to the evidence of motor relearning and neural plasticity, which is significant for stroke patients (33).

Therefore, the current study evaluated the long-term effects of a VR-based intervention, i.e., at 6 months and 1 year post-intervention, using biomechanical analyses of lower extremity motor function, balance function and gait pattern.

Given the above-mentioned contradictory results and no reported long-term follow-up result, our study aimed to clarify whether a 3-week course of VR-based lower extremity exercises can effectively improve gait parameters and motor function in post-stroke inpatients in the subacute stage, and whether the effects of these exercises on motor function and gait are sustained at a 1-year follow-up.

Materials and methods

Study participants

Inpatients in the subacute phase after cerebral infarction stroke were recruited from the Seventh Affiliated Hospital and the First Affiliated Hospital, Sun Yat-Sen University, China. Adults without neurological pathology were recruited through advertisement. This study was approved by the Human Subjects Ethics Subcommittee of the Affiliated Hospitals (NO.2019SYSUSH-019), Sun Yat-Sen University, China. Clinical trial registration number is ChiCTR-IOC-15006064. Written consent was obtained from all participants prior to inclusion in the study. The study was conducted from October 2019 to June 2022.

Potential post-stroke inpatients were recruited by physicians at the rehabilitation center using the following inclusion criteria: post-stroke inpatients with (1) Mini-Mental State Examination scores >24 (34); (2) National Institute of Health Stroke Scale scores <20 to exclude heavy ischemic stroke (35); (3) diagnosis of cortical and subcortical schemic stroke (confirmed by magnetic resonance imaging or computer tomography) <6 months before their inclusion in this study; (4) Brunnstrom stage for lower-extremity ≥ 1; (5) no previous VR-based rehabilitation training experience; (6) Modified Ashworth Scale scores of the lower-limbs ≤ 2; (7) the ability to maintain sitting balance for more than 20 min and walking for over 10 meters; and (8) adults under the age of 75. The exclusion criteria were (1) patients who had previously received VR-based training, and (2) patients with other diseases, such as cerebellar and brainstem injuries, severe cognitive impairment, joint stiffness, convulsive crisis, congestive heart failure, deep vein thrombosis of a lower extremity, malignant progressive hypertension, respiratory failure, active liver disease, severe hepatic and renal insufficiency, history of mental illness and inability to cooperate. Normal age-matched adults were included, if they have no previous and current central nervous system diseases and severe musculoskeletal diseases.

Study design

The study was a single-blinded, randomized controlled trial to explore the effects of VR gait training on the motor function of patients with subacute cerebral infarction. All participants were randomly allocated to either a VR group or a CT group. The baseline and post-intervention assessments and training sessions were conducted in the hospital's inpatient rehabilitation department, and post-intervention and 3-month, 6-month, and 1-year follow-up assessments were performed in the outpatient rehabilitation center. Sample size estimation was performed by G*Power software (Düsseldorf, Germany), considering a Minimal Clinically Important Difference (MCID) change of walking speed equal to 0.13 m/s (36, 37) as the expected effect of the treatment, with a pooled Standard Deviation (SD) of 0.23. Thus, for $\alpha = 0.05$, $\beta = 0.2$, with an f effect size $= 0.57$, it provides an estimated total sample size of 42 subjects. Moreover, considering a 10% dropout, 47 total subjects were considered sufficient for statistical analysis.

An independent researcher conducted the random allocation of participants based on a randomization sequence generated by a statistics expert from Sun Yat-sen University. Allocation numbers were sealed in opaque envelopes. The researchers performing the assessments were blinded to treatment allocation, but the participants and the therapists providing the interventions could not be blinded due to the nature of the interventions.

Intervention

The interventions in this study mainly focused on the functional ability of the lower extremities, including lower limb movement, balance training and gait exercise. All participants received 5-h rehabilitation programs (either VR-based or CT) on 5 days per week for 3 weeks. Specifically, the VR group received 15 physical training sessions combined with VR-based training, while the CT group underwent routine CT-based rehabilitation training for the same duration. In each session of the two programs, the training intensity was adjusted by experienced physical therapists in line with the participants' progress, safety and movement quality. VR techniques adopted in the VR group included the Wii exergame training system, an active and passive trainer with a VR screen, a VR balance training system and a VR gait training system based on the non-immersive VR techniques with feedback including visual, auditory, and numbers. The examples of them are shown in Figure 1 (trajectory tracking, car driving and etc.) and each VR training system is detailly descripted in the Table 1. Therapists introduced, demonstrated and guided the patients at the first time of VR intervention, they also supervised the intervention of training of patients during the following sessions. The difficulty level of VR training was modified by experienced therapists based on the abilities and therapeutic goals of each participant, and the system displayed the outcome of each VR training session for the participants and therapists once the training ended.

FIGURE 1
Examples of VR interventions. **(a)** Wii exergame training; **(b)** an active and passive trainer with a VR screen; **(c)** a VR balance training system; **(d)** lower extremity training in a VR gait training system.

Outcome measures

The outcomes of the intervention participants were measured before and immediately after the 3-week intervention and at 3-month, 6-month, and 1-year follow-ups using standard operating procedures. The collected data included demographic data (i.e., age, gender, affected side), clinical assessment outcomes of National Institute of Health stroke scale (NIHSS), Mini Mental State Examination (MMSE), Fugl-Meyer assessment (FMA-LE) and BBS, as well as biomechanical parameters recorded using a 3D gait analysis system, the walking speed parameter of which is the primary outcome of this study. Intention-to-treat analyses were done during the data analysis. The gait performance of twelve age-matched healthy adults were also assessed for comparison. All biomechanical data on gait was obtained and analyzed using a real-time motion tracking/capture system, namely, the standard PlugInGait model with Vicon Nexus software (version 1.7.1; Vicon Motion Systems, UK), as shown in Figure 2. Six infrared 100-Hz cameras recorded the location of 16 markers of pelvic and both lower-extremities during the data collection under the guidance of model sets of PlugInGait model, including the midline sacrum at the level of the posterior superior iliac spines, anterior superior iliac spines, lower lateral 1/3 and 1/2 surface of left and right thigh, lateral epicondyle of knee, lower lateral 1/3 and 1/2 surface of left and right shank, lateral malleolus, the second metatarsal head, and the calcaneus at the same height as the toe marker. The spatiotemporal and lower-extremity joint kinematic data was obtained from the model. During the gait assessment process, each participant was asked to wear flat shoes and close-fitting pants and to walk independently for 10 meters without any crutches or ankle foot orthoses, turn around and return to the starting point at a self-selected walking speed. One researcher collected gait data and calculate the number of successful gait cycles for minimum of six. In addition, during clinical outcome assessments, the post-stroke participants' FMA-LE (38) and BBS scores for lower limb performance were obtained (39, 40).

Data processing and analysis

Gait data from successful gait cycles, specifically the spatiotemporal and kinematic parameters, were analyzed using Polygon (version 3.5.1; Vicon Motion Systems, UK). Heel strike

TABLE 1 VR training systems applied in the study.

Catagories	Sensor used	Movement executed
Wii exergame training system	Camera	Balance training (dynamic)
An active and passive trainer with a VR screen	Sensors (speed and moment)	Cycling
A VR balance training system	Pressure transducers	Balance training (standing)
A VR gait training system	Sensors (speed and direction)	Walking, stepping and lower extremity training

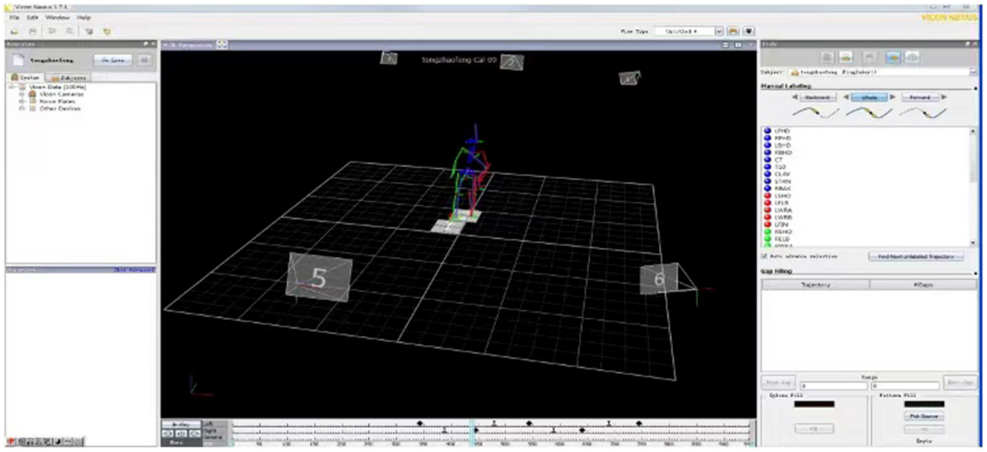

FIGURE 2
Three-dimensional data capture.

events from each walking trial were determined by visual inspection, with reference to the Vicon Nexus software output, and were used to define the beginning and end of each walking cycle. The following spatiotemporal parameters were collected and analyzed: cadence, stride time, opposite foot off, opposite foot contact, step time, single support, double support, opposite foot off, stride length, step length and walking speed.

Additionally, the angles of the hip, knee and ankle joints of the affected lower limbs were measured. Subsequently, from the mean profile of selected strides, data on the following joint kinematic parameters in the sagittal plane were extracted: the maximum angle, minimum angle and range of motion for the hip, knee and ankle joints. For comparison, these joint kinematic parameters from the gait data of 12 adults without neurological pathology were also analyzed.

Statistical analysis was performed using GraphPad Prism version 9.0.0 for macOS (GraphPad Software, San Diego, California USA). The normality of data on parameter was checked using the Shapiro–Wilk test and a normal Q–Q plot, and the normality of each outcome was confirmed. Unpaired *t*-test and X2 test were used to compare between-group differences at baseline for continuous variables and for categorical variables, respectively. Repeated-measures two-way ANOVA was used for detection of within-group differences from pre-intervention to post-intervention to follow-ups, while a *post-hoc* analysis with Bonferroni's correction was used for between-group differences at all time points.

Results

Forty-four participants with post-stroke hemiparesis were included in this pilot study and randomly allocated to the VR or CT group. According to the randomization sequence, 23 participants were allocated to the VR group and 21 to the CT group. At the 3-month follow-up, the number of participants in the VR and CT groups has been decreased to 17 and 19, respectively. At the 6-month and 1-year follow-ups, the number of participants in the VR and CT groups was 16 and 18, respectively. The outcome of those 16 and 18 participants in the VR and CT groups were analyzed. The demographic characteristics of the participants, the outcomes of clinical scales and the walking speed are presented in Table 2 and were not significantly different between the two groups.

Balance and lower limb motor function

Compared with the BBS scores at baseline, those after intervention, at 3-month, 6-month, and 1-year follow-ups were

TABLE 2 Demographic characteristics (Mean ± SD) at baseline for three groups.

	Normal	VR group	CT group	*P*-value
Age	58.17 ± 8.12	53.25 ± 8.72	55.00 ± 10.27	0.599
Gender (male/female)	6/6	14/4	13/3	0.803
Affected side (right/left)		10/8	6/10	0.292
NIHSS		4.69 ± 2.50	4.56 ± 2.854	0.888
MMSE		28.56 ± 1.83	28.06 ± 1.73	0.412
BBS		36.94 ± 10.55	38.28 ± 14.05	0.758
FMA-LE		23.10 ± 5.89	23.50 ± 4.46	0.834
Walking speed		0.42 ± 0.20	0.43 ± 0.21	0.812

MMSE, Mini Mental State Examination; NIHSS, National Institute of Health Stroke Scale; BBS, Berg Balance Scale; FMA-LE, Fugl-Meyer Assessment-Lower Extremity.

TABLE 3 Balance and lower motor function results of pre, post and follow-ups between CT and VR group.

Variable	VR group					CT group				
	Baseline	Post	3 m follow-up	6 m follow-up	1 yr follow-up	Baseline	Post	3 m follow-up	6 m follow-up	1 yr follow-up
BBS	36.94 ± 10.55	38.38 ± 8.72*	48.88 ± 5.74*	52.00 ± 4.66*	53.00 ± 3.74*	38.28 ± 14.05	35.86 ± 13.15*	43.00 ± 10.47*	44.71 ± 11.25*	47.00 ± 10.42*
FMA-LE	23.10 ± 5.89	21.63 ± 5.55*	25.88 ± 5.06*	27.13 ± 4.29*	27.50 ± 4.07*	23.50 ± 4.46	23.00 ± 5.35	24.14 ± 5.93*	25.43 ± 5.26*	25.71 ± 4.92*

*Significant difference between pre and follow-ups of intervention ($P < 0.05$).

significantly greater in both the VR group ($p = 0.006$, 0.002, <0.001, and <0.001, respectively) and CT group ($p \geq 0.001$, 0.002, 0.001, and <0.001, respectively) (Table 3). Meanwhile, compared with the FMA-LE scores at baseline, those after intervention, at 3-month, 6-month, and 1-year follow-ups were significant increased in the VR group ($p = 0.03$, <0.001, 0.003, and <0.001, respectively), and at 3-month, 6-month, and 1-year follow-ups in the CT group ($p = 0.02$, 0.004, and <0.001, respectively). Notably, both the BBS and FMA-LE scores before the intervention, immediately post-intervention and at the follow-ups were not significantly different between the VR and CT groups.

Spatiotemporal gait parameters

In the VR group, the walking speed after intervention, at 3-month, 6-month, and 1-year follow-ups were significantly greater than baseline ($p = 0.01$, <0.001, 0.007, and <0.001, respectively); additionally, cadence at 3-month, 6-month, and 1-year follow-ups were significantly greater than baseline ($p = 0.002$, 0.02, and <0.001, respectively). Stride time at 3-month and 1-year follow-ups and opposite foot contact at 6-month follow-ups were significantly greater than baseline in the VR group ($p = 0.04$ and 0.002, respectively). In addition, the decrease of step time ($p = 0.03$, 0.01, 0.007, and 0.008, respectively) and the increase of stride length ($p = 0.003$, 0.002, 0.002, and <0.001, respectively) after intervention, at 3-month, 6-month, and 1-year follow-ups changed significantly from baseline, while the decrease of double support ($p = 0.006$, 0.01, and 0.01, respectively) and the increase of step length ($p = 0.009$, 0.02, and <0.001, respectively) at 3-month, 6-month and 1-year follow-ups differed significantly from baseline. No significant change was found in the CT group. The outcomes of all spatiotemporal parameters were not significantly different between the VR and CT groups at all time points. All spatiotemporal gait data are provided in Table 4.

Kinematic parameters

In the VR group, the maximum knee joint angle in the sagittal plane enhanced significantly at 6-month follow-up from that at baseline ($p = 0.04$) and no significant difference was found in any other parameter. In the CT group, no significant difference was found between baseline and other time points. Moreover, all kinematic parameters were not significantly different between the VR and CT groups at all time points. All kinematic gait parameters are provided in Table 5.

Figure 3 demonstrates the mean kinematic curves for the hip, knee and ankle joints in the sagittal plane for all participants of both groups at baseline, immediately post-intervention and follow-ups.

TABLE 4 Spatiotemporal results of pre, post and follow-up among three groups.

Variable	Normal	VR group					CT group				
		Pre	Post	3 m follow-up	6 m follow-up	1 yr follow-up	Pre	Post	3 m follow-up	6 m follow-up	1 yr follow-up
Walking speed	0.96 ± 0.13	0.42 ± 0.21	0.52 ± 0.24*	0.65 ± 0.28*	0.65 ± 0.27*	0.73 ± 0.24*	0.43 ± 0.21	0.50 ± 0.24	0.55 ± 0.28	0.57 ± 0.24	0.62 ± 0.23
Cadence	108.13 ± 10.65	74.63 ± 16.06	79.35 ± 18.16*	87.78 ± 16.34*	88.05 ± 13.01*	93.36 ± 14.53*	72.62 ± 24.12	77.21 ± 27.67	77.07 ± 22.40	77.78 ± 20.05	82.09 ± 17.52
Stride time	1.12 ± 0.11	1.70 ± 0.43	1.62 ± 0.42	1.42 ± 0.28*	1.40 ± 0.21	1.32 ± 0.22*	1.84 ± 0.63	1.76 ± 0.65	1.70 ± 0.55	1.66 ± 0.49	1.56 ± 0.48
Opposite foot off	11.14 ± 1.35	15.88 ± 4.93	15.61 ± 7.25	12.52 ± 4.97	12.68 ± 3.35	12.61 ± 3.04	18.60 ± 12.00	18.91 ± 0.80	16.49 ± 10.53	15.46 ± 9.07	20.34 ± 20.41
Opposite foot contact	49.60 ± 1.36	44.57 ± 6.07	47.21 ± 5.39	47.63 ± 3.65	49.28 ± 5.48*	46.70 ± 3.34	45.94 ± 6.12	45.65 ± 4.72	48.96 ± 6.38	46.62 ± 6.95	45.41 ± 7.78
Step time	0.56 ± 0.06	0.95 ± 0.30	0.86 ± 0.25*	0.75 ± 0.17*	0.71 ± 0.14*	0.71 ± 0.15*	1.01 ± 0.41	0.98 ± 0.43	0.86 ± 0.26	0.90 ± 0.35	0.87 ± 0.37
Single support	0.43 ± 0.04	0.47 ± 0.11	0.49 ± 0.09	0.49 ± 0.09	0.51 ± 0.10	0.44 ± 0.06	0.50 ± 0.08	0.44 ± 0.14	0.52 ± 0.10	0.49 ± 0.07	0.37 ± 0.35
Double support	0.25 ± 0.04	0.61 ± 0.29	0.54 ± 0.31	0.38 ± 0.19*	0.37 ± 0.12*	0.38 ± 0.16*	0.67 ± 0.50	0.73 ± 0.50	0.57 ± 0.42	0.55 ± 0.35	0.58 ± 0.42
Foot off	60.82 ± 1.90	63.54 ± 5.80	63.29 ± 6.09	61.25 ± 4.57	62.78 ± 5.29	62.27 ± 4.27	62.63 ± 7.71	65.45 ± 6.38	62.78 ± 5.20	62.18 ± 5.04	61.00 ± 5.53
Stride length	1.06 ± 0.11	0.65 ± 0.20	0.76 ± 0.21*	0.85 ± 0.25*	0.87 ± 0.28*	0.93 ± 0.20*	0.69 ± 0.20	0.75 ± 0.22	0.81 ± 0.28	0.84 ± 0.23	0.88 ± 0.22
Step length	0.54 ± 0.07	0.33 ± 0.11	0.38 ± 0.11	0.44 ± 0.11*	0.44 ± 0.13*	0.48 ± 0.10*	0.38 ± 0.11	0.38 ± 0.11	0.43 ± 0.11	0.43 ± 0.12	0.46 ± 0.11

*Significant difference between pre and follow-ups of intervention ($P < 0.05$).

TABLE 5 Kinematic results in the sagittal plane of pre, post and follow-up among three groups.

Variable	Normal	VR group					CT group				
		Pre	Post	3 m follow-up	6 m follow-up	1 yr follow-up	Pre	Post	3 m follow-up	6 m follow-up	1 yr follow-up
Hip-max	30.20 ± 7.85	20.85 ± 7.02	24.80 ± 6.18	21.26 ± 11.17	24.82 ± 10.43	20.91 ± 10.07	20.94 ± 8.77	21.90 ± 9.57	19.55 ± 10.39	21.08 ± 9.81	22.14 ± 9.88
Knee-max	57.28 ± 10.36	29.82 ± 16.14	36.04 ± 14.62	38.07 ± 14.63	43.87 ± 21.34*	44.43 ± 21.62	32.67 ± 15.61	36.50 ± 17.08	31.85 ± 16.30	31.66 ± 18.29	37.84 ± 18.75
Ankle-max	9.84 ± 7.14	13.41 ± 3.82	13.61 ± 6.03	12.91 ± 8.67	13.77 ± 2.11	11.36 ± 3.66	11.95 ± 7.82	12.11 ± 6.51	12.74 ± 6.56	9.82 ± 3.91	12.77 ± 4.21
Hip-min	−8.56 ± 7.49	−7.21 ± 9.79	−6.75 ± 11.51	−11.09 ± 16.51	−8.53 ± 12.72	−13.51 ± 1.25	−6.75 ± 9.91	−8.65 ± 13.23	−11.37 ± 8.68	−9.29 ± 9.95	−10.04 ± 7.72
Knee-min	5.63 ± 4.67	2.65 ± 7.53	4.00 ± 7.77	0.83 ± 9.09	2.90 ± 5.56	0.75 ± 6.14	−0.71 ± 8.81	0.53 ± 8.64	−1.31 ± 1.71	−3.24 ± 7.39	−1.88 ± 7.58
Ankle-min	−16.47 ± 7.21	−5.36 ± 5.93	−6.91 ± 8.80	−6.28 ± 8.49	−4.63 ± 5.63	−8.84 ± 5.85	−9.67 ± 7.96	−8.19 ± 6.73	−10.22 ± 5.02	−9.49 ± 5.11	−8.75 ± 6.10
Hip-range	38.76 ± 3.68	28.05 ± 8.68	31.56 ± 10.95	32.35 ± 8.89	33.35 ± 11.28	34.42 ± 7.4	27.69 ± 8.10	30.55 ± 8.98	30.92 ± 10.83	30.37 ± 11.61	32.18 ± 10.57
Knee-range	51.65 ± 8.45	27.17 ± 14.48	32.05 ± 15.20	37.24 ± 16.82	40.97 ± 20.46	43.68 ± 18.82	33.38 ± 12.33	35.96 ± 14.06	33.15 ± 14.74	34.91 ± 6.98	39.72 ± 16.71
Ankle-range	26.30 ± 5.84	18.77 ± 6.59	20.52 ± 7.39	19.19 ± 5.02	18.40 ± 6.30	20.20 ± 6.75	21.62 ± 9.07	20.30 ± 6.23	22.96 ± 6.95	19.31 ± 3.13	21.52 ± 4.57

*Significant difference between pre and follow-ups of intervention ($P < 0.05$).

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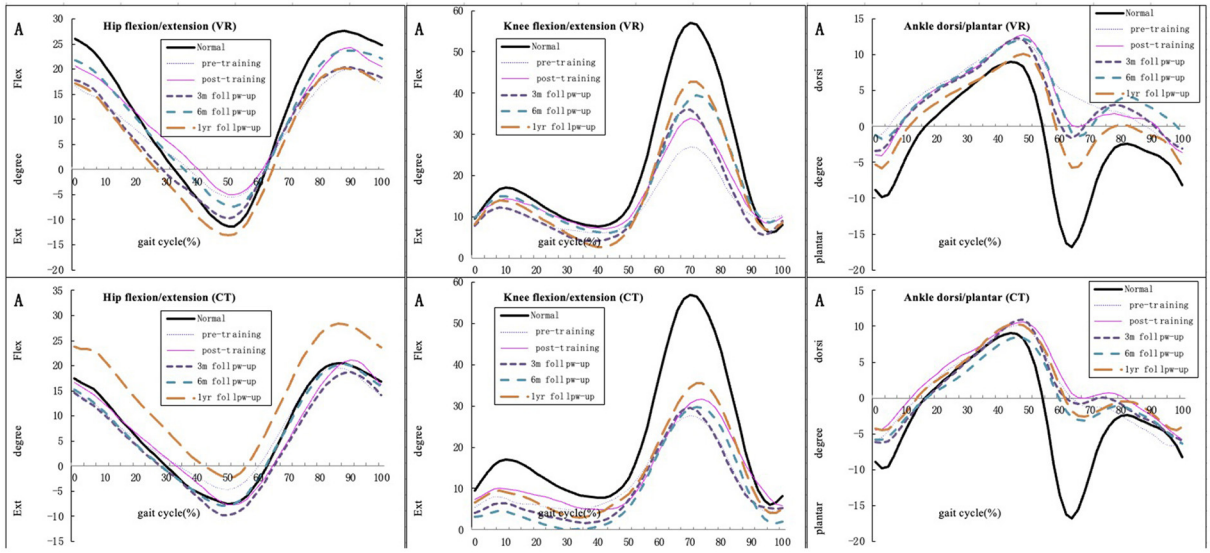

FIGURE 3
Mean hip, knee, and ankle joint kinematic curve for all participants in the sagittal plane of both groups during pre-, post-training and follow-up (compared with normal gait cycles).

Discussion

The objective of this study was to determine whether non-immersive VR-based training can improve motor function and gait capability in patients with post-stroke hemiparesis and whether its short- and long-term effectiveness in enhancing lower-limb motion function recovery is greater than that of CT. Overall, our results demonstrated that VR-based training improved lower-limb motion function and gait performance, but non-immersive VR techniques were not more effective than CT techniques.

The outcome of balance capacity evaluated based on BBS scores was improved immediately after the intervention and at 3-month, 6-month, and 1-year follow-ups in both the VR and CT groups, with no significant changes between two groups at any time point. This result is consistent with previous studies that demonstrated that VR intervention is effective in improving balance performance in post-stroke patients both immediately post-intervention and at follow-ups (28, 29, 41). However, another study that adopted videogame-based training for post-stroke patients showed no significant improvement in BBS scores (32). These results indicate the importance of therapists' assistance and selecting the appropriate type of intervention. According to the FMA-LE results, lower limb motor function was improved only at the 3-month, 6-month, and 1-year follow-ups in the CT group, while VR group's outcome was improved immediately after the intervention and at 3-month, 6-month, and 1-year follow-ups; in addition, no significant difference between two groups. This finding is in accordance with previous studies that have reported immediate improvement in lower limb motor function after VR-based training (27, 28). One review concluded that VR-based therapies do not contribute to improvements in outcomes, especially when the interventions last for <3 weeks and VR is non-immersive (42). However, non-immersive VR in our study still contributed to the improvement of lower-extrenity motor performance after intervention. Some authors have pointed out that the FMA-LE only indicates abnormal synergistic motor patterns in voluntary and isolated movement tasks and is therefore insufficient to capture all of the necessary information about complicated walking performance, as walking is cyclical and involves considerable sensorimotor integration (43). The hip and knee range of motion increased in our study due to appeared isolated movement, including improvement of hip extention and knee flexion and decreased abnormal joint movement such as knee over-extention. This scale is also not sensitive enough to detect minor changes in physical function, which may have led to our finding of no differences between the VR and CT groups.

At the follow-ups, significant improvements compared with the baseline were observed in some gait parameters in the VR group. The parameters of walking speed, cadence, stride time, opposite foot contact, step time, double support, stride length and step length changed significantly from baseline to the follow-ups in the VR group, but not in the CT group; in addition, the inter-group differences were also not significant at these time points. This suggests that although the improvements in these parameters may have arisen due to recovery, VR-based training tended to contribute more to the improvements than CT. Our results on walking speed and cadence are consistent with those reported previously. In previous studies, the increases

in walking speed, which is regarded as an important indicator of gait performance in post-stroke patients, were significantly greater in the VR groups than in the CT groups (15, 44–46). Another study found that walking speed changed significantly after VR intervention in participants with mild stroke than in those with moderate and severe stroke (28). The findings of our study could also be attributable to the participants learning compensatory strategies while getting accustomed to using a VR system. Allen et al. (47) also emphasized this possibility and demonstrated that participants tended to self-select more effective walking speeds by adopting compensatory strategies with the non-paretic limb. Another possible explanation for no significant differences of spatiotemporal gait parameters is that the sample size of the VR group was smaller than that of the control group due to randomized allocation and drop-out of the participants. Studies have shown that improvement in dynamic balance capability is associated with velocity and cadence (48), while lower extremity dysfunction is highly correlated with walking speed (49). In addition, step length is affected by forward propulsion, which is generated by the stance leg to enable the trunk to move forward with dynamic balance control (47). Another possible explanation for the non-significant improvements after VR-based training in our study is that the VR environment we adopted was not ecologically valid enough to be more effective than CT. Multiple studies have highlighted the technical limitation that the majority of current VR-based rehabilitation systems do not provide users with a realistic environment or real-life situations (5, 50). The VR tasks are more like simple games rather than real-world scenarios, which affects rehabilitation effectiveness and creates a potential gap between training and actual daily function.

Nevertheless, some of the kinematic parameters, especially the maximum knee joint angle in the sagittal plane, were significantly improved from baseline to 6-month follow-ups in the VR group. Though kinematic performance of hip joint had no significant difference from baseline, our study found the hip extention has been increased at follow-ups. The performance of hip and knee joint tends to a more fluent and normal gait pattern instead of stiff knee and hip pattern after the intervention in the VR group. These results suggest that VR-based training enhances knee flexion and decreases knee overextension. A study suggested that VR can improve knee strength and performance, and lower limb motor control is highly associated with balance and gait capability (51). Taken together, improvement in knee motion contributes to improved balance capacity, which is reflected in the BBS scores. Simonsen (52) pointed out that improved joint performance in the sagittal plane is correlated with enhanced walking speed, which is consistent with the findings of our study. Similarly, the possible reason for the negative result is that VR training in our study was non-immersive, which may have reduced the participants' concentration and training effectiveness. Despite some evidence supporting the benefits of an early exercise program on functional recovery, evidence supporting the use of early VR interventions to enhance functional recovery is still lacking (14).

The mechanism of performance improvements induced by VR-based training may involve neuroplasticity, motivation and high training intensity. VR is reported to enhance post-stroke experience-dependent neuroplasticity and motor learning by activating related brain regions, inducing cortical reorganization and strengthening the mirror neuron system involved in motor planning, learning and execution (25). VR also increases training motivation and engagement by reducing the perception of exertion, contributing to effortless and sustained exercise (50, 53, 54). The intrinsic and extrinsic feedback on performance and progress given by VR programs can reinforce patients' correct behavior and help maintain their level of action (25). Meanwhile, user-dependent tasks, objective progression and repetitive training, all of which are part of VR-based training, play important roles in promoting motor learning strategies in clinical practice (11). The augmented feedback from a VR-based rehabilitation system has been shown to benefit participants by enhancing their learning rate and training the mirror neuron system (50, 55).

Our study has several limitations. First, the duration of intervention in our study was not sufficient, as an intervention of at least 8 weeks is required to observe notable effects of VR-based training due to physical adaptation (18). Second, the calibration of the VR games' difficulty was not accurate in our study and acceptability of VR was not tested among patients, which may have led to poor methodological quality and lack of a clear rationale for the intervention program, particularly in terms of treatment intensity, personalized training and task variation. Third, the sample size in this study is small, so we will conduct a further study with a larger sample size. Lastly, our study analyzed only some kinematic parameters and two clinical scales, but no kinetic parameters, cognitive or physiological changes with clinical scales. Further indexes and instruments such as the hip flexor index and gait deviation index could be used to measure gait patterns (56).

In conclusion, our current study findings using non-immersive VR to demonstrate that non-immersive VR-based training improves balance and gait performance among subacute stroke patients and contributes to normal gait pattern appearance, but the effectiveness of non-immersive VR techniques is not superior to CT-based training for balance and motor function. Non-immersive VR-based training could be applied as a clinical rehabilitation therapy as well as conventional therapy.

Trial status

The trial is still ongoing both in the Seventh Affiliated Hospital, Sun Yat-sen University and the First Affiliated Hospital, Sun Yat-sen University. The first participant was

included in October 2019 and the patient recruitment in this study was completed in June 2022.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Seventh Affiliated Hospital of Sun Yat-sen University and the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. 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 identifiable images or data included in this article.

Author contributions

YM, DH, and MB designed the study. MB and YS recruited the participants. YW provided training instruction. YM, MB, and YS captured the gait data and three-dimensional data. YH and LW assessed the clinical scales. MB, YM, YS, and SH interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

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

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A case report: Upper limb recovery from stroke related to SARS-CoV-2 infection during an intervention with a brain-computer interface

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COVID-19 may increase the risk of acute ischemic stroke that can cause a loss of upper limb function, even in patients with low risk factors. However, only individual cases have been reported assessing different degrees of hospitalization outcomes. Therefore, outpatient recovery profiles during rehabilitation interventions are needed to better understand neuroplasticity mechanisms required for upper limb motor recovery. Here, we report the progression of physiological and clinical outcomes during upper limb rehabilitation of a 41-year-old patient, without any stroke risk factors, which presented a stroke on the same day as being diagnosed with COVID-19. The patient, who presented hemiparesis with incomplete motor recovery after conventional treatment, participated in a clinical trial consisting of an experimental brain-computer interface (BCI) therapy focused on upper limb rehabilitation during the chronic stage of stroke. Clinical and physiological features were measured throughout the intervention, including the Fugl-Meyer Assessment for the Upper Extremity (FMA-UE), Action Research Arm Test (ARAT), the Modified Ashworth Scale (MAS), corticospinal excitability using transcranial magnetic stimulation, cortical activity with electroencephalography, and upper limb strength. After the intervention, the patient gained 8 points and 24 points of FMA-UE and ARAT, respectively, along with a reduction of one point of MAS. In addition, grip and pinch strength doubled. Corticospinal excitability of the affected hemisphere increased while it decreased in the unaffected hemisphere. Moreover, cortical activity became more pronounced in the affected hemisphere during movement intention of

the paralyzed hand. Recovery was higher compared to that reported in other BCI interventions in stroke and was due to a reengagement of the primary motor cortex of the affected hemisphere during hand motor control. This suggests that patients with stroke related to COVID-19 may benefit from a BCI intervention and highlights the possibility of a significant recovery in these patients, even in the chronic stage of stroke.

KEYWORDS

COVID-19, BCI - brain computer interface, stroke, hemiparesis, case report

Introduction

It is estimated that 1 to 6% of hospitalized patients due to COVID-19 will develop a stroke (1, 2). It has been hypothesized that SARS-CoV-2 infection can create a prothrombotic environment due to an inflammatory response, invasion of vascular endothelial cells and imbalance of angiotensin converting enzyme 2 (ACE2) and renin-angiotensin system (RAS) axis interactions, thus, increasing the risk of ischemic stroke (3). Evidence of stroke related to COVID-19 has been presented as cases. For example, Quenzer et al. (4) reported a large cerebellar stroke in a 32-year-old patient that was associated with severe COVID-19 infection with no initial respiratory symptoms. Rajae et al. (5) described an ischemic stroke in frontal, temporal, and parietal regions presenting as the primary manifestation of COVID-19. Prasad et al. (6) reported a patient that developed ischemic stroke in several vascular territories after recovering from hypoxic respiratory failure due to COVID-19. However, to the authors' knowledge, clinical outcomes, and recovery mechanisms during the rehabilitation process of stroke related to COVID-19 have yet to be reported. Specifically, the neural plasticity mechanisms involved during upper limb motor recovery, one of the main rehabilitation challenges in stroke-related hemiparesis (7), could bring valuable insights for developing rehabilitation strategies for these patients. One promising rehabilitation strategy is comprised by brain-computer interface (BCI) interventions since they have shown evidence of efficacy for the upper limb motor recovery of stroke patients (8, 9). A BCI decodes information from the central nervous system and translates this information into commands for external devices, such as rehabilitation robots (10). In this sense, we report a BCI intervention's clinical and physiological effects in a case of COVID-19-related stroke. The rehabilitation was provided as part of the patient's participation in a clinical trial for stroke neurorehabilitation with a BCI. It is presumed that the presented case is, unique to date since neural plasticity mechanisms during the clinical recovery process in stroke related to COVID-19 are described using transcranial magnetic stimulation (TMS), electroencephalography (EEG), dynamometry, and upper limb clinical measurements.

Materials and methods

Patient

A 41-year-old female of Mexican ethnicity, without any previous relevant diseases, presented an ischemic stroke (diagnosed using brain computed tomography) on the same day as being diagnosed with COVID-19 (diagnosed with a PCR test). Her husband, a healthcare worker, had tested positive 7 days earlier for COVID-19. The patient did not have stroke risk factors or previous diagnoses of neurological diseases, was an active athlete at the time of the stroke onset, having completed a dozen marathons, and had not been vaccinated for COVID-19. The only other related COVID-19 symptom before the stroke was the loss of smell and taste. Her blood test results were within normal ranges, including D-dimer. She received acute stroke treatment in the COVID-19 ward of a regional hospital, and after a week was discharged having left hemiparesis. She had outpatient and home-care physical therapy as hemiparesis treatment for 8 months and received two doses of botulinum toxin in her paretic upper extremity as a treatment for spasticity. The main concern of the patient was that she wanted to regain independence lost mainly due to hemiparesis, and that she was not satisfied with her rehabilitation improvement. For these reasons she decided to participate in a clinical trial at the National Institute of Rehabilitation "Luis Guillermo Ibarra Ibarra" (Trial Registry: NCT04724824). The trial aims to evaluate the clinical effects of a BCI therapy for upper limb stroke rehabilitation. Figure 1 shows a timeline with relevant information regarding the episode of care. Figure 2A shows the patient's middle cerebral artery ischemic stroke that comprised the insula, the head of the right caudate nucleus and adjacent white matter.

BCI intervention

The patient started her participation in the trial after 8 months since stroke onset and was randomly assigned to the experimental group of the clinical trial. Patients in this group underwent a BCI intervention. The Ethical and

Research Committees of the National Institute of Rehabilitation "Luis Guillermo Ibarra Ibarra" (Registry Number 25/19AC) approved the research. The patient signed a written informed consent. She received a total of 30 BCI intervention sessions (5 per week, during 6 consecutive weeks). This was the only upper limb therapy administered to the patient during her participation in the clinical trial. The BCI system's acquisition stage was comprised of the recording of 16 channels of electroencephalography (EEG) located in positions F3, FC3, C3, CP3, P3, C5, C1, FCz, Cz, F4, FC4, C4, CP4, P4, C6, and C2, with reference in the right earlobe, and ground in AFz. An amplifier (g.USBAMP, g.tec medical engineering GmbH, Austria) with active electrodes (g.LADYbird, g.tec medical engineering GmbH, Austria) were used for EEG acquisition. The BCI system classified between the motor intention (MI) of the patient's paretic hand (the patient was instructed to attempt to close her fingers to slowly grasp a baseball placed below her hand, without moving her other limbs) and a baseline period in which she was instructed to keep her eyes open while not performing any action. The online processing stage used the filter-bank common spatial pattern algorithm (FBCSP) for feature extraction (11), and linear discriminant analysis (LDA) for classification. A subject-specific model for calibrating the BCI system was computed offline using the data of the previous session. The processing stage is described in the work of Cantillo-Negrete et al. (12). If the system recognized that the patient was performing MI, then it sent wirelessly a command to a robotic hand orthosis that provided passive movement flexion to the paretic hand. In each intervention session, the patient performed 4 runs, each comprised of 20 trials, with every trial containing the temporal sequence described in Figure 2B.

The baseline period comprised the first 4 s of a trial, a white cross was shown on a computer screen during this period and a beeping sound reproduced at the 3rd s indicated to the patient that the MI task was about to begin. After the baseline period, an arrow pointing to the left signaled the patient to initiate the MI of her paretic hand. This arrow was shown for 1.5 s, afterwards, the screen turned black until the 9th s of the trial. The patient was instructed to perform MI during this 5 s period. Windows of 1 s were analyzed by the BCI system processing stage, and if MI was detected during the first 4 s of the MI period, (4th to 8th s of the trial) then for each of these windows detected as MI, the orthosis would perform one-fourth of the maximum flexion displacement of the patient's fingers. Therefore, if MI was detected in all 4 s of the instructed MI period, the patient's fingers were flexed to the maximum displacement capacity of the orthosis. After the 9th s of the trial, the screen turned grey, and the orthosis returned to its original position by performing finger extension. In the 14th s the screen turned blue indicating the patient to relax and move if she needed to, with a random duration of this interval between 4 and 6 s to avoid habituation. BCI success rate in triggering the robotic hand orthosis (i.e., BCI sensitivity) was measured. The system usability scale (SUS) was also measured to assess the user experience with the BCI (13).

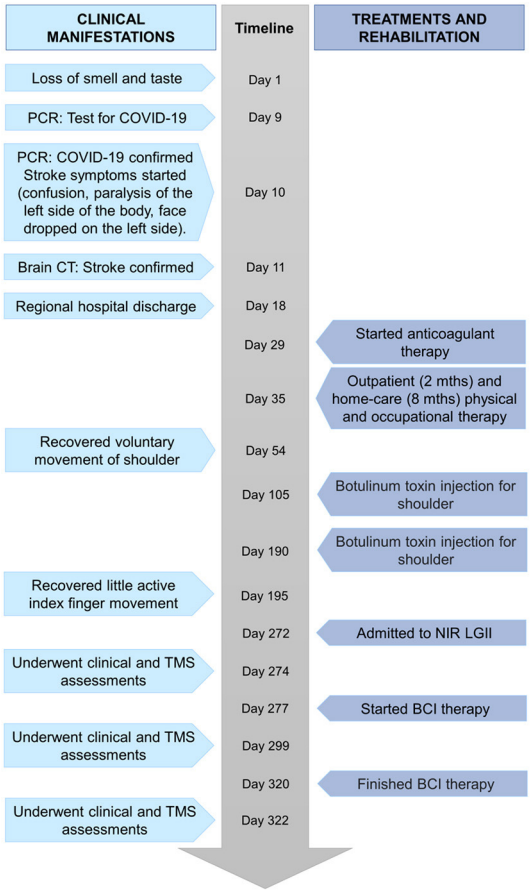

FIGURE 1
Timeline with relevant clinical information.

Clinical and physiological outcomes

The Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) and the Action Research Arm Test (ARAT) were measured to record the upper limb motor function (14, 15). The FMA-UE is comprised by 30 items for motor function and 3 items for reflex assessment. Each item must be scored from 0 to 3, with a total score range from 0–66, with a lower score being related with a higher degree of hemiparesis (14). The ARAT is a 19-item scale categorized in the subscales of grasp, grip, pinch, and gross movement, using specially crafted objects for performing each item of the scale. Each item is graded from 0 to 4, and has a total score range from 0–57, with a lower score being associated with the lack of movement of the upper limb (15). The Modified Ashworth Scale (MAS) was used for assessing upper limb spasticity. The MAS is assessed by grading

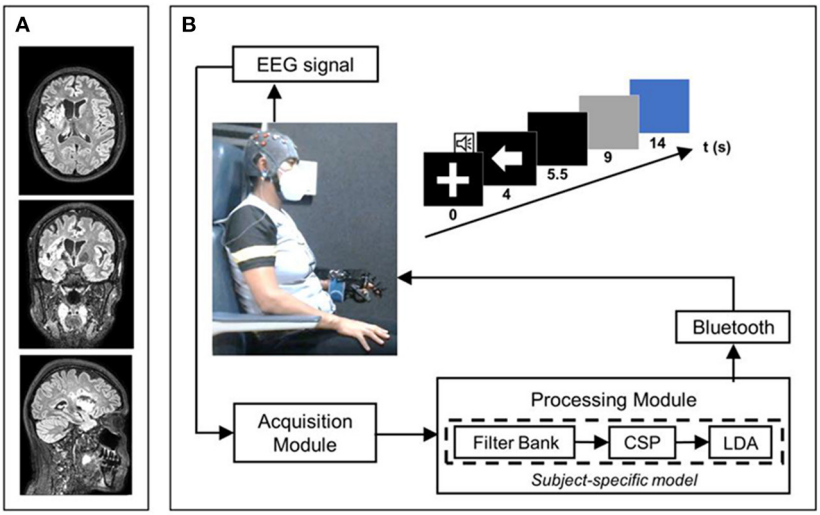

FIGURE 2
Stroke imaging and depiction of the BCI system. **(A)** Patient's T2 FLAIR MRI sequences were obtained with a 3T Philips Ingenia device at the onset of the BCI intervention. **(B)** BCI system stages and its associated trial timing structure.

the degree of muscle tone observed while performing flexion and extension movements of the graded limb using a score between 0 to 4 with a higher score related to an increase in muscle tone (16, 17). The Barthel Index (BI) was measured to assess the patient's performance in activities of daily living. It assesses 10 activities of the daily living, including the ability to dress and feed, with a total score ranging from 0 to 100, with a higher score associated with a greater independence (18, 19). The International Classification of Functioning, Disability and Health (ICF) was measured to assess disability of the upper extremity (20), specifically, the b730 item that measures weakness of the hand's muscles was used, graded with an ordinal score from 0 to 4, with the highest score associated with a complete impairment. FMA-UE, ARAT, MAS, BI and ICF were performed by the same rehabilitation physician.

Grip and pinch strength of the paretic limb were separately measured using a Biometrics E-link evaluation system (Hand Grip Dynamometer and Pinchmeter). For each variable, three measurements were acquired, first in the unaffected and then, in the affected hand. Measurements were repeated three times or until the coefficient of variation was below 15% (21).

Corticospinal tract integrity and excitability were evaluated using a transcranial magnetic stimulator (Magstim Rapid^2, Magstim Co. Ltd., UK) with a figure-of-eight coil. Motor evoked potentials (MEPs) were recorded with electromyography in the first dorsal interosseous muscle of the unaffected and affected hemisphere, in that order, following the procedure recommended for diagnostic transcranial magnetic stimulation (TMS) by the International Federation of Clinical Neurophysiology (22). The resting motor threshold (RMT) was estimated for the patient and afterwards, a cortical excitability curve was calculated from MEPs' amplitudes, at 100%, 120% and 140% of the RMS for both hemispheres (30 MEPs for each intensity), using an automated software (23).

Cortical activity was estimated using event-related desynchronization/synchronization (ERD/ERS). These EEG recordings were planned for evaluating cortical activity during 80 trials per session, in which the patient was instructed to perform hand MI without feedback, using the same cues and trial time structure presented to the patient during BCI intervention sessions. The acquisition was performed using two interconnected g.tec, g.USBAMP devices for recording 32 channels with g.LADYbird active electrodes. In this study, sixteen channels (F3, FC3, C3, CP3, P3, C5, C1, FCz, Cz, F4, FC4, C4, CP4, P4, C6, and C2) were used for the computation of ERD/ERS related to the MI of the patient's paretic hand, to be consistent with the electrodes used for acquiring brain activity with the BCI system during therapies. The preprocessing consisted of 30th order FIR filters, an 8 Hz high-pass filter, a 32 Hz low-pass filter, and a 58 Hz to 62 Hz notch filter, followed by a common average reference spatial filter. Then, a visual inspection was performed to remove trials with excessive artifacts. Afterwards, Complex Morlet wavelets were used to calculate time-varying power in the range of alpha and beta (24) for ERD/ERS computation (25). To assess if there were statistically significant differences ($p < 0.05$) in ERD/ERS across the BCI intervention, a cluster-based permutation test was used. This analysis is based on non-parametric cluster randomization with a multiple comparison procedure (MCP) that has shown higher statistical sensitivity than traditional MCP methods such

TABLE 1 Upper limb motor function and strength. Higher scores imply less upper limb motor impairment (FMA-UE, ARAT), higher independence for performing activities of daily living (BI), higher upper extremity disability (ICF), or higher spasticity (MAS).

Clinical score	Pre-therapy	Mid-therapy	Post-therapy
FMA-UE	45	49	53
ARAT	30	38	54
MAS	1	1	0
BI	90	90	100
ICF	3	2	1
Grip unaffected hand	28.7	30	29.6
Grip affected hand	3.4	8.2	7.8
Pinch unaffected hand	3.5	2.8	3.6
Pinch affected hand	0.9	1.2	1.8

Upper limb strength was measured using dynamometry (kgf) in the affected and unaffected hands.

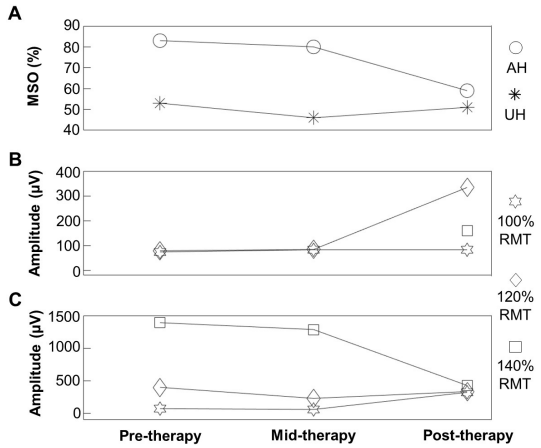

FIGURE 3
(A) Resting-state motor threshold (RMT) for the affected (AH) and unaffected (UH) hemispheres. **(B)** Motor evoked potential amplitude in the affected hemisphere (AH) at 100%, 120%, and 140% of the RMT at pre-therapy, mid-therapy, and post-therapy. **(C)** Motor evoked potential amplitude in the unaffected hemisphere (UH) at 100, 120, and 140% of the RMT at pre-therapy, mid-therapy, and post-therapy.

as the Bonferroni correction (26). All clinical and physiological measurements were acquired at pre-therapy (before BCI interventions), mid-therapy (after 15 intervention sessions) and post-therapy (after the last intervention session).

Results

Table 1 shows the patient's FMA-UE, ARAT, BI, ICF, and MAS scores throughout the BCI intervention. Upper limb motor function at pre-therapy was limited since FMA-UE scores of 32 to 47 encompass a limited function, as well as scores of 22-42 of ARAT (27). Both FMA-UE and ARAT had gains across the BCI intervention, with an increase of 8 score points for FMA-UE and 24 points for ARAT. The patient had the greatest gain in upper limb motor function in the second half of the intervention. On the other hand, independence for daily living improved from needing help for feeding and dressing/undressing tasks, to being completely independent. The ICF also showed that the patient had a severe upper limb disability that changed to a moderate disability in mid-therapy and further changed to a mild upper limb disability in post-therapy. Moreover, pre-therapy spasticity measured with MAS showed that the patient presented mild spasticity, which changed to an absence of perceived post-therapy spasticity. The affected hand grip strength increased by more than double at post-therapy with the most pronounced increase observed after the first 15 sessions of therapy. Pinch strength also increased during the intervention reaching the twice pre-therapy strength force. At post-therapy, the affected hand had a grip and pinch strength of 25 and 50% of the unaffected hand strength, respectively.

Figure 3 shows the patient's RMT of each hemisphere, obtained using TMS, as well as MEP amplitudes at 100%, 120%, and 140% of the RMT along the BCI intervention. It can be observed that the RMT of the affected hemisphere lowered slightly from 83 to 80% at mid-therapy. However, at post-intervention, became lower, reaching 59% of the maximum stimulator output. The RMT in the unaffected hemisphere remained stable across the intervention with 53, 46, and 51% of the maximum stimulator output at pre-therapy, mid-therapy, and post-therapy, respectively. MEPs amplitude in the affected hemisphere could only be measured at 140% of the RMT at post-therapy due to 140% of the RMT surpassing the maximum possible stimulator output in the pre-therapy and mid-therapy measurements. In the unaffected hemisphere, MEPs amplitude was lower at post-therapy reaching 427 μV at 140% of the RMT compared to the pre-therapy and mid-therapy measurements that presented higher amplitudes, 1,390 μV and 1,286 μV, respectively, at 140% of the RMT.

Figure 4 shows the topographic ERD/ERS maps across the intervention. It also shows significant differences computed with the cluster-based permutation test between intervention recordings. During pre-therapy, cortical activations shown as ERD were observed in the unaffected hemisphere. However, at mid-therapy and post-therapy, ERD was also elicited in the affected hemisphere in electrode C2 located over the primary motor cortex. Significant clusters implied that differences of more pronounced ERD were observed in both the affected and unaffected hemispheres, which was observed at mid-therapy, and remained post-therapy.

The BCI success rate was 61.3%. This shows that the patient was able to successfully activate the robotic orthosis with the MI of her paralyzed hand in more than half of the time during the performed attempts. The SUS score reported by the patient was

graded as 92.5 out of 100 points, with this score being in the range of the "Best Imaginable" user experience (28).

Discussion

The patient had a good adherence to the intervention, measured by an attendance to all the 30 sessions of therapy, and good tolerability, since she was able to complete 80 trials of the MI task, in every single BCI session. There were no adverse or unanticipated events during the BCI intervention. After the BCI intervention, the patient had an upper limb motor recovery above the minimal clinically significant difference of 5.25 points for FMA-UE (29). In addition, the recovery measured with ARAT was more than 4 times the minimal clinically significant difference of 5.7 points (30), implying that the patient presented an improvement from a limited to a notable upper limb motor function (27). This degree of recovery is not commonly observed in chronic stroke patients. For example, Dromerick et al. reported an improvement of 2.41 ± 2.2 points of ARAT after a task-specific motor intervention (31), and Ackerley et al. reported an improvement of 2 points of ARAT after 1 month of intermittent theta-burst TMS treatment (32). Moreover, the recovery of the patient was higher than the reported in stroke populations that underwent the BCI intervention reported by Ramos-Murguialday et al. (33) with a gain of 3.4 ± 2.2 points of FMA-UE, and by Frolov et al. (34) with an average gain of 5 points of FMA-UE and 2 points of ARAT. Furthermore, according to the BI there was an improvement in the performance of activities of daily living that require the use of the upper extremities, such as feeding and dressing, and a reduction of the disability shown in the upper extremity measured with ICF. Also, spasticity was reduced to the point of being undetectable after the BCI intervention, which is in line with a reported association between a lower degree of spasticity and a higher upper limb motor function (35). Therefore, the patient presented a significant clinically measured recovery that was noticeable after the BCI intervention.

Upper limb strength and corticospinal excitability also showed differences across the intervention. Grip and pinch strength doubled, which was within the range of the recovery observed in moderately impaired stroke patients after a high-intensity upper limb-focused therapy for 6 to 12 weeks (36). On the other hand, corticospinal excitability increased in the affected hemisphere, while it decreased in the unaffected hemisphere after the intervention, which has been described as a mechanism of stroke recovery (37). Furthermore, the high degree of observed recovery, seen in patients that do not need to recruit secondary motor regions such as the dorsolateral premotor cortex or the supplementary motor cortex (38), coupled with the enhanced cortical excitability in the affected hemisphere, allow suggesting that recovery mechanisms involved the primary motor cortex. Cortical

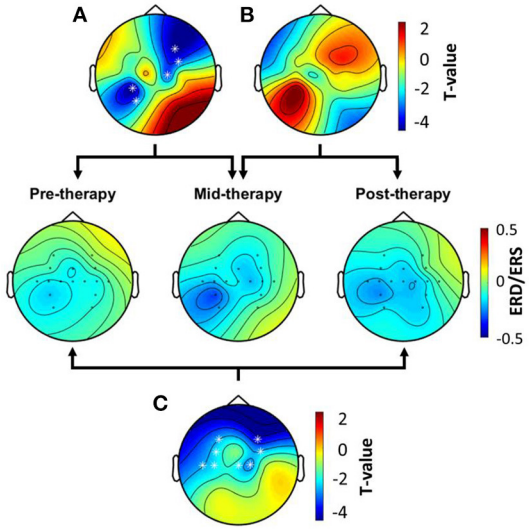

FIGURE 4
Topographic maps showing ERD/ERS over time. **(A)** Significant ERD/ERS differences between pre-therapy and mid-therapy assessed with the cluster-based permutation test. **(B)** Significant ERD/ERS differences between the mid-therapy and post-therapy. **(C)** Significant ERD/ERS differences between the pre-therapy and the post-therapy. Significant clusters across therapy stages are marked with white asterisks.

activations computed from EEG also support this hypothesis, since electrodes located over the primary motor cortex of the affected hemisphere recorded a significantly enhanced activity after the intervention. This is important since enhanced cortical activity over the affected hemisphere's primary motor cortex has been associated with a significant recovery of upper limb motor function (39). Therefore, the neuroplasticity mechanism that was involved in the recovery of the patient's upper limb motor function, was the reengagement of the primary motor cortex for movement control, which allowed to reestablish the functional integrity of the affected hemisphere's corticospinal tract.

Stroke and COVID-19 have been associated across several studies (1, 2, 4, 5, 40), even in young patients of 33 to 49 years of age with a low prevalence of risk factors, as was the case with the patient in the study (41). Interestingly, the present case shared features with a patient from a case series reported by Diaz-Segarra et al. (42) including being a young patient, having non-severe COVID-19, being diagnosed on the same day of presenting the stroke with COVID-19, having a mid-cerebral artery stroke, being discharged after a week from hospitalization, and presenting hemiparesis. Hence, young patients that present a stroke associated with non-severe COVID-19 could be potentially a new stroke subgroup in which rehabilitation effects have not been previously studied. It is possible that the young age of these patients, combined with the recovery of COVID-19 and the associated decrease of the

thrombotic environment observed during the disease, could make possible the promotion of neuroplasticity mechanisms during rehabilitation regimes, even in the chronic stage of stroke. Experimental therapies, such as those based on BCIs could be a potential complementary intervention in COVID-19-related stroke, which is supported by the significant degree of upper limb motor recovery observed in the present case. Furthermore, the patient's high degree of recovery was observed only after the intervention with the BCI system during the chronic stage of stroke. This is remarkable since this amount of recovery could have been more likely in the subacute stage, in which the patient received physical therapy, due to spontaneous recovery mechanisms that are hypothesized to be responsible for most of the motor gain observed in stroke (43, 44). Thus, implying that the BCI intervention was directly associated with the significant observed stroke recovery. A novelty of the present study is that it shows it is possible for a patient with a COVID-19-related stroke to reengage their lesioned hemisphere, shown by an increase in the cortical excitability of this hemisphere, while recovering upper limb motor function. This provides insights into similar recovery mechanisms compared to stroke of other etiologies and highlights the importance of acquiring physiological measurements such as TMS, EEG, and dynamometry for assessing recovery mechanisms in stroke, which are not all reported in BCI stroke interventions (8, 34, 45, 46). Furthermore, a strategy for improving therapies for these patients, and for looking at specific physiological mechanisms can be derived for being used in further interventions regarding stroke related to COVID-19. Also important, is that the patient achieved an acceptable success rate, which is within the range of the performance reported in a BCI intervention for stroke (34). Although BCI performance using MI tasks by stroke patients has been reported, it has not been previously reported in stroke related to COVID-19 implying that a BCI system can be controlled by these patients. In addition, the patient reported to felt comfortable using the BCI, implying that the degree of complexity of the system is adequate for stroke patients.

The present study has limitations that need to be acknowledged. The first one is that one case is presented, not allowing to fully infer the clinical effects of the BCI intervention in stroke related to COVID-19. However, to the authors' knowledge, this is the first report of the upper limb rehabilitation in stroke related to COVID-19 spanning most of the patient's rehabilitation process, and it provides for the first-time evidence that a significant recovery of the upper limb motor function is achievable. This is important since several studies have highlighted the significance of assessing complete rehabilitation scenarios of these patients (40, 42, 47). Another limitation is the assessment of a single possible stroke related to COVID-19 subgroup, comprised of young patients that have at least some degree of preserved corticospinal integrity in their affected hemisphere. Other stroke-related COVID-19 subgroups should also be analyzed in rehabilitation scenarios. Nevertheless, it is likely that the presented case will provide valuable information for the upper limb rehabilitation and neuroplasticity processes in stroke related to COVID-19 and could aid in the development of new complementary rehabilitation strategies using BCI systems.

Conclusions

A significant upper limb motor recovery was possible in the chronic stage of stroke related to COVID-19 using an experimental BCI intervention. The main neuroplasticity mechanism associated with this recovery was the reengagement of the primary motor cortex for upper limb control. Although a particular case is presented, it provides evidence that young patients with stroke related to COVID-19, with measurable corticospinal excitability in the affected hemisphere, may have a good degree of recovery with BCI-based experimental interventions.

Patient perspective

"I am very grateful to the team that made this research possible, today I open my hand with greater control, I can give a real hug to each member of my family. I can ride a bicycle, since I am able to break and control the steering wheel better, this has made me very happy. I have recovered part of my life, self-esteem and even faith."

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 Research and Ethics Committees of the National Institute of Rehabilitation "Luis Guillermo Ibarra Ibarra". 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

JC-N, RC-E, AR-N, and OA-C conceived and designed the study. JC-N, RC-E, MR-G, AR-N, JQ-F, and EO-R performed data collection. JC-N, RC-E, MR-G, and RV-C analyzed the data. JC-N, RC-E, and OA-C drafted and edited the manuscript. JQ-F,

AR-N, EO-R, and RV-C provided critical revisions. All authors have approved the final version of the manuscript submitted for publication.

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Conflict of interest

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

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Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review

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Introduction: To date, a few studies have used somatosensory evoked potentials (SEP) to demonstrate cortical sensory changes among healthy subjects or to estimate cortical plasticity and rehabilitation prognosis in stroke patients after peripheral electrical stimulation (PES) intervention. The primary aim was to systematically review whether PES has a role in changing latencies and amplitudes of SEPs in healthy subjects and stroke patients. Moreover, we searched for a correlation between sensory and motor function assessments and changes in SEP components of included studies.

Methods: The following databases were searched: Pubmed/MEDLINE, Scopus/ScienceDirect, Web of Science/Clarivate, Cochrane Library, The Physiotherapy Evidence Database (PEDro), and ClinicalTrials.gov. Titles and abstracts, as well as full-text reports, were screened for eligibility by two independent reviewers according to a priori defined eligibility criteria. There were no study limitations concerning the treatment of the upper limb, lower limb, or torso with PES.

Results: The final systematic search resulted in 11,344 records, however only 10 were evaluated. We could not find enough evidence to confirm use of SEP as a predictor to estimate the rehabilitation prognosis after stroke. However, we found a correlation between different sensory and motor function assessments and changes in SEP components. The stroke studies involving PES that initiate a voluntary contraction used for a specific movement or task indicate a positive relationship and correlation to assessments of motor function. It could be indicated that PES have a predictive impact of sensory reorganization, as mirrored by the change in SEP amplitude and latency. However, it is not possible to verify the degree of connectivity between SEP and cortical plasticity. To confirm this hypothesis, we propose the conduction of randomized controlled trials in healthy volunteers and stroke patients.

Systematic review registration: https://doi.org/10.17605/OSF.IO/U7PSY.

KEYWORDS

peripheral electrical stimulation, somatosensory evoked potentials (SEP), stroke rehabilitation, sensory and motor recovery, somatosensory cortex

Introduction

Peripheral electric stimulation (PES) is a rehabilitative technology that uses electrical currents to the peripheral nerves. It has been proposed that somatosensory stimulation in the form of electromyographically triggered neuromuscular electrical stimulation to the peripheral nerve can influence functional measures of motor performance in stroke patients and can additionally produce changes in cortical excitability (1, 2). In this way, PES provides restoration of walking or arm movements in individuals with complete or incomplete spinal cord injury, stroke, or other upper motor neuron lesion (2–4).

The literature offers multiple terms for peripheral electrical stimulation: transcutaneous electric nerve stimulation (TENS) (5–8), functional electrical stimulation (9–12), cutaneous electrical stimulation (13), somatosensory stimulation (14), neuromuscular electrical stimulation (1, 15) or combination of terms "percutaneous" and "neuromodulation".

Sheffler and Chae (16) devoted important consideration to the use of electrical stimulation for motor relearning. They described three types of electrical stimulation available for motor learning: functional electrical stimulation (FES), electromyography or biofeedback mediated FES, and application of neuroprostheses. In the first case the patient is a passive participant in the FES training and no cognitive investment is necessary. The second type of exercises combines afferent feedback information with FES induced repetitive movements. During training with neuroprosthesis, functional tasks can be performed (2). The multiple PES terms used in the present review can be classified into one or more stimulation types described by Sheffler and Chae. Furthermore, for all terms the same technique is being used: placing surface electrodes on the skin overlaying sensory-motor nerve structures, establishing an electric field between two electrodes and ions, generating a current in the tissue. In the following text, only the term PES will be used exclusively.

In many studies, it has been found that the stroke patient's walking speed, endurance, and coordination improved with the use of PES (2, 17–19). The same modality on motor cortical excitability is described by recording motor evoked potentials (20–22), transcranial magnetic stimulation (23, 24) or fMRI (1, 25). On the other hand, the influence of PES on somatosensory function has been frequently overlooked in clinical context and research in the field of stroke rehabilitation (15). Prediction of upper limb (UL) and lower limb (LL) motor recovery in stroke patients is generally based on clinical examination (26). The prognosis is typically based on clinical impression, incorporating clinical and demographic factors such as stroke severity and age (27). Moreover, clinicians cannot know whether the prognoses they make at the acute stage are correct unless they do not routinely assess each of their patients several months later (27). This gestalt approach can produce differing opinions about prognosis and these seem to produce variation in discharge planning (28). According to Feys et al. (26) the combination of the motor score and somatosensory evoked potentials (SEPs) is best able to predict an outcome especially in the acute stroke phase, since neurophysiological measures alone are of limited value in predicting a long-term effect. The finding by Kato et al. (29) who examined the SEPs of the median and the tibial nerves in patients with hemorrhagic lesions, confirmed that 60 out of 65 arms (92.3%) and 50 out of 62 legs (80.6%) showed abnormalities in SEPs. These findings may indicate SEP measures quantifying latencies, thresholds, and evoked responses at high stimulator intensities had high reliability and require small sample sizes to power a study adequately (30). Therefore, the validation of SEP as a new standard neurophysiological tool for assessing the rehabilitation prognosis after stroke seems a reasonable decision.

SEPs are time-locked potentials evoked by electric stimulation of the sensory or mixed peripheral nerves and recorded along with the large fiber somatosensory (dorsal column–medial lemniscus) pathway. SEPs record transmission of an electrical signal/action potential between recording sites along the impulse pathway, thereby allowing the identification of abnormalities that help to localize a lesion (31).

Urasaki et al. (8) found that the dorsal column nucleus has the main role in CNS sensory amplification and that PES suppresses this amplification phenomenon in the medial lemniscus pathway. Consequently, use of PES as an intervention to verify SEP as a new standard neurophysiological tool could be a good method to observe changes in cortical somatosensory pathways.

The effects of PES on somatosensory cortical representation in healthy subjects have not been fully investigated yet, since little is known about the functional features of mismatch deviant and standard responses across different sensory brain modalities (32). This controversy of sensory changes and cortical plasticity persists in stroke patients and changes in corticomotor excitability still remains elusive (33).

To our knowledge, the role of PES in changing latencies and amplitudes of SEPs in healthy subjects or whether effects of PES aiming at motor rehabilitation after stroke have an impact on the improvement of pathological SEPs have not yet been studied. Furthermore, one of the aims of the present study was to examine the evidence on sensorimotor assessment and changes in SEP components after PES treatment for clinical correlations, so that SEP can be used at best as a predictor for estimating rehabilitation prognosis after stroke.

Abbreviations: PES, peripheral electrical stimulation; TENS, transcutaneous electric nerve stimulation; FES, functional electrical stimulation; SEP, somatosensory evoked potentials; UL, upper limb; LL, lower limb; CNS, central nerve system; MEP, motor evoked potential; FIM, Functional Independence Measure; NIH, National Institutes of Health; RCT, randomized controlled trial.

TABLE 1 PICO criteria.

P	Patient/Subjects	Healthy subjects Stroke patients
I	Intervention	Transcutaneous electric nerve stimulation, functional electrical stimulation, cutaneous electrical stimulation, somatosensory stimulation, neuromuscular electrical stimulation or combination of terms "percutaneous" and "neuromodulation"
C	Comparison	No PES intervention, placebo, inactive intervention, or waiting-list
O	Outcome	Latency and amplitude of somatosensory evoked potentials

Materials and methods

The study protocol was prospectively registered at the open science framework (OSF) with the registration DOI: https://doi.org/10.17605/OSF.IO/YW6PT on the 14th of March 2021 and an update protocol was registered in OSF (https://doi.org/10.17605/OSF.IO/U7PSY) on the 27th of August 2022. The PICO (34) model was implemented to answer the primary clinical questions: Do the effects of PES on motor rehabilitation in post-stroke patients have an impact on the latencies and amplitudes of pathological SEPs and does PES alter the latencies and amplitudes of SEPs in healthy subjects? (Table 1).

This systematic review was conducted using "The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement 2020" (35) and followed recommendations from the Cochrane handbook (36).

Study selection

A team of four healthcare professionals, including two physiotherapists (MM, AJ), and two physicians (PY, BS), established the study's aim, its primary outcome measures, the search strategy, and its eligibility criteria. The search construct consisted of two main subjects: peripheral electric stimulation and somatosensory evoked potentials. The following databases were searched: Pubmed/MEDLINE, Scopus/ScienceDirect, Web of Science/Clarivate, Cochrane library database, The Physiotherapy Evidence Database (PEDro), and ClinicalTrials.gov. The cut-off date of the search was the 28th of August 2022.

Because only 8 eligible studies were identified with the initial search, it was decided to repeat the search, include additional databases, use a revised search strategy, and publish an update registration protocol (see above). All search strategies (from the first search and from the update search) can be found in each registration protocol in OSF. Screening of all articles published in English and German was performed independently by two authors (MM, AJ) using the Rayyan QCRI software (37) and no automation tools were used in the process. The research team defined inclusion and exclusion criteria in advance. Reference sections of relevant review and research articles were used to identify additional pertinent articles. The full text of articles identified by the title and/or abstract as possibly applicable was retrieved, and the final decision on the inclusion was made by both reviewers independently. Disagreements between reviewers were resolved by consulting a third and fourth reviewers (PY, BS). The mesh term SEP was introduced in 1982 by PubMed, consequently the search time limit was set from January of the same year. If required, additional information was requested from the article authors. Data regarding the number of probands, study design, duration of treatments, and PES adjustments (Table 2) were extracted from each report. In addition, the researchers evaluated all found cortical latencies and amplitudes of SEPs fragments. The data of SEP fragments from healthy individuals and from patients with stroke regarding PES are presented separately to avoid misunderstanding of the evaluated fragments (Tables 3, 4).

Exclusion/inclusion criteria

All type of non-randomized and randomized intervention studies were included. Moreover, intervention studies with no control group were also included since it was anticipated that the available data to answer the research question would be limited. No restrictions were set with regard to the body parts treated (UL, LL or torso) with PES. Studies in which only electroacupuncture was used were excluded since the piercing through dermis can affect additional neurological afferent pathways associated with pain giving misleading SEP results (43). Studies that measured SEP only during the intervention without follow-up measure were excluded since the study search is limited on SEP use as a change predictor. No limits were set regarding the outcome measures used to determine motor impairment and/or functional performance. Data from abstracts, letters, pilot studies, case studies and review articles were excluded from the study. Studies involving children and animals were not considered either. No limitations were applied regarding the type of stroke (ischemic or hemorrhagic), the time elapsed since the last occurrence, or the stroke location. In the text, the term stroke is used for both, ischemic and hemorrhagic stroke. The studies which focused on the effect of electrical stimulation on any of the following conditions were excluded:

TABLE 2 Peripheral electrical stimulation effect—characteristic summary.

Study	Study design	Healthy or stroke population; no. of participants	Duration of treatments	Location of peripheral electrical stimulation	Form of stimulation; pulse amplitude; pulse duration; pulse frequency	Outcome measures
Studies made on healthy volunteers						
Ashton et al. (6)	Case-matched study; three group; pre-post test	32 healthy volunteers; Group A/Placebo (11n); Group B/TENS (10n); Group C/Aspirin (11n)	TENS 5 cycles randomly varied between 30 and 33 stimuli ∼5 min duration	TENS with two 8 cm^2—disposable electrodes were placed on the ventral surface of the forearm between the elbow and the wrist.	Monophasic electric shock stimulation; Not Provided (individual); 0.2 ms; 100 Hz	Not provided
Cogiamanian et al. (38)	One-group; pre-post test	12 healthy volunteers; Group A/(12n) tsDCS + (5n) (Placebo) same volunteers as in group A	Transcutaneous spinal (anodal and cathodal) direct current stimulation for 15 min	2 pair of saline-soaked synthetic sponge electrodes placed on tenth thoracic spinal vertebra and other above the right shoulder.	Constant current pulses; 2.5 mA; Not provided; Not provided	Not provided
Schabrun et al. (33)	(Crossover model) One-group; pre post test	13 healthy volunteers; Motor Movement PES Intervention and Sensory PES 100 Hz Interventions	Each subject participated in two sessions (30 min of PES) separated by at least 72 h	On each occasion, a different electrical stimulation intervention was administered to the right ABP	Constant current pulses; **1.** Motor movement: Stimulus intensity set to sufficient to induce a mid-range thumb abduction; 0.1 ms; 30 Hz; **2**. Sensory 100 Hz: set at the point where the subject first reported perception of the stimulus; 0.1 ms; 100 Hz	TMS, MEP, EEG
Kang et al. (39)	(Crossover model) one-group; pre-post test	20 healthy volunteers; Sham TENS 2 Hz; TENS 2 Hz EA	The application of sham TENS, 2 Hz TENS and 2 Hz EA lasted for 15 min	Sham TENS and TENS electrodes were placed on the fibular side of the tibial tuberosity (electrode size is not provided)	Bidirectional symmetric square-wave pulses; 12 to 24 mA; Not provided; 2 Hz	Not provided
Rocchi et al. (40)	One-group; pre-post test	15 healthy volunteers	Subjects underwent 45 min of HF-RSS	Stimulation was delivered separately to the third phalanx of the right and left thumb and index finger using surface electrodes separated by 0.5 cm (anode placed distally to the cathode)	Constant current stimulator in the form of square-wave pulses; Not provided (individual); 200 μs; 20 Hz	TMS, STDT, tactile spatial acuity and short intracortical inhibition

(Continued)

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TABLE 2 (Continued)

Study	Study design	Healthy or stroke population; no. of participants	Duration of treatments	Location of peripheral electrical stimulation	Form of stimulation; pulse amplitude; pulse duration; pulse frequency	Outcome measures
Zarei et al. (41)	Case-matched study two group; pre-post test	40 healthy volunteers; Group A/(20n) TENS; Group B (20n) (Placebo)	TENS two blocks of 40 trials applied for 20 min	The electrical pulses were delivered through the same electrodes (4 × 4.6 cm) as used in the SEP procedure (left-MN of the non-dominant hand)	Constant current stimulator in the form of square-wave pulses below the motor threshold (individual); 1 ms; 100 Hz	EEG
Studies made on stroke population						
Bao et al. (12)	Retrospective case-matched study two groups; pre-post	Group A / BWSTT / 90 stroke patients; Group B / FES plus BWSTT/ 90 stroke patients	Group A / BWSTT for 30 min daily; Group B / FES for 45 min twice a day, plus BWSTT for 30 min daily for 8 weeks	FES of paretic leg 6 cm X 9 cm and 4 cm x 4 cm electrodes four output channels and a one-foot switch	Bidirectional symmetry square-wave pulses; 15 mA; 0.3 ms; 30 Hz	Walking speed, step length, step cadence, LL-fMa, CSS, 10MWt, TBT and MEP
Peurala et al. (13)	Case-matched study three-group; pre-post test	Group A / 32 stroke patients, active treatment of the paretic hand; Group B / 19 stroke patients, active treatment of the paretic foot; Group C/8 stroke patients, placebo treatment in the paretic hand	Group A and B active FES for 20 min twice a day Group C Placebo for 21 days	Cutaneous stimulation of paretic hand or paretic foot treatment 6 cm diameter electrode *via* glove/sock electrode	Monophasic constant current twin pulses; Not provided (individual); Not provided; 50 Hz	MMAS, 10MWt, paretic limb function, limb skin sensation
Giaquinto et al. (42)	Case-matched study two-group; pre-post test	Group A / 20 stroke patients; Group B / 82 stroke patients (control group)	Twice a day (morning and afternoon)	Target or non-target stimulation of the impaired or non-impaired hand, shoulder or hip using feedback system (electrode size is not provided)	Constant current pulses; 25 mA, above the threshold; 0.1 ms; Not provided;	CT scan and/or NMR, FIM, CIRS 14 and EEG signals
Tashiro et al. (15)	Case-matched study one-group; pre-post test	23 stroke patients	HANDS therapy system, applied for 8 h each day for 21 days	A hybrid electrode (10 mm diameter) for EMG detection and stimulation was placed on the belly of the affected EDC. An electrode (10 mm) for stimulation was placed on the affected EIP.	Not provided; Not provided (individual); Not provided (individual); Not provided (individual)	SWMT, TLT, FMA, MAS, SIAS, and MAL-14

BWSTT, Body Weight-Supported Treadmill Training; FES plus BWSTT, Functional Electrical Stimulation plus Body Weight-Supported Treadmill Training; FES, Functional Electrical Stimulation; tsDCS, Transcutaneous spinal (anodal and cathodal) direct current stimulation: MEP, Magnetic Evoked Potential; LL-fMa, Fugl-Meyer Lower-limb Scale; CSS, Composite Spasticity Scale; 10MWt, 10-Meter Walk Test; TBT, Tinetti Balance Test; MMAS, Modifed Motor Assessment Scale; NMR, Nuclear Magnetic Resonance; CT scan, Computed Tomography; FIM, Functional Independence Measure; CIRS 14, Cumulative Illness Rating Scale; EEG, Electroencephalography; HANDS, Hybrid Assistive Neuromuscular Dynamic Stimulation; EDC, Extensor Digitorum Communis; EIP, Extensor Indicis Propris; SWMT, Semmes–Weinstein Monofilament Test; TLT, Thumb Localizing Test; FMA, Fugl-Meyer Assessment for the UL; SIAS, Stroke Impairment Assessment Set; MAS, Modified Ashworth Scale; Mal-14, Motor Activity Log-14; TENS, Transcutaneous Electrical Nerve Stimulation; EA, Electroacupuncture; PES, Peripheral Electrical Stimulation; ABP, Abductor Pollicis Brevis; TMS, Transcranial Magnetic Stimulation; HF-RSS, High Frequency Repetitive Somatosensory Stimulation; STDT, Somatosensory Temporal Discrimination Threshold.

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TABLE 3 Latencies and Amplitudes of SEP Components—Pre–Posttest—Studies made on healthy volunteers.

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Ashton et al. (6) 32 healthy volunteers	MN at the wrist, troughs and peaks utilizing latency criterion of: P1:60-100 msec, N1:100-160 msec, P2: 160-260 msec, N2 and P3: 260-360 msec	Pretreatment/- 15 min Post-I/0 min Post-II/+15 min Post-III/30 min Post-IV / +45 min 1-way ANOVA and 2-way ANOVA	Consideration of means showed a decrease of N1P2 amplitude and increase of N1 latency in the TENS group as compared to placebo or aspirin group. For the SEP total excursion measure, a significant effect occurred in the time epoch 30 min post-treatment ($F = 3.92$, $df = 2, 29$, $P < 0.05$) and a marginal effect in the last time epoch 45 min post-treatment ($F = 2.79$, $df = 2, 29$, $0.10 > P > 0.05$).
Cogiamanian et al. (38) 12 healthy volunteers	The SEP of MN at the wrist: P14, N20 latency and amplitudes and TN SEPs at the ankle: N9, N22, P30, P39, latency and amplitudes	Baseline Post-I/0 min Post-II/+20 min 1-way ANOVA and 2-way ANOVA Post hoc analysis	Compering changes in TN and MN SEPs after anodal tsDCS over the thoracic spinal cord con- firmed that P30 component elicited by TN stimulation decreased by 49% in amplitude (baseline 0.78 ± 0.12 lV, T0 0.40 ± 0.07 lV; *t*- test: $p = 0.01$), but remained statistically unchanged in latency (baseline 28.8 ± 0.67 ms, T0 28.5 ± 0.57 ms; *t*-test: $p =$ NS). After thoracic tsDCS all the median nerve SEP components remained unchanged (P14 amplitude: baseline 0.68 ± 0.10 lV, T0 0.70 ± 0.04 lV; *t*-test: $p =$ NS; P14 latency: baseline 13.9 ± 0.48 ms, T0 13.7 ± 0.48 ms; *t*-test: $p =$ NS).
Kang et al. (39) 20 healthy volunteers	The SEP of MN at the wrist: N13, N20, P25, N30 latency and amplitudes	Baseline During the stimulation period Post-I / + 20 min 1-way ANOVA and Scheffe's post hoc correction	EA demonstrated a higher mean amplitude in N20 during the stimulation and post- stimulation periods compared with baseline. In N30 the difference only appeared during the stimulation period when treated with EA. These effects were not observed when subjects were treated with sham TENS or 2 Hz TENS. No significant differences were observed in other components of MN-SEPs, either for mean latency or amplitude.
Schabrun et al. (33) 13 healthy volunteers	The SEP of MN at the wrist: peak-to-peak amplitudes: P14-N20, N20-P25, P25-N33, N13, N9 and latencies N9, N14 and N20	Before and after completion of the stimulation period 1-way ANOVA Linear regression analyses Where appropriate, *post-hoc* tests were performed	Neither motor or sensory PES induced a change in the latency of the N13/N20 1. Motor movement: Motor PES increased the amplitude N20-P25 (*post-hoc* pre vs. post $p = 0.007$,) no change in the P14-N20 (*post-hoc* pre vs. post $p = 0.34$) or P25-N33 (*post-hoc* pre vs. post $p = 0.77$) components. 2. Sensory 100 Hz: Sensory PES increased the amplitude of P14-N20 (*post-hoc* pre vs. post $p = 0.01$,) and reduced P25-N33 (*post-hoc* pre vs. post $p = 0.001$) The N20-P25 component was unchanged by sensory PES (*post-hoc* pre vs. post $p = 0.34$).
Rocchi et al. (40) 15 healthy volunteers	Digital nerves of the right index finger were stimulated The UL SEPs: amplitudes: P14, N20-P25 and N20 peak latency	Before and 5 min after the completion of the 45 min stimulation period 2-way ANOVA and dependent Student's *t*-test	HF-RSS increased the amplitude of N20-P25 ($p < 0.001$) and P14 ($p < 0.001$) immediately after HF-RSS was applied. No changes in N20 or P14 latency were observed (p values of all *t*- tests > 0.05)
Zarei et al. (41) 40 healthy volunteers	The SEP of MN at the hand: N100, P200, and N400 latency and amplitudes	Baseline Post-I / 0 min Post-II/+30 min Post-III/60 min 2-way ANOVA Where appropriate, *post-hoc* tests were performed	The magnitude of N100, P200 waves, and theta and alpha band power was significantly suppressed following the TENS intervention. The suppression of the magnitude of the N100 wave lasted at least an hour. However, the effects of TENS on the magnitude of P200 only remained for 30 min after the intervention.

MN, Median nerve; TENS, Transcutaneous Electrical Nerve Stimulation; EA, Electroacupuncture; UL, Upper limb; Frequency Repetitive Somatosensory Stimulation; LL, Lower limb; TN, Tibial nerve; tsDCS, Transcutaneous Spinal (anodal and cathodal) Direct Current Stimulatio.

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TABLE 4 Latencies and Amplitudes of SEP Components—Pre–Posttest –Studies made on stroke population.

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Bao et al. (12) 90 stroke patients	Not provided	Baseline, end of week 8 Paired *t*-tests and McNemar tests, 1-way ANOVA, $\chi 2$ tests	Significant differences in latency and peak value of SEP between the two groups at the end of the eighth week ($p < 0.05$), but not at baseline ($p > 0.05$).

	Latency (ms)			Peak (μV)		
	Baseline	**8 weeks**	**P value**	**Baseline**	**8 weeks**	**P value**
Group A	43.7±5.56	38±3.6	P<0.05	1.44±0.52	2.13±0.51	P<0.05
Group B	44.1±6.97	27.3±5.36	P<0.01	1.53±0.46	2.94±0.59	P<0.01
P-value	0.89	P<0.01		0.7	P<0.01	

Peurala et al. (13) 59 stroke patients	The SEP of MN at the wrist: N20, N30, N60, (patients with hand stimulation treatment) and TN SEPs at the ankle: P40, N80, (patients with foot stimulation treatment)	Baseline, end of week 3 Paired samples *t*-test, nonparametric Wilcoxon and marginal homogenity test	SEP normality classification improved significantly in paretic UL ($p < 0.01$) and in paretic LL ($p < 0.05$) in the stimulated group (n = 51) after 3 weeks of rehabilitation.

Hand SEP* (n = 8)	**Before**	**After**	**Foot SEP* (n = 19)**	**Before**	**After**
1	0	0	1	0	2
2	3	3	2	10	10
3	5	5	3	9	7

*SEP: 1, normal; 2, minor change; 3, abnormal

Giaquinto, et al. (42) 102 stroke patients	The UL SEP N20 latency, affected and unaffected side	Baseline, end of week 8 Mann–Whitney *U*-test, Student's *t*-test, Spearman correlation	The mean amplitude N20 on the affected side increased compared to the baseline. Latencies did not change.

	N20: Mean Amplitude SD		N20: Mean Latencies and SD	
	Unaffected Hemisphere	**Affected Hemisphere**	**Unaffected Hemisphere**	**Affected Hemisphere**
Before	−3.4 μV (1.5)	−1.8 μV (1.4) df = 18, *t* = 3.716, *P* = 0.002	20.5ms (1.5)	17.7ms (7.9) df = 18, *t* = 1.489, ns
After (1.3)	−3.4 μV	−2.6 μV (1.2) df = 16, *t* =−2.270, *P* = 0.003	20.1ms (1.2)	19.2ms (5.1) df = 16, *t* = 0.735, ns
Before and after comparison	df = 016, *t* = 0.363, ns df = 16, *t* = 4.932, *P* = 0.0001			

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TABLE 4 (Continued)

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Tashiro et al. (15) 23 stroke patients	NI(N20), PI(P25), NII(N33), PII(P45), NIII(N60) of the MN at the wrist and N31, P35, N42, P53, N66 of the TN at the ankle	Baseline, end of week 3; Wilcoxon signed-rank tests Student's *t*-test	The Wilcoxon signed-rank test indicated that the number of cortical peaks significantly increased in the MN, but not in the TN in the non-paretic side (MN, $p = 0.008$; TN, $p = 0.11$). No significant changes in the MN between peak latencies of central SEP peaks and N18. Remarkable differences were detected in shortening of the latency between NI(N20) – PII(P45) after the intervention.

MN, Median nerve; TENS, UL, Upper limb; HF-RSS, High Frequency Repetitive Somatosensory Stimulation; LL, Lower limb; TN, Tibial nerve.

spinal cord injuries, Parkinson's disease, multiple sclerosis, pain or cranial nerve. Furthermore, the studies that used transcranial direct current stimulation, transcranial magnetic stimulation, or deep brain stimulation were excluded.

Methodological quality

The Cochrane risk of bias in non-randomized studies (ROBINS-I) tool developed by Sterne et al. (44) was used to assess the risk of bias of observational studies that compare health effects of two or more interventions. ROBINS-I is a tool for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups. ROBINS-I'S fundamental underlying principle is to compare the risk of bias associated with the current evaluated non-randomized trial with a target randomized controlled trial (RCT) hypothesized to be conducted with the same group of participants, even though this RCT may not be feasible or ethical (45). The ROBINS-I tool includes seven domains to assess the risk of bias that may arise in a non-randomized study: (1) bias due to confounding; (2) bias in selection of participants into the study; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes (or detection bias); (7) bias in selections of the reported results. The categories for risk of bias judgments are Low risk, Moderate risk, Serious risk and Critical risk. The risk of bias is first assessed for each domain, and then the overall judgement of the study's risk of bias is made (44).

The "Quality Assessment Tool for Before-After (Pre-post)" developed by the National Institutes of Health (NIH) was used to rate the methodological quality of pre-post studies without a control group (46). The questions in the NIH quality assessment tool were designed to help reviewers focus on the key concepts for evaluating the internal validity of a study. Critical appraisal of a study involves considering the potential for selection bias, information bias, measurement bias, or confounding. Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed throughout the tool which can be found in Table 5. High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of fair and good quality (46).

The overall certainty of evidence and strength of recommendation was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE handbook) methodology (47). According to the GRADE approach, the evidence is graded as high, moderate, low, or very low certainty of evidence. Furthermore, a body of evidence from observational studies begins with a low certainty of evidence-rating which could be downgraded due to five reasons: risk of bias, indirectness, inconsistency, imprecision

TABLE 5 Methodological quality of included studies according to the "Quality Assessment Tool for Before-After (Pre-post)".

	Studies made on healthy volunteers				Study made on stroke population
	Cogiamanian et al. (38)	Schabrun et al. (33)	Kang et al. (39)	Rocchi et al. (40)	Tashiro et al. (15)
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No	No	No	No	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	No	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes	Not reported	Not reported	Not reported	Yes
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Not reported	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests were done that provided *p*-values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	No	Yes	Yes	No
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No	NA	NA	NA	NA
Quality rating	Fair	Fair	Poor	Fair	Good

and publication bias (36). There are three factors that permit rating up the certainty of evidence: large magnitude of an effect, dose-response gradient, and effect of plausible residual confounding (47).

Results

The systematic search resulted in 11,351 references. The search from Pubmed/MEDLINE database resulted in 2,963 records, Scopus/ScienceDirect database resulted in 1,882 records, Cochrane library database resulted in 4,176 records, Web of Science/Clarivate resulted in 4,877 records and the database PEDro resulted in 10 records. The registry ClinicalTrials.gov was searched manually, and four studies were included for further evaluation. We excluded 2,561 duplicate studies using Rayyan QCRI software (37). Based on the titles and abstracts 69 reports were included for full-text reading. Additionally, six articles were found after the screening of reference lists. Ten articles were included in the review after applying the inclusion and exclusion criteria. The search process is presented in the PRISMA flow diagram (Figure 1).

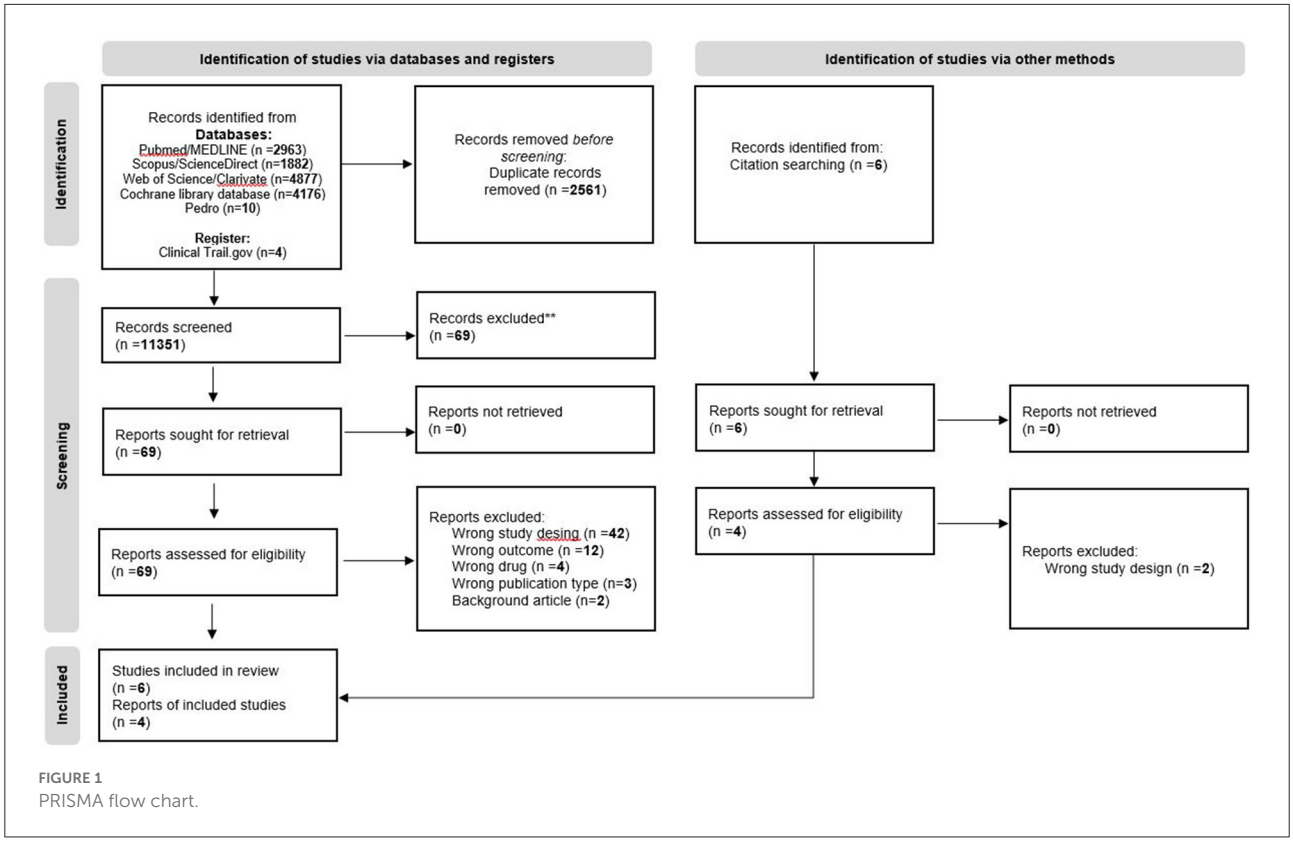

FIGURE 1
PRISMA flow chart.

Intervention procedure and the time frame between the SEP measurements

The different forms of stimulation, stimulation devices, location of PES, amplitude, duration, and frequency pulse as well as test time and follow-up of SEP were examined in each study. All data are summarized in Table 2. The total amount of participants in the reviewed studies was 496. Of these, 364 were stroke patients and 132 were healthy participants. Five studies involved one (12, 41, 42) or two (6, 13) control groups. The study by Kang et al. (39) applied: Sham TENS, 2Hz TENS or 2Hz electroacupuncture and the study from Schabrun et al. (33) applied Motor Movement PES or Sensory PES 100 Hz intervention. On the other hand Tashiro et al. (15) used SEP of the tibial nerve as a reference to SEP for the median nerve and Cogiamanian et al. (38) measured five subjects from the first group a second time using sham stimulation. A wide range of sensory-motor assessments was used to examine the effect of PES in studies of stroke patients and healthy participants (Table 2). The assessment of SEP in two studies on stroke patients (12, 42) was performed at baseline and 8 weeks post PES intervention. In the other two studies (13, 15) the assessment was performed at baseline and 3 weeks post PES intervention. The SEP in healthy participants in all six studies was assessed before, at baseline, and 0,15/20/30/45/60 min after the intervention (6, 33, 38–41). In the majority of studies on stroke patients the SEP measurements were performed on the median nerve. In the study by Peurala et al. (13) SEPs on the UL were performed in those patients who received hand stimulation and SEPs on the LL were performed in those patients who received foot stimulation while in the study from Tashiro et al. (15) SEPs from tibial nerves were used as a control measurement. Bao et al. (12) reported an improvement of latency and peak value of SEPs between the two groups at the end of the 8th week without further explanation of how the measurement was performed. No study showed a loss of peaks after the intervention. Details about SEP changes in latencies and amplitudes components can be found in Tables 3, 4. The following body location were stimulated with PES: tenth thoracic spinal vertebra (38), shoulder (38, 42), arm, hand or fingers (6, 13, 15, 33, 40–42), lower limb and foot (12, 13, 39) and hip (42). The found data about stimulation form, stimulation devices, location of PES, amplitude, duration, and frequency pulse as well as test time and follow-up of SEP could not be standardized so we decided to analyzed data separately.

Methodological quality of included studies

Five non-randomized studies (6, 12, 13, 41, 42) with serious to moderate risk of bias (Figure 2) and five pre-post studies (15, 33, 38–40) without a control group with poor to good methodological quality (Table 5) were included and assessed

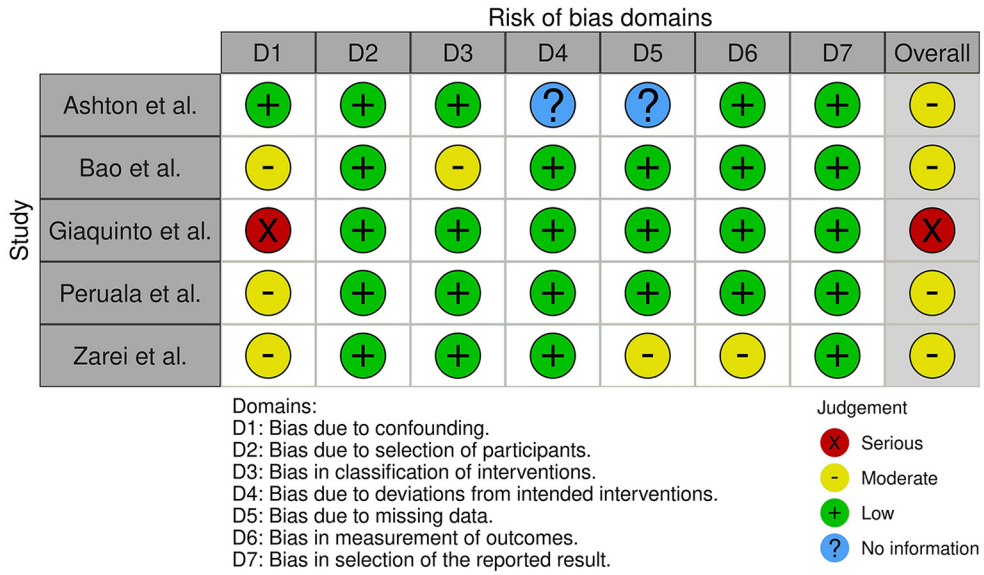

FIGURE 2
Results of the ROBINS-I tool to assess risk of bias domains.

in the present review. No randomized trials were found. Low overall risk of bias in non-randomized trials, which can be compared to a well-performed randomized trial, was not found in any of the included studies (6, 12, 13, 41, 42). Due to the fact that the Robins-I tool uses strict criteria to evaluate confounding bias, one study was classified as having serious risk of bias (42). Four studies were evaluated as having moderate risk of bias because the data was collected retrospectively (12), insufficient information was given about the potential confounding bias (13, 41), or no explanation of the source of information about intervention status was reported (6). In accordance with the NIH tool, one pre-post study had good (15), tree studies had fair (33, 38, 40), and one had poor (39) methodological quality. The eligibility criteria and the outcome measures were prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants, except for the study by Kang et al. (39). According to the NIH tool, the sample size should be large enough to provide confidence in the findings and outcome assessors should be blinded to the participants' exposures, and interventions. Only the study by Tashiro et al. (15) managed to meet these important criteria.

The overall certainty of evidence was very low for all outcomes (Supplementary Table 1). All available evidence was downgraded for limitations in study design and risk of bias (6, 12, 13, 15, 33, 38–42), imprecision (6, 12, 13, 15, 33, 38–42), or indirectness (6, 12, 39, 41) to very low certainty of evidence. There were no legit reasons to rate up the certainty of evidence. Thus, there is insufficient evidence for or against the use of SEP to monitor therapeutic effects.

Synthesis of results

It was planned to perform a meta-analysis, if enough homogenous data were available, using mean difference and random effects model. However, quantitative synthesis was not possible due to limited and heterogenous eligible studies. Therefore, a qualitative synthesis was performed. Table 6 features a summary of SEP latency and amplitude outcomes in studies using same measurement instruments.

Discussion

Studies made on healthy volunteers

By evaluating motor function and control, corresponding to changes in SEP components in healthy participants, the study by Rocchi et al. (40) suggested that high frequency repetitive somatosensory stimulation leads to improved performance in behavioral tests of temporal discrimination and contributes to improved performance in tests of spatial detection. Nevertheless, high frequency repetitive somatosensory stimulation also affects short-latency inhibition in M1. Together these changes in S1 and M1 may underlie reported improvements in manual motor performance (40). The correlation in healthy individuals between SEP and similar neurophysiological procedures as described in the study by Schabrun et al. (33). The magnitude and direction of the change in corticomotor excitability induced by sensory and motor PES was positively correlated with the difference in the cortical SEP components ($r = 0.71$, p

TABLE 6 SEP latency and amplitude outcomes synthesis in studies using same measurement instruments.

Outcomes/study	Measurement instruments	Significant effects
Studies made on stroke population		
Amp N20/P25/UL (13, 15, 42)	The UL SEP N20 amplitude was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex. Affected and unaffected side was measured.	The signal amplitude N20 **increased**. Student's *t*-test ($P = 0.0001$) (42) SEP normality classification **improved** significantly in paretic UL. Paired samples *t*-test ($p < 0.01$) (13) The number of cortical peaks **increased** significantly The Wilcoxon signed-rank test ($p = 0.008$) (15)
Lat N20/UL (13, 15, 42)	The UL SEP N20 latency was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex. Affected and unaffected side was measured.	Latencies **did not change**. Student's *t*-test ($p > 0.05$) (42) SEP normality classification **improved** significantly in paretic UL. Paired samples *t*-test ($p < 0.01$) (13) **No significant changes** between peak latencies ($p > 0.05$) (15)
Amp P40/LL (12, 13)	Not provided (12) The TN SEP P40 amplitude was recorded using surface electrodes placed in anatomically identified locations of the LL area of the primary somatosensory cortex. Affected and unaffected side was measured (13)	The signal amplitude N20 **increased**. Paired samples *t*-test ($p < 0.05$) (12) SEP normality classification **improved** significantly in paretic LL. Paired samples *t*-test ($p < 0.05$) (13)
Lat P40/LL (12, 13)	Not provided (12) The TN SEP P40 latency was recorded using surface electrodes placed in anatomically identified locations of the LL area of the primary somatosensory cortex. Affected and unaffected side was measured (13)	Latency **improved** after intervention. Paired *t*-tests ($p < 0.05$) (12) SEP normality classification **improved** significantly in paretic LL. Paired samples *t*-test ($p < 0.05$) (13)
Studies made on stroke population		
Amp N20/P25/UL (33, 38–40)	The UL SEP and N20/P25 amplitude was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex.	The signal amplitude **decreased**. paired *t*-tests $p = 0.01$ (38) **No significant differences** observed in amplitude. One-way analysis of variance shown as mean±SD (39) Motor PES **increased** the amplitude (*post-hoc* pre vs. post $p = 0.007$,) (33) The signal amplitude **increased**. Dependent *t*-tests were ($p < 0.001$) (40)
Amp N100/UL (6, 41)	The EEG signals was recorded during the sensory evoked potential (SEP) phases.	The signal amplitude **decreased.** 2-way ANOVA ($P > 0.05$) (6) The magnitude was significantly **decreased**. 2-way ANOVA ($P > 0.05$) (41)
Lat N100/UL (6, 41)	The EEG signals was recorded during the sensory evoked potential (SEP) phases.	Latency **increased** after intervention. 2-way ANOVA ($P > 0.05$) (6) Latencies **did not change**. 2-way ANOVA ($P > 0.05$) (41)

UL, Upper limb; LL, Lower limb; Amp, Amplitude: Lat, Latency.

< 0.001), as confirmed by linear regression between cortical SEP components (N20-P25 and P25-N33) and corticomotor excitability motor evoked potential (MEP) amplitude. Similar changes as already described in the study from Rocchi et al. (40) showed a correlation between PES, high-frequency oscillations analysis and N20-P25 recovery curve. The first conclusion considered from the obtained results is a good validity between SEP, TMS and its correlation with PES. In other terms, not only

somatosensory brain areas are affected through PES. Moreover, the motoric brain regions are part of this process. Despite those fact it is necessary to note that all studies made on healthy volunteers assess SEP maximum 1 h after PES and that the studies (38, 41) showed selectively reduced amplitudes in primary somatosensory cortex direct after stimulation. However, we did not identify enough data to provide a clear relationship between SEP and motor performance subsequently to PES in healthy individuals. The lack of observation studies over extended periods of time is the main problem when it comes to drawing a clear conclusion about the impact of PES on SEP.

Studies made on stroke patients

In the stroke study (13) SEP and Modified Motor Assessment Scale results were not compared, but both measures showed improvement. Moreover, in a study (42) significant negative correlation between the time interval for the appearance of somatosensory event-related potentials and the functional independence measure (FIM) score at the time of discharge ($r = -0.53$, $p < 0.01$). The study on stroke patients by Tashiro et al. (15) observed significant improvements in behavioral assessment scores for proprioception followed by PES interventions. We could conclude that assessments of motor performance correspond to changes in SEP components in UL and LL. Additionally, the studies on stroke patients involving PES that initiate a voluntary contraction used for a specific movement or task (12, 13, 15, 42), indicate a positive relationship and correlation to assessments of motor function. This hypothesis is supported by findings in a meta-analysis on stroke motor recovery of UL functions (48) and therapeutic effects of peroneal stimulation on gait and motor recovery (18). Moreover, simple sensory stimulation, unrelated to the movement, was of limited functional value for motor recovery for the rehabilitation of the hand in stroke patients and no correlation was described (49).

SEP results in healthy subjects compared to stroke patients

Somatosensory event-related potentials accompanied with SEP in a study from Giaquinto et al. (42) were adequate to follow changes in primary somatosensory area N20. The Bao et al. (12) found significantly improved latency and peak value of SEP and MEP. Furthermore, those changes respond to sensory and motor nerve conduction velocity at the end of the 8 week ($p < 0.05$). This finding indicates the relevance of evaluating electrophysiological methods and may verifies the use of SEP in stroke patients. All SEP set on stroke patients demonstrated several subcortical or cortical reorganization changes after treatment with PES on the paretic side. However, an unrelated time frame and insufficient data were collected to analyze the relationship between the form of stimulation, pulse amplitude, pulse duration, or location of stimulation and changes in SEP. Perhaps it should be emphasized that in stroke studies in which high pulse amplitude inducing muscle contraction was delivered, the increase of amplitude N20-P25 (15, 42) was seen. The same was observed in healthy participants (33, 40). In order to confirm this hypothesis, we suggest conduction of randomized controlled study on healthy subjects and stroke patients using standard SEP procedure define by Muzyka et al. (31), and clearly described used PES parameter. Based on the GRADE approach to assess the quality of evidence, no outcome that provided a strong recommendation was found. There is thus far insufficient evidence to support a decision for or against use of SEP to monitor therapeutic effects and the results of this analysis cannot be generalizable.

It is known that there are substantial anatomical interconnections linking the brain's motor and somatosensory regions. Cortical motor areas receive direct inputs from primary and second somatosensory cortex and inversely, somatosensory areas get direct cortical inputs from primary motor cortex, premotor cortex, and from supplementary motor area (21, 50). A change in somatosensory function in association with motor learning would seem to be a natural by-product of this anatomical connectivity (21, 50). Findings in this review suggest that PES may shift the response of somatosensory to motor areas of the brain. On the other hand, it could be hypothesized that SEP can indirectly recognize the changes in motor area of the brain. Moreover, it appears that SEPs have sufficient sensitivity to detect even the smallest changes in action potential of neural cortical network after stroke and is probably able to assess the effect of various sensory therapies: cryotherapy, thermotherapy, occupational tactile therapy, or robotic tactile therapy more directly.

Limitations of the study

First, we cannot confirm that all PES studies were identified because the meaning of the term "peripheral electrical stimulation" varies widely and is understood differently. We tried to minimize this limitation by searching more databases. Second, we were aware that EEG measurement can also be used to record SEP, and the lack of keywords and terms to describe this process limited our desire to include all of these studies. However, we used the term "evoked potentials" to increase the number of studies identified in our database search and to include studies using EEG. We also tried to use all PES terms indexed in PubMed to find an optimal data set and minimize this limitation.

Conclusion

From the results of this review, the repetitive task-oriented treatment enriched with PES could likely become a different approach to be applied in stroke patients to improve daily living activities since we have hints that PES may impact changes in motor neuroplasticity. We suggest that more studies (especially RCTs) should be conducted to evaluate whether SEP measures can be used to monitor the therapeutic effects of PES in the rehabilitation of stroke patients, as there is insufficient evidence to do so but SEP remains a promising tool to estimate rehabilitation prognosis after stroke.

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.

Author contributions

MM, AJ, BS, and PY contributed to conception and design of the study. MM organized the database and wrote the first draft of the manuscript. MM and AJ performed the qualitative analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1036891/full#supplementary-material

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Brain-computer interface combined with mental practice and occupational therapy enhances upper limb motor recovery, activities of daily living, and participation in subacute stroke

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Background: We investigated the effects of brain-computer interface (BCI) combined with mental practice (MP) and occupational therapy (OT) on performance in activities of daily living (ADL) in stroke survivors.

Methods: Participants were randomized into two groups: experimental (n = 23, BCI controlling a hand exoskeleton combined with MP and OT) and control (n = 21, OT). Subjects were assessed with the functional independence measure (FIM), motor activity log (MAL), amount of use (MAL-AOM), and quality of movement (MAL-QOM). The box and blocks test (BBT) and the Jebsen hand functional test (JHFT) were used for the primary outcome of performance in ADL, while the Fugl-Meyer Assessment was used for the secondary outcome. Exoskeleton activation and the degree of motor imagery (measured as event-related desynchronization) were assessed in the experimental group. For the BCI, the EEG electrodes were placed on the regions of FC3, C3, CP3, FC4, C4, and CP4, according to the international 10–20 EEG system. The exoskeleton was placed on the affected hand. MP was based on functional tasks. OT consisted of ADL training, muscle mobilization, reaching tasks, manipulation and prehension, mirror therapy, and high-frequency therapeutic vibration. The protocol lasted 1 h, five times a week, for 2 weeks.

Results: There was a difference between baseline and post-intervention analysis for the experimental group in all evaluations: FIM (p = 0.001, d = 0.56), MAL-AOM (p = 0.001, d = 0.83), MAL-QOM (p = 0.006, d = 0.84), BBT

($p = 0.004$, $d = 0.40$), and JHFT ($p = 0.001$, $d = 0.45$). Within the experimental group, post-intervention improvements were detected in the degree of motor imagery ($p < 0.001$) and the amount of exoskeleton activations ($p < 0.001$). For the control group, differences were detected for MAL-AOM ($p = 0.001$, $d = 0.72$), MAL-QOM ($p = 0.013$, $d = 0.50$), and BBT ($p = 0.005$, $d = 0.23$). Notably, the effect sizes were larger for the experimental group. No differences were detected between groups at post-intervention.

Conclusion: BCI combined with MP and OT is a promising tool for promoting sensorimotor recovery of the upper limb and functional independence in subacute post-stroke survivors.

KEYWORDS

stroke, brain-computer interface, occupational therapy, mental practice, rehabilitation

Introduction

Epidemiological data suggest that about one-third of the 16 million/year patients with post-stroke worldwide remain with significant limitations in engaging in meaningful activities of daily living (ADL) and performing tasks with satisfactory upper limb (UL) function (1).

The inability to use the affected UL after injury may be related to sensory and motor brain impairments due to decreased cortical excitability and an imbalance of interhemispheric competition (2–5). Thus, elucidating the mechanisms that will optimize neuroplasticity during rehabilitation treatment, increase cortico-cerebral excitability, and facilitate long-term functional recovery becomes a significant challenge (6).

Artificial intelligence and neuroengineering technologies such as the brain-computer interface (BCI) can promote improved brain plasticity and functional reorganization of the brain, which is a promising approach for post-stroke rehabilitation, especially to improve arm motor function (6).

In its entirety, BCI is an innovative intervention that decodes neural signals by electroencephalogram (EEG) in real-time, transferring to digital signals that activate a device, prostheses, or robots, triggering and providing instant multimodal feedback (visual, sensory, and kinesthetic) to the coupled member (7). In EEG-based non-invasive BCI, movement intention or mental practice (MP) is decoded in real-time from the ongoing electrical activity of the brain (6). The EEG can analyze related brain waves in the premovement period: Bereitschaftspotential (which can be recorded over the vertex region), and during the movement tasks, mu and beta rhythms were found to reveal event-related synchronization and desynchronization (ERS/ERD) over the sensorimotor cortex (8).

Notably, studies showed that BCI was able to promote increased activation of the primary (M1) and frontal motor cortex, thus promoting a process of brain reorganization and neuroplasticity (1, 7, 9, 10).

Recent studies have shown the effectiveness of applying BCI using mental practice in motor recovery for subacute and chronic stroke patients with hemiparesis (6, 11–19). Furthermore, a relevant rehabilitation study combing BCI and mental practice showed promising results for the recovery of cognitive skills (executive functions, language, memory, attention, and visuospatial skills) in post-stroke patients (20).

As demonstrated, it is understandable to perceive the potential of BCI as a supporting strategy for improving brain plasticity and UL motor functions after stroke. However, knowing that the improvement of a skill *per se* may not reflect the improvement of functional independence for activities of daily living, social participation, and occupational performance. The World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF), describes the activity as the performance of a task or action by an individual and participation as its involvement in real situations of daily life (21).

Thus, this study aimed to investigate the effects of BCI combined with MP and occupational therapy (OT) on the manual function to improve performance in executing ADL and increase the social participation of stroke survivors in the subacute phase.

Materials and methods

Study design

A randomized clinical trial, characterized by double blinding (evaluator and statistician) was conducted. The study was approved by the Ethics Committee in Research with Human Beings of the Health Sciences Center, Federal University of Sergipe, Brazil (65123016.5.0000.5546). The present study

followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

The study was carried out at the Laboratory of Studies in Neurological Learning and Rehabilitation (LEARN) at the University of the Federal University of Sergipe, located in Lagarto, from August 2019 to May 2022.

Once the participants were recruited, an initial screening was performed to determine the eligibility criteria. For participants included, a battery of assessments was performed using the instruments for the primary and secondary outcomes. After being evaluated, the participants were randomized and allocated to the trial groups.

Experimental group

BCI; mental practice with functional tasks; and OT with training in ADL, muscle mobilization, reaching tasks, manipulation and grip, mirror therapy, and high-frequency therapeutic vibration. The protocol lasted 80 min, five times a week, totaling ten intervention sessions.

Control group

A protocol was carried out only with the occupational therapy intervention, which included training in ADL, muscle mobilization, reaching tasks, manipulation and grip, mirror therapy, and high-frequency therapeutic vibration. Patients in the control group did not do imagery tasks. Only the occupational therapy protocol was used (no mental practice with functional tasks or BCI).

The protocol lasted 80 min, five times a week, totaling ten intervention sessions.

Population

Individuals were recruited through social media and referred by local hospitals, rehabilitation centers, and health centers. The sample consisted of individuals with a confirmed diagnosis of ischemic or hemorrhagic stroke, who had been affected by a single episode in the early subacute stage (from 3 weeks to 3 months of stroke) and late subacute stage (from 3 to 6 months after the stroke) (22), who were between 35 and 80 years of age with motor impairment in the UL, and who had partially preserved cognitive function.

Individuals who had partially preserved motor and sensory function according to the Fugl-Meyer assessment scale (with scores between 10 and 60 in the motor domain and 2 and 10 in the sensory domain) in the UL contralateral to the lesion and who were partially cognitive were included in the study (cut-off point of 18 in the Mini-Mental State Examination). Due to the need for at least partially preserved cognitive ability so that the participant could perform the movement imagination, we decided to exclude those with severe cognitive deficits. We defined no deficit as scores between 24 and 30, mild impairment as scores between 18 and 24, and severe impairment as scores between 0 and 17 (23, 24).

Exclusion criteria included: individuals who underwent external rehabilitation treatments with multiple brain injuries or other neurological diseases or musculoskeletal and psychiatric disorders, individuals who had a history of seizures, individuals with UL amputations, individuals undergoing decompressive craniectomy or with metallic implants in the head, and individuals who did not sign the free and informed consent form.

Randomization and blinding

The participants were randomized and allocated to two groups of equal size. A stratified block allocation based on stroke onset and age was generated at www.randomization.com by an independent researcher and packaged into sequentially numbered, opaquely sealed envelopes. A researcher who did not participate in the evaluations or interventions generated the random allocation sequence, enrolled participants, and assigned participants to the interventions. Those evaluating and analyzing the outcomes and participants were blinded to the treatment arm.

Intervention

The interventions were conducted by a qualified healthcare professional. The sessions took place in a reserved, ventilated room at the Laboratory of Studies in Neurological Learning and Rehabilitation (LEARN-UFS).

The experimental group received BCI therapy (30 min), combined with mental practice (15 min), and occupational therapy (35 min). The Occupational Therapy protocol consisted of ADL training (according to the patient's functional needs), mirror therapy; reaching, manipulating, and releasing objects tasks; muscle mobilization; and therapeutic vibration. The control group received only the occupational therapy protocol (80 min), without BCI or mental practice.

Brain-computer interface

The equipment used for BCI was developed by Neurobots® (Exobots System Software: 1.10.0, Exobots Firmware version 2, EEG Firmware version 1). Exobots Battery: Li-Ion 3.6 V 3,000 mAh; EEG Battery: Li-Po 3.7 V 1,300 mAh. Equipment power supply voltages and frequencies: Exobots: 220 V and Freq 50/60 Hz. EEG: USB 2.0 port—12 V continuous frequency. EEG conditioning: 24 bit AD conversion resolution; sample rate: 250 Hz. Biomarkers (from EEG): alpha-band desynchronization.

Initially, the participant was registered in the software, and then the electroencephalogram (EEG) capture electrodes were mounted. The electrodes were placed on the regions of FC3, C3, CP3, FC4, C4, and CP4, according to the international 10–20 EEG system. FC3/FC4 lies over the premotor cortex, and C3/C4 lies over the primary motor cortex. CP3/CP4 corresponds to the supramarginal gyrus, which is part of the somatosensory association cortex. These six electrodes covered the major part of the mirror neuron system. A ground electrode was placed on the forehead, and the reference electrode was placed on either A1 or A2 in the earlobe (25–27). The affected hand rested on a pillow with the exoskeleton individually adjusted for each participant. The wrist was kept in a neutral position. A UL exoskeleton, i.e., the Exobots, was positioned over the user's wrist and fingers and fixed with five velcros that were adjusted on the fingertip and two velcros placed on the forearm. The EEG was linked to a connector consisting of six electrodes. The EEG and the electrodes were fixed to a cap placed on the participant's head (Figure 1).

During the therapy session, the individual was instructed on four auditory commands given by the software, each with a different meaning: "Relax," "Prepare," "Think," and "Move." During the "Relax" phase, the patient was instructed to remain with an empty mind without thinking and just follow the command. The software detected and showed the relaxed state quantitatively on a feedback bar. In the "Prepare" and "Think" phases, the individual was instructed to imagine performing specific movements with the most affected hand (i.e., opening or closing the hand). If the system detected a continuous activation in the primary motor, premotor, or primary somatosensory cortices above the threshold shown on the screen (i.e., 70 points) for at least 3 s, the exoskeleton opened and closed the participant's hand. Finally, in the "Move" phase, the exoskeleton automatically opened and closed the individual's hand (without motor imagery). At the end of each trial, a score representing the degree of motor imagery was shown on the screen next to the brain areas that were most activated during the session.

When performing motor imaginary (i.e., mental practice), neurons increase their activation in the motor cortex by synchronizing their action potential at a high frequency (76–100 Hz) (28). This phenomenon is known as event-related synchronization (ERS) (29). Conversely, there is a reduction in neuronal activation in motor areas at low frequencies (8–32 Hz), a phenomenon known as event-related desynchronization (ERD) (29). Interestingly, real-time feedback of cortical activation may amplify ERS at high frequencies and ERD at low frequencies, showing that BCI can potentially promote neuronal activation in cortical areas (28).

In order to capture the motor imagery through non-invasive electrical sensors, a better signal-to-noise ratio is obtained at low frequencies, thus, the software needs to identify when the user performs an ERD in the μ frequency range (8–13 Hz). To calculate the ERD, the following formula is adopted: ERD % $= (R - A)/R \times 100$ (29), where R is the neuronal activation power at the μ frequency during the reference period ("Relax" phase), and A is the power of neuronal activation during motor imagery ("Think" phase). Then, the ERD is calculated on the six electrodes positioned over the motor cortex, and a degree of motor imagery is computed from the sum of the ERD of all electrodes. The degree of motor imagery was the nomenclature used by the manufacturer's BCI system, representing the ERD achieved by the user during motor imagery. During the "Think" phase, the exoskeleton was activated if there was a degree of motor imagery above an established threshold for 3 s. This time window was established to avoid false positives. The threshold was defined based on the expected ERD activity (i.e., from 50 to 100%) that occurs during motor imagery in the μ frequency range on electrodes placed over the motor cortex (29). The manufacturer defined 70% of ERD (i.e., 70 points) as the activation threshold, an intermediate value between the observed percentage ranges.

Eight electroencephalogram (EEG) electrodes attached to a cap, positioned in the region of FC3, FC4, C3, C4, CP3, CP4, ground and reference electrode of EEG system 10-10 marking. The exoskeleton is positioned over the patient's hand with articulated fingers to be fitted to the individual's fingers.

The training with the BCI consisted of 10 sets with 10 repetitions of the "Relax," "Prepare," "Think," and "Move" phases. At the end of each series, a 30-s interval allowed the participant to rest and receive the results. At the end of the process, the software showed the general results of the session (i.e., degree of motor imagery and activated brain areas).

In summary, the system is controlled through the ERD value (28, 29), obtained from the imagination of the movement. Six active EEG electrodes capture the ERD value and send it to software developed by Neurobots. If the ERD value is $\geq$70 points and lasts for at least 3 s, a command to move the exoskeleton is sent. Thus, the exoskeleton is moved by the opening and closing of the hand in imagination. The software also automatically moves the exoskeleton after the "think" phase. This is important to offer parameters to learn the ideal movement.

Mental practice with functional tasks

The MP sessions were individualized, focusing on ADL training according to the individual's needs. Each ADL was divided into kinematic components, i.e., the practice of each motor component that built a whole motor task. During MP, the participant observed the movement (made by the occupational therapist), imagined each component of the task with closed eyes, and finally performed the movement, completing the functional task. Note that MP with the functional task was administered to the experimental group.

FIGURE 1
Schematic drawing of the BCI equipment.

Occupational therapy intervention

The set of activities performed by the occupational therapist consisted of ADL training according to the patient's functional needs. Furthermore, rehabilitation interventions were administered: mirror therapy; reaching, manipulating, and releasing objects tasks; muscle mobilization; and therapeutic vibration.

For the mirror therapy protocol, the subject was positioned comfortably seated in front of a table, with both ULs forward. The affected UL was positioned behind a mirror (size 50 × 50 cm), and only the unaffected limb performed the activities. The participant was encouraged to follow all the exercises while being instructed by the occupational therapist. The following movements were performed: elbow flexion and extension, forearm pronation and supination, wrist flexion and extension, finger flexion and extension (30), and functional tasks, e.g., eating and combing hair.

Reaching, manipulating, and releasing objects were trained to favor the functional independence of individuals in their ADL. The task consisted of performing a reaching task with an everyday object positioned on the table, holding and manipulating it, moving the object in several directions around the table, simulating its functional use, and finally releasing the object.

Muscle mobilization was performed over the flexor and extensor muscles of the UL [i.e., mechanical stimulation of the muscle area, using tension and shear pressure at different intensities to improve flexibility and range of motion of the entire limb, (31)]. Mobilization was performed only in muscles that showed increased tone in the hemiparetic UL. High-frequency therapeutic vibration was also used as a sensory treatment. It consisted of the use of a mechanical device that administers vibrational stimuli of low amplitude, with high frequency (50 Hz), on a focal point in order to target specific muscle and tendon areas; its main objective was to increase sensory input and facilitate muscle contraction (32).

Outcomes and outcome measures

The outcomes and assessment instruments were selected according to the domains of the International Classification of Functioning, Disability, and Health (ICF) of body function, activity, and participation.

As a primary outcome measure, independence to perform ADL and participation were assessed through the motor activity log (MAL), the functional independence measure (FIM), the box and blocks test (BBT), and the Jebsen hand function test (JHFT).

For the secondary outcome, sensory and motor functions were assessed using the Fugl-Meyer Assessment of the upper extremity. The degree of motor imagery and number of exoskeleton activations by imagination recorded by the Neurobots® software were also evaluated for the experimental group.

Motor activity log (MAL)

The MAL test was administered to measure the real-world amount of UL function in the most affected arm (33, 34). The MAL comprises 30 items on two ordinal Likert-type scales related to the amount of use (MAL-AOM) and quality of movement (MAL-QOM). Each item is scored from 0 to 5, where a lower score indicates worse performance. A total score is obtained by computing the average of each scale; the higher the average, the better the quantity and quality of use of the UL (33). On both scales, the minimum clinically important difference (MCID) is 1.0 points if the paretic limb is non-dominant or 1.1 points if the paretic limb is dominant. The patient self-reported UL dominance (35).

Functional independence measure (FIM)

The FIM was used to measure functional independence during daily activities by evaluating: personal care, toilet training, mobility, locomotion, communication, and social knowledge (36, 37). In the present study, the FIM was administered through interviews. Each item was scored from 1 to 7, according to the patient's need for assistance. The FIM reported an MCID of 22 points (38).

Box and blocks test (BBT)

The BBT measures a patient's manual dexterity. Participants were instructed to transport as many blocks as possible from one compartment to another within 60-s. The individual's score equals the number of blocks transported in 60-s. Higher scores indicate better patient's manual dexterity. The test was performed bilaterally to verify that the participant understood the instructions; however, only the score of the paretic hand was considered (39–41). The MCID is 5.5 blocks per minute (42). Individuals who did not transport any blocks within the required time were not considered for the analysis of this outcome.

Jebsen hand function test (JHFT)

The JHFT consists of six tasks: turning cards, turning common small objects, simulating feeding, stacking chips, moving large lights, and moving heavy objects (43, 44). Each task was timed, and the patient had a maximum of 120 s to perform each task. Longer times indicate worse performance. Participants who did not perform each task within the given time were not considered for the analysis of results for this evaluation.

Fugl-Meyer assessment (FMA)

The FMA for the UL was administered to evaluate sensorimotor impairment. The FMA comprises two domains: motor and sensory. Each item consists of a three-point ordinal scale (0-not able to perform, 1-performs partially, 2-performs fully), with a total score of 66 and 12 points for the motor and sensory domains, respectively (45, 46). The MCID is 5.25 points for the motor domain and 1.2 points for the sensory domain (47).

Degree of motor imagery and amount of exoskeleton activations

The Neurobots® software recorded the neurophysiological signals, through non-invasive electrical sensors, during the mental practice (movement imagination) and transformed them into a degree of motor imagery. If the measured degree of motor imagery was maintained above the minimum threshold of 70 points (i.e., amount of desynchronization calculated by the software algorithm) and remained above 70 points for a minimum of 3 s, it would lead to the movement of an exoskeleton that was attached to the patient's hand (for details, refer to "Brain-computer interface" section). At the end of each exercise and session, the software computed an average of the degree of motor imagery reached during the mental practice, the amount of exoskeleton activations, and a heat map indicating which area of the cerebral cortex was more activated during the exercise session. The representation of the image with darker/warmer colors indicated greater brain activation. It was expected that an increase in the degree of motor imagery would also increase the number of exoskeleton activations.

Data analysis

For the study, we performed distribution analysis using the Shapiro-Wilk test. In order to analyze differences in baseline characteristics between groups, independent sample t-test (normal data distribution) or Mann–Whitney *U*-test (non-normal distribution) was used while for categorical variables, Fisher's exact test was applied. Given the non-normal distribution of post-intervention data of primary outcomes, non-parametric statistics (Mann–Whitney *U*-test) were used between baseline and post-intervention, and between-group comparisons were evaluated using the Wilcoxon and Mann–Whitney sign tests, respectively. The results were interpreted according to Cohen (48) as trivial for $d < 0.20$, small for $0.20 \leq d < 0.50$, moderate for $0.50 \leq d < 0.80$, and large for $d \geq 0.80$. The chi-square (χ^2) test and odds ratio were used to compare differences between groups in the proportion of participants who achieved minimum clinically important difference (MCID) values. The MCID was descriptively analyzed to understand which therapy was superior to help the participant achieve the minimum expected difference for each outcome measure. The sample size was determined based on the expected effect size (dz) = 0.7, for within-group analysis. Thus, for $\alpha = 0.05$ and $\beta = 80\%$, a sample size of $n = 19$ subjects (+15% accounting for possible dropouts) per group was estimated (*t*-tests–matched pairs, G*power) (49). The Statistical Package for the Social Sciences (SPSS) version 22 software was used for all statistical analyses, adopting a significance level of $p \leq 0.05$.

Results

Figure 2 shows the flow describing the participants in each study phase. There were no demographic and clinical differences between groups at the baseline (Table 1). No adverse events were reported. Seven participants in the experimental group and four in the control group were unable to perform the JHFT.

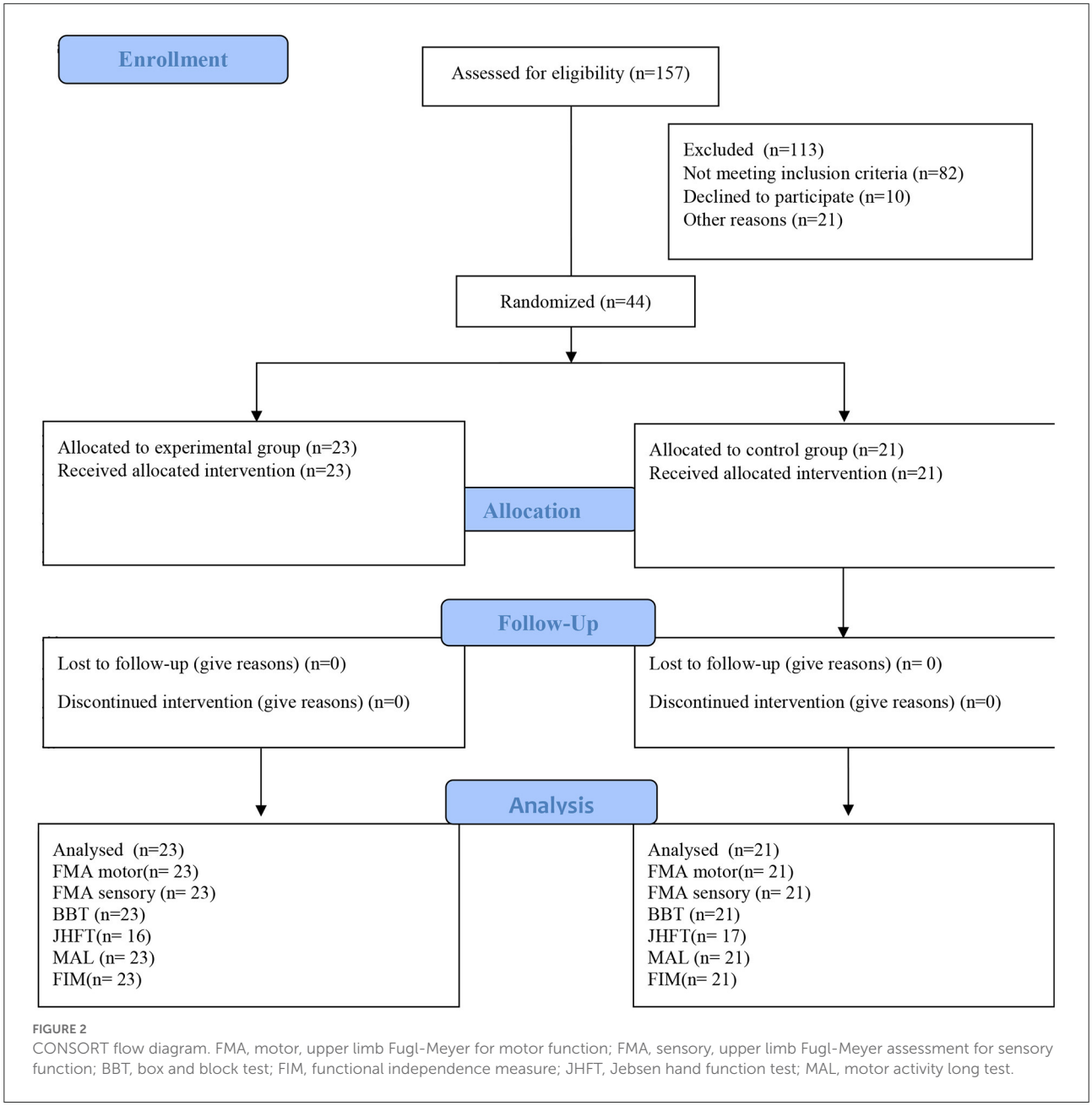

FIGURE 2
CONSORT flow diagram. FMA, motor, upper limb Fugl-Meyer for motor function; FMA, sensory, upper limb Fugl-Meyer assessment for sensory function; BBT, box and block test; FIM, functional independence measure; JHFT, Jebsen hand function test; MAL, motor activity long test.

There was a difference between baseline and post-intervention analysis for the experimental group in all assessments (FIM, MAL—AOM and QOM, BBT, and JHFT). There was a statistical difference for the control group only for the MAL and BBT. Although both groups showed differences for the MAL and BBT, the effect size was greater for the experimental group (Table 2). In the between-group analysis, post vs. post, no differences were found for MAL-QOM (Mann–Whitney U-test, $p = 1.00$), MAL-AOM (Mann–Whitney U-test, $p = 1.00$), BBT (Mann–Whitney U-test, $p = 0.396$), FIM (Mann–Whitney U-test, $p = 0.128$), and JHFT (Mann–Whitney U-test, $p = 0.65$).

Secondary outcome

There was a statistical difference in the FMA for the experimental group in the motor ($p = 0.001$, Cohen's $d = 0.6$) and sensory function ($p = 0.001$, Cohen's $d = 0.8$) as well as for the control group in the motor ($p = 0.005$, Cohen's $d = 0.3$) and sensory function ($p = 0.012$, Cohen's $d = 0.5$). Notably, the effect size was larger in the experimental group (Figure 3). At post-treatment, there was no difference between groups for the FMA motor domain (Mann–Whitney U-test, $p = 0.224$) and sensory domain (Mann–Whitney U-test, $p = 1.00$).

TABLE 1 Demographic and stroke characteristics for each group at baseline.

	Experimental ($n = 23$)	Control ($n = 21$)	p-value
Age	62.2 ± 9.8	61 ± 3	0.769[b]
Gender (male)	12 (52.2%)	11 (52.4%)	0.989[a]
Dominance (right)	21 (91.3%)	19 (90.5%)	0.924[a]
Hemiparesis (right)	10 (43.5%)	11 (52.4%)	0.555[a]
Stroke time (weeks)	13.9 ± 6	12.5 ± 6.7	0.388[b]
Ischemic stroke	21 (91.3%)	17 (80.9%)	0.318[a]
MMSE	23.6 ± 4	21.8 ± 3.8	0.107[b]
FMA-motor	32.1 ± 16.8	37 ± 13.5	0.410[b]
FMA-sensory	6.6 ± 2.4	7.7 ± 2.5	0.191[b]
MAL-AOM	0.5 ± 0.6	0.4 ± 0.3	0.981[b]
MAL-QOM	0.6 ± 0.9	0.7 ± 0.6	0.202[b]
BBT	12.2 ± 12.6	11.1 ± 9.8	0.915[b]
JHFT	254.6 ± 239.8	222 ± 171	0.122[b]
FIM	97.6 ± 22.2	99.4 ± 20.4	0.823[b]

Data are mean ± standard deviation and percentages; MMSE, mini mental state examination; FMA, Fugl-Meyer Assessment; MAL, motor activity log; AOM, quantitative; QOM, qualitative; BBT, box and blocks test; JHFT, Jebsen hand function test; FIM, functional independence measure.
[a]Chi-square test.
[b]Mann–Whitney U-test.

There was a statistical difference from baseline to post in the experimental group for the degree of motor imaginary ($p < 0.001$) and the amount of exoskeleton activations during the BCI treatment ($p < 0.001$) (refer to Figure 4).

Minimum clinically important difference (MCID)

The proportion of patients who achieved MCID is depicted in Figure 5. Table 3 shows the differences between pre- and post-intervention within each group. Statistical differences were found in the percentage of participants that achieved the MCID in the experimental group compared to the control group for MAL-AOM [$\chi^2_{(1,n=44)} = 3.988$, $p = 0.046$; odds ratio = 5.067, 95% CI (0.934, 27.484)], MAL-QOM [$\chi^2_{(1,n=44)} = 6.080$, $p = 0.014$; odds ratio = 10.667, 95% CI (1.201, 94.738)], and FMA motor domain [$\chi^2_{(1,n=44)} = 9.031$, $p = 0.003$: odds ratio = 7.200, 95% CI (1.879, 27.592)]. No statistical differences were detected for BBT, FMA sensory function, and FIM.

Discussion

Several neurorehabilitation interventions have investigated UL sensorimotor recovery ADL and participation in post-stroke individuals [e.g., (50, 51)]. While most clinical trials were developed on specific neurorehabilitation interventions, less attention was given to motor control (52) combined with OT and quality of movement (53, 54). The present study aimed to investigate the effects of BCI combined with MP and occupational therapy (OT) on the manual function to improve performance in executing ADL and increase the social participation of stroke survivors in the subacute phase.

The current study showed significant improvements for the experimental group in all outcomes after the BCI combined with MP and OT. Notably, following BCI intervention, the experimental group showed improvements in the degree of motor imagery and the amount of exoskeleton activations. In the control group, post-intervention differences were detected for MAL-AOM, MAL-QOM, and BBT. While no differences were found between groups at post-intervention, the experimental group showed larger effect sizes than those in the control group. Overall, the present study finding highlighted the positive impact of BCI combined with MP and OT on UL sensorimotor recovery, ADL performance improvement, and participation in subacute post-stroke individuals.

Brain-computer interface is a promising strategy for treating and recovering functions, specifically UL motor skills (55). A meta-analytic study with 235 subjects suggested that BCI may be an effective intervention for post-stroke UL motor rehabilitation (6).

In the same sense, it is clinically known that improvement in motor skills does not always mean improvement in functional independence and performance in ADL. Few studies using the BCI clearly showed functional motor responses in the UL (18, 55, 56). However, the question remains whether UL motor improvements can favor performance in ADL.

In order to clarify this scientific gap, this study aimed to investigate the effects of BCI combined with MP and occupational therapy (OT) on the manual function to improve performance in executing ADL and increase the social participation of stroke survivors in the subacute phase.

The experimental group showed a statistically significant improvement in all activity and participation assessments. This fact explains why BCI can provide an additional opportunity to engage in ADL, taking advantage of a good window of plastic recovery of the central nervous system in a shorter time, increased cortical excitability, and reorganization of the neural network of the injured hemisphere, as well as, allowing relearning of movement patterns more similar to what was expected in daily activities with a positive impact on performance in real-world ADL (57, 58).

TABLE 2 Result of the primary outcome performance in activities of daily living and participation assessed by the functional independence measure, motor activity log, box and blocks test, and Jebsen hand functional test.

	Experimental				Control			
	Baseline	Post	*p*	Cohen's *d*	Baseline	Post	*p*	Cohen's *d*
FIM	97.6 ± 22.2	109.6 ± 20.4*	0.001	0.56	99.4 ± 20.4	105.3 ± 19.4	0.072	0.29
MAL-AOM	0.5 ± 0.6	1.4 ± 1.3*	0.001	0.83	0.4 ± 0.3	0.7 ± 0.5*	0.001	0.72
MAL-QOM	0.6 ± 0.9	1.7 ± 1.6*	0.006	0.84	0.7 ± 0.6	1 ± 0.6*	0.013	0.50
BBT	12.2 ± 12.6	17.9 ± 15.3*	0.004	0.40	11.1 ± 9.8	13.5 ± 11.2*	0.005	0.23
JHFT	254.6 ± 239.8	159 ± 176.3*	0.001	0.45	222 ± 171	232.8 ± 210.1	0.683	0.05

Cohen's *d*: trivial for $d < 0.20$, small for $0.20 \leq d < 0.50$, moderate for $0.50 \leq d < 0.80$, and large for $d \geq 0.80$. FIM, functional independence measure; MAL, motor activity log; AOM, amount of movement; QOM, quality of movement; BBT, box and blocks test; JHFT, Jebsen hand functional test. *$p \leq 0.05$.

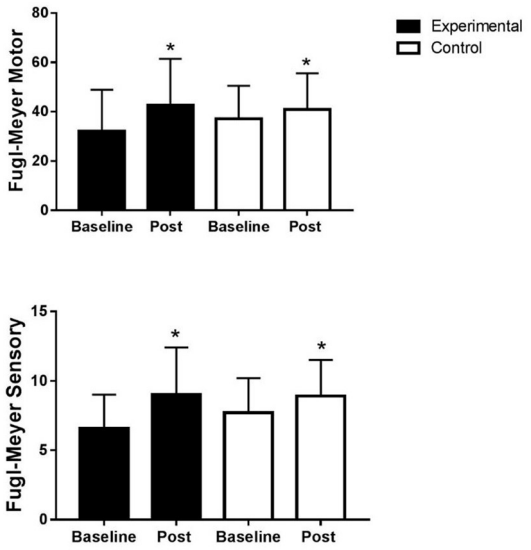

FIGURE 3
Motor and sensory function of the upper limb assessed by Fugl-Meyer. Fugl-Meyer experimental motor domain (32.1 ± 16.8 vs. 42.6 ± 18.8), sensory domain (6.6 ± 2.4 vs. 9 ± 3.4), control motor domain (37 ± 13.6 vs. 40.9 ± 14.7), and sensory domain (7.7 ± 2.5 vs. 8.9 ± 2.6). *Wilcoxon test, $p \leq 0.05$.

The improvement in functional independence and the marked increase in activity/participation in the experimental group are explained by the fact that during the BCI protocol, functional tasks were trained using mental practice and later in the effective training of these same functional tasks. In addition, mental practice with functional tasks improved the quality of movement and performance in ADL on the affected side (56, 59).

In the same sense, teaching through observation, imagination, and execution with parameters of the best forms and movement patterns to perform an activity during mental practice with functional tasks has also influenced the quantity and quality of the use of the UL in ADL, evaluated by the motor activity log.

An interesting result was that the control group showed a significant response in two of the four scales for the primary outcome (MAL—qualitative and quantitative and in the BBT), with the effect size for the experimental group being larger. Similar results were observed in a randomized clinical trial using BCI in combination with other therapies, where both groups showed functional improvement after the interventions (55). However, the functional gains obtained on standardized scales were greater in the experimental group, demonstrating the positive role of BCI in post-stroke rehabilitation.

The combined use of BCI with rehabilitation interventions such as physical therapy and occupational therapy appears promising for treating functional problems. Previous studies have found similar results when using BCI associated with conventional therapy, especially in improving motor function (11, 60, 61). Thus, the association between BCI, mental practice, and occupational therapy may have enhanced the reorganization of cortical function, offered centrally and peripherally, improving motor control more than in patients undergoing isolated therapies.

Previous studies suggest [reviewed in (62)] that combined multimodal therapies, similar to those used in our study, probably enhance the effectiveness of each technique, resulting in individual effects on cortical excitability while simultaneously improving sensory-motor processing. Multimodal therapies may partially explain the improvement observed in the experimental group. This approach may be more successful in promoting post-stroke functional recovery by allowing simultaneous access to the injured cortical network at the central and peripheral levels.

Finally, combining peripheral rehabilitation therapies with therapies that directly promote cortical excitability can help to lengthen the therapeutic window, thus offering a greater opportunity for physical and occupational therapies to promote recovery in everyday activities (63).

Both groups showed a statistically significant improvement for the secondary outcome, sensory and motor function, assessed by FMA. A likely explanation is that the groups received conventional therapy with a specific OT protocol. In parallel, the control group improved sensorimotor functions in the same way as the experimental group, probably because they were in the subacute stage of stroke. Bernhardt et al.

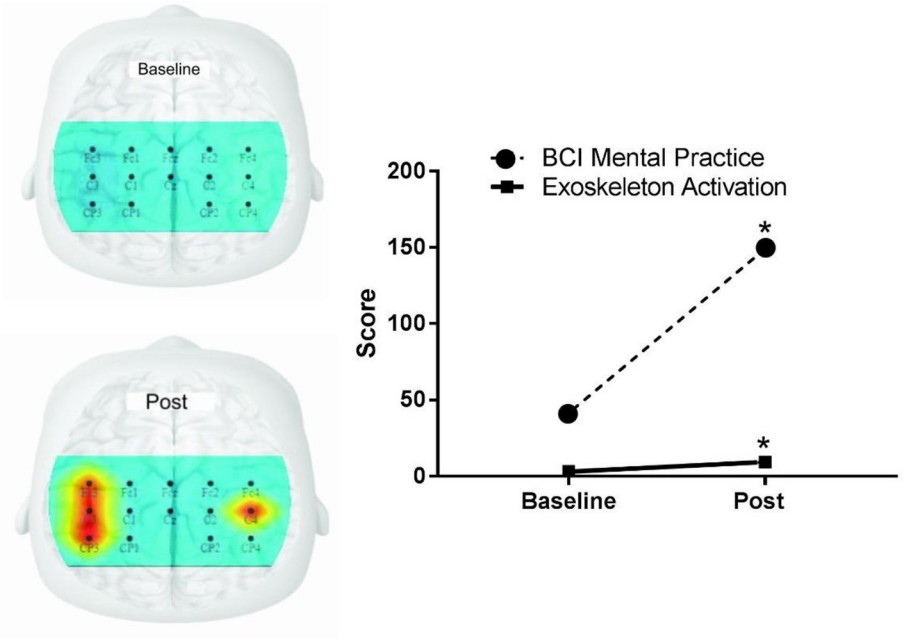

FIGURE 4
Activation of the premotor cortex, primary motor, primary somatosensory brain areas, degree of motor imaginary, and exoskeleton activations through imagination. BCI, brain-computer interface. The image represents the target brain areas of the premotor cortex, primary motor, and primary somatosensory, measured using the 10-10 electroencephalogram system. The hot color indicates greater activation in both cerebral hemispheres. Skeletal activation indicates how many times the orthosis has been moved through thought.

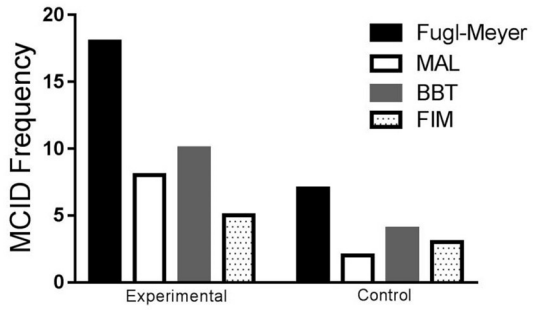

FIGURE 5
Frequency of participants that achieved the minimum clinically important difference in both groups for the Fugl-Meyer, MAL, BBT, and FIM. MCID, minimal clinically important difference; MAL, motor activity log (MCID 1.0); Fugl-Meyer (MCID 5.25); BBT, box and blocks test (MCID 5.5/min); FIM, functional independence measure (MCID 22).

(22) showed that in the subacute stage of stroke, there is a decrease in neuroinflammation and an increase in spontaneous cortical reorganization. Finally, this spontaneous reorganization is often associated with limited restoration of function, and the rehabilitation process is essential for directing and supporting adaptation to avoid the maladaptive plasticity of neural circuits (7, 9).

TABLE 3 Delta and minimal clinically important difference.

	Experimental	Control	MCID
	Delta	Delta	
FIM	12 ± 1.8	5.9 ± 1	22
MAL-AOM	0.9 ± 0.7	0.3 ± 0.2	1.0
MAL-QOM	1.1 ± 0.7	0.3 ± 0	1.0
BBT	5.7 ± 2.7	2.4 ± 1.4	5.5
JHFT	95.6 ± 63.5	10.8 ± 39.1	–

FIM, functional independence measure; MAL, motor activity log; AOM, amount of movement; QOM, quality of movement; BBT, box and blocks test; JHFT: Jebsen hand functional test. Delta represents differences between pre- and post-intervention within each group. MCID represents the cut-off values; for more details, refer to the "Methods" section.

Promisingly, BCI may be instrumental in opening an instant window into brain activity and mechanisms that support functional recovery, even if brain activation is not in the specific injured area. However, improving synaptic projections and connections can promote overall improvement in the functioning brain. The view is that BCI not only allows direct control of a robotic device to restore or improve patients' performance but also feeds back into ongoing brain changes related/induced by the BCI-guided exercise itself. Despite the improvement in sensory and motor function in both groups, the experimental group showed larger effect sizes.

Another finding, referring to the secondary outcome, was the increase in the degree of motor imagery and the number of activations of the exoskeleton device during the "Think" phase. The software used captures the neurophysiological signals during the mental practice and transforms them into a degree of motor imagery, which, if kept by the patient within the minimum threshold, leads to activations of the orthosis. Therefore, it is expected that increasing the degree of motor imagery will also result in an increase in the number of activations. This finding about the increase in imagery and device activations can be explained by the learning generated from the repetitions that the BCI provides and the stimulus to mental practice.

The minimum clinically important difference is an important metric, as not every score increase can be translated into clinically relevant improvements. The proportion of patients who achieved MCID was higher in the experimental group compared to the control group. Specifically, concerning the MAL-AOM, MAL-QOM, and FMA motor domains, the fraction of participants receiving BCI combined with MT and OT who reached clinically meaningful improvements was higher than that of the control group. No differences were found in other outcomes. One of the explanations could be that treatment in the experimental group focused more on the upper extremity motor impairments, while gross manual dexterity and functional independence were equally targeted in both arms of the trial. Additionally, it should be noted that the MCID is affected by the initial severity of the impairment, the sample's heterogeneity, and the scale's ordinal nature (64, 65). Thus, the responsiveness along Likert-type scales could be affected (66).

Although no differences were found between the groups, participants in the experimental group showed statistically significant differences at baseline and post-intervention in outcomes that the control group did not achieve. An improvement was expected in the control group because the patients were undergoing an occupational therapy protocol and they were in the subacute phase, in which recovery following rehabilitation is expected (51). Remarkably the experimental group showed improvements in more outcomes than the control group.

This study has some limitations. The sample size ($n = 44$) was small. Nevertheless, the error for type II sample analysis was not influenced. Some subjects ($n = 11$) were unable to perform the JHFT; thus, the effect of the study interventions on fine and gross motor hand functions should be interpreted cautiously. Additionally, even if the outcome measures for assessing UL sensorimotor performance used in the study report satisfactory psychometric properties, laboratory-based assessments such as the kinetics and kinematics of UL could provide more information on the quality of movement. We also consider the large heterogeneity of the sample as a limitation, represented by the large standard deviation in each sample; we suggest that future studies time-stratify stroke onset. Finally, the study design did not control for relevant social participation factors of participants, i.e., work status and retirement. The factors mentioned above should be considered when planning future studies.

Conclusion

The study showed a positive trend in the clinical effects of the combined use of BCI with mental practice and occupational therapy in the aspects of sensory, motor, and functional independence recovery. BCI is a potential new strategy to improve performance in ADL and social participation in individuals with stroke, specifically in the subacute phase. Future studies are needed to confirm these findings and determine new neurofunctional bases.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee for Human Research at the Federal University of Sergipe. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AZ: idea conception, text writing, and collected the data. DP: text writing and data analysis. VS: text writing and collected the data. KS, MBa, and LS: text writing. MBo: data analysis and revision process. SS: revision process, results' analysis, editing, language, grammar, and concept revision. KM-S and RD: revision process and results' analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Descriptive analysis of post-stroke patients in a neurological physical therapy unit

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Introduction: Physical therapy (PT) is the mainstay treatment in functional recovery after suffering a stroke. It is important in the acute phase of hospitalization after a stroke and later in the ambulatory phase.

Patients and methods: The present study aimed to analyze the data provided by the clinical history (CH) of people with stroke (pwS) who received PT treatment in order to establish a "preferential patient profile" (PPP) that may benefit more from an early PT treatment. This was an observational, descriptive, and cross-sectional study. A total of 137 pwS who had been treated with PT were selected. Information provided age, gender, stroke type and localization, and start and end dates of the different PT treatments. A descriptive analysis of the variables was conducted using absolute frequencies and percentages for the qualitative variables. Student's *t*-test or the Mann–Whitney *U*-test was used to determine the relationship between the time and variables "stroke type," "outpatient," and "occupational therapy." The Kruskal–Wallis *H*-test was applied for the "localization" variable.

Results: Of the entire sample, 57.7% were men, 65% had an ischemic stroke, and 48.9% had a stroke on the left side. The patients with hemorrhagic stroke had an increased number of hospital PT sessions ($p = 0.01$) and were younger (59.58 years) than patients with ischemic stroke (65.90 years) ($p = 0.04$).

Discussion and conclusion: Our results do not show significant differences between the persons <65 years and the number of outpatient physiotherapy sessions performed, although the resulting values are close to significance. Our results suggest that the PPP is a young person, with a hemorrhagic and left or bilateral stroke.

KEYWORDS

stroke rehabilitation, outpatients, inpatients, neurological rehabilitation, physical therapy department, hospital, early ambulation

Introduction

Cerebrovascular accident (CVA), due to its high rate and prevalence, is a disease of great health and social impact. In Europe, the estimated prevalence of stroke is 9.2%, with a rate of 191.9/100,000 people/year (1). In Spain, according to the Spanish Institute of Statistics, in the year 2020, a total of 25,817 people died of cerebrovascular diseases (2). It is estimated that between 25 and 74% of persons who survive this disease require assistance or become fully dependent on their activities of daily living (3). The main residual post-stroke disabilities include motor disorders, paralysis, cognitive deterioration, dysphagia, and speech disorders (4). Therefore, CVA is one of the pathologies with greater social and economic repercussions at the international level, as well as one of the most important causes of disability in adults (5, 6). Currently, the social impact of this disease is even greater than the increase of CVA cases in young adults of working age, with ∼5–10% of strokes occurring in people under 50 years of age (7), which results in the loss of years of healthy life and productivity (8). In the last decades, Spain has been advancing in diagnosing and treating these persons, improving their care and recovery (9).

Depending on the phase of the disease, there are two main scopes of assistance in pwS (9): (1) the hospitalization phase or acute phase (from the onset of the symptoms to the hospital discharge), in which the treatment must be applied by a multidisciplinary team, including physical therapy (PT) (10); and (2) the subacute phase (3–6 months after the stroke), in which the PT treatment is essential to prevent complications and recover the patient's maximum functional capacity possible, to maximize his/her personal autonomy and his/her family and social reintegration (11). In this phase, PT can be performed as outpatient treatment (home care), in a hospital scope (12), and a medium- or long-stay center or hospice, depending on the clinical and/or social situation of the pwS. Hospital PT after suffering a stroke produces improvements in all patients, regardless of their age; however, age reversely predicts a good functional result (13) (the younger the patient, the better the results). There is a third and final phase of sequelae, in which some authors report a functional improvement after 12 months, in cases who received PT treatment, and a progressive functional deterioration in the absence of specific therapies (14, 15).

The role of PT in pwS must begin after an initial evaluation aimed at establishing a PT diagnosis from the results obtained in it. This diagnosis is based on the International Classification of Functioning, Disability, and Health (ICF), which considers deficiencies in bodily functions and structures, activity limitation, participation restriction, and existing contextual factors, both environmental and personal (12, 16). This allows for establishing the prognosis and the treatment objectives and developing a PT intervention plan (17, 18).

The pwS's degree of recovery depends on different factors, such as the amount of brain tissue affected, age, localization of the damaged area, early rehabilitation, and environmental and psychosocial factors (19). Studies such as that of Kleim and Jones (20) support the idea of experience-dependent plasticity, which is understood as the capacity of the brain to re-adapt in response to an experience or task (20). Although the capacity of the brain to adapt and compensate for the effects of an injury is lower in adults than in earlier stages of life, it has been reported that the capacity to recover is present in all ages (21). Moreover, there are genetic and non-genetic protective factors that influence the process of neuronal plasticities, such as age, education, the importance of the injury, and the behavioral characteristics of the patient (6, 22).

Thus, the aim of PT is to help the pwS to maintain the existing abilities after the CVA, recover the lost abilities, and learn new abilities (23) through neuroplasticity.

The aim of the present study was to associate the variables, stroke type (hemorrhagic/ischemic), brain localization, and person's age and sex, with the number of sessions received in the different phases of both hospital and outpatient PT, as well as the waiting time between sessions. Specifically, we analyzed whether the preference criteria for starting the outpatient PT treatment, monitored in the Neurological PT Unit of a Spanish hospital, for pwS under 65 years of age, correlated with significant differences in the number of PT sessions performed, in order to establish a "preferential patient profile" (PPP) that could benefit more from an early start of the outpatient PT treatment.

Materials and methods

Study design

A descriptive, cross-sectional, and correlational study was carried out with 137 pwS who had been treated with PT in the hospital phase or ambulatory phase in the Neurological PT room of Virgen del Rocio University Hospital (Seville, Spain).

Participants

The inclusion criteria were as follows: pwS treated in the PT unit (hospital or ambulatory phase) affected by ischemic or hemorrhagic stroke during the period between 10 July 2014 and 25 April 2018 (4 years). On the other hand, the study excluded those persons who had suffered more than one stroke event, died during the study, or received the PT treatment in the sequelae phase (at least 1 year after the stroke) (Figure 1).

A total of 172 clinical histories (CHs) were reviewed, of which 35 were discarded for being incomplete or not meeting the inclusion criteria. Finally, 137 pwS were included, who were attended to in the abovementioned period (Figure 1).

Interventions

After fulfilling the eligibility criteria, the CH of each pwS was analyzed, guaranteeing the safety and confidentiality of the gathered data at all times. The data were extracted from the computer-based registry, which included the following variables:

- Demographic data: age and sex.
- Clinical PT treatment; the start and end dates from the hospital data: stroke type (hemorrhagic/ischemic); lesion side (right/left/bilateral); start date of the hospital PT treatment;

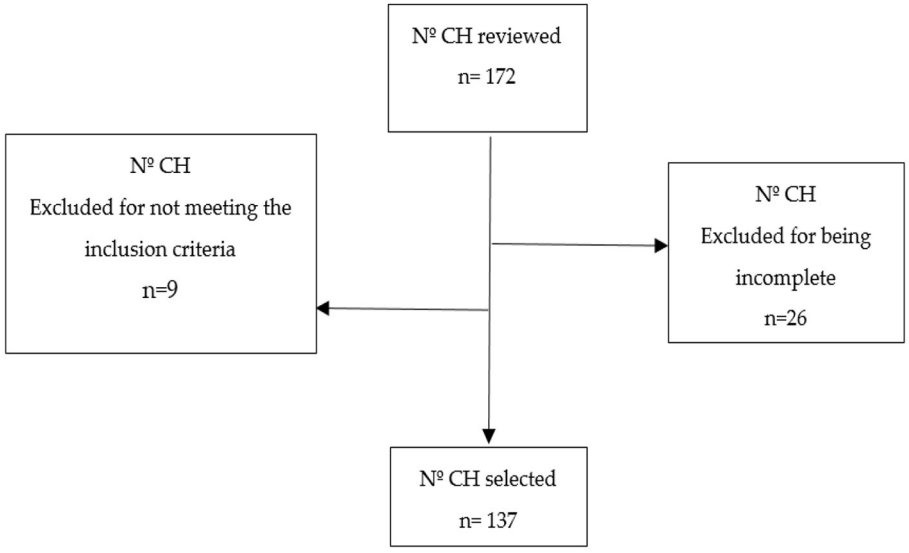

FIGURE 1
Sample selection process. CH, clinical history.

hospital discharge date (which coincides with the end of the hospital PT treatment); start date of the outpatient PT treatment (in the neurological PT room); PT discharge date; having or not having received home PT treatment from the rehabilitation and PT mobile units (from the hospital discharge to the start of the outpatient PT treatment); and having or not having received occupational therapy treatment in the outpatient phase.

Outcome measures

A senior PT with over 10 years of clinical experience in neurological PT collected the CH at the beginning of the analysis. The gathered data were registered in a database created with Microsoft Excel 2013 software for Windows.

Statistical analysis

The statistical processing of the data was conducted with IBM SPSS statistical package Version 19.0. A descriptive analysis of the study variables was conducted using absolute frequencies and percentages for the qualitative variables. The quantitative variables, based on their asymmetry, were summarized as M ± SD (mean and standard deviation) and range (minimum and maximum) or P50 [P25–P75] (median, interquartile range). The normality of the distributions was verified using the Kolmogorov–Smirnov test. To determine the relationship between the time and variables "stroke type," "outpatient," and "occupational therapy," a Student's *t*-test or Mann–Whitney *U*-test was conducted, depending on the normality of the variables. In the case of the variable "localization," the Kruskal–Wallis *H*-test was applied since the time did not follow a normal distribution. After verifying the times' distribution normality, the association among them was determined through Spearman's correlation coefficient (rho), as they did not show a normal distribution. The level of statistical significance was established at $p < 0.05$.

Role of the funding source/ethics

No sponsor was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

The trial design complied with the ethical guidelines set in the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of Virgen Macarena and Virgen del Rocio University Hospitals of Seville (code: TFG-ICT-2018-01).

Data availability

The data associated with the article are not publicly available, although they are available from the corresponding author upon reasonable request.

Results

One-hundred and thirty-seven pwS (79 men, 57.7%; 58 women, 42.3%; mean age 63.69 ± 12.377 years) were included in the study. The division of the sample is shown in Figure 2.

Of the 137 pwS, 107 received PT treatment during their hospital stay, with an average of 16.98 ± 23.063 treatment days. There was an average period of 9.91 ± 7.372 days between the stroke event and the beginning of the PT treatment. After the hospital discharge, the pwS waited 44.97 ± 27.087 days until the start of the outpatient PT treatment, which had an average duration of 121.27 ± 67.456 days (Table 1).

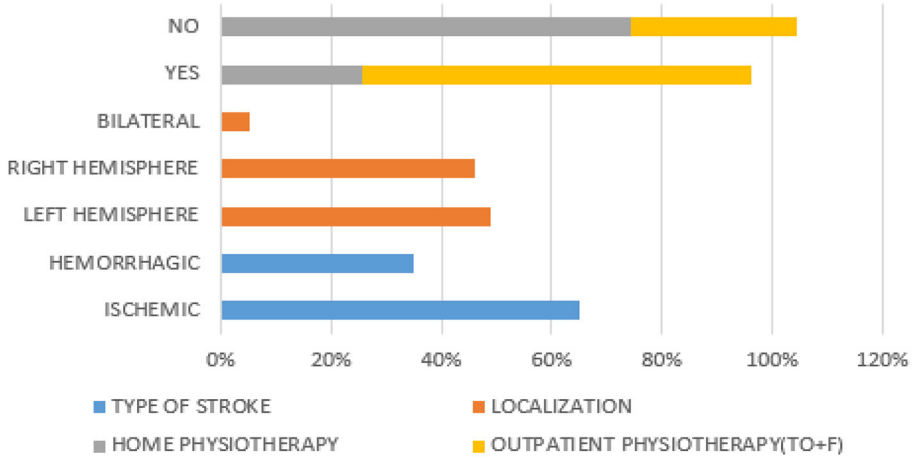

FIGURE 2
Proportional distribution of study outcomes.

TABLE 1 Variables "stroke type" and "localization": Student's *t*-test and weighted average.

	TS	M ± SD	P_{50}	Localization	M ± SD	P_{50}	Median	SD
Age	H	59.58 ± 12.06	59	B	61.71 ± 12.33	60	63.69	12.377
	I	65.69 ± 12.038	69	R	64.68 ± 10.65	66		
				L	62.96 ± 13.90	66		
Outpatient physiotherapy	H	134.40 ± 80.33	130.5	B	122.29 ± 36.45	147	121.27	67.456
	I	114.03 ± 58.433	106	R	11.56 ± 63.28	100		
				L	130.01 ± 72.88	122		
Hospital physiotherapy	H	26.02 ± 28.328	13.5	B	19.25 ± 12.31	15	16.98	23.063
	I	11.14 ± 16.689	6	R	14.46 ± 22.66	6.50		
				L	19.02 ± 24.04	10		
Early physiotherapy	H	12.93 ± 10.15	9	–	–	–	9.91	7.372
	I	8 ± 3.905	7					
Waiting time in the room	H	43.85 ± 26.715	39	–	–	–	44.97	27.087
	I	45.70 ± 27.515	39					

General statistical values of the study variables of the sample. TS, type of stroke; M ± SD, mean ± standard deviation; H, hemorrhagic; I, ischemic; B, bilateral; R, right; L, left.

The sample was differentiated based on the variables "stroke type" and "stroke localization," performing a descriptive analysis and establishing correlations of each of them with the rest of the variables, especially with the duration (in days) of the different PT phases. With respect to the localization of the brain hemisphere affected, we differentiated among the right, left, and bilateral (massive) strokes. The mean number of PT sessions received, during both the hospitalization and outpatient phases, was larger in bilateral and left strokes (Table 1). A larger number of pwS had ischemic strokes with an affectation of the right hemisphere [45], followed by a left ischemic stroke [41] (Table 1).

The number of PT sessions received, both during the hospital stay and in the outpatient room, and the number of days between the stroke event and the start of the PT treatment (early PT) were larger in persons with hemorrhagic strokes. However, the waiting time between hospital discharge and the start of the outpatient PT was similar in both stroke types (Table 1).

The sample was differentiated based on the variables "stroke type" and "localization," performing a descriptive analysis and establishing correlations of each of them with the rest of the variables, especially with the duration (in days) of the different phases of the PT treatment. A larger number of pwS had an ischemic stroke of the right hemisphere [45], followed by a left ischemic stroke [41] (Table 2).

To determine the correlations of "stroke type" with "age" and "outpatient PT," Student's *t*-test was used (Table 3), obtaining a significant difference ($p = 0.04$) in patient age in relation to the type of stroke, with hemorrhagic strokes being less frequent (in younger pwS). Student's *t*-test was also applied to analyze the correlation between the variable "occupational therapy" and the number of sessions of outpatient PT performed, obtaining a significant result

TABLE 2 Contingency table: Localization type of stroke.

			TS-H	TS-I	Total
Localization	B	Count	4	3	7
		% Type of stroke	8.3%	3.4%	5.1%
	R	Count	18	45	63
		% Type of stroke	37.5%	50.6%	46.0%
	L	Count	26	41	67
		% Type of stroke	54.2%	46.1%	48.9%
Total		Count	48	89	137
		% Type of stroke	100.0%	100.0%	100.0%

TS, type of stroke; H, hemorrhagic; I, ischemic; B, bilateral; R, right; L, left.

TABLE 3 Correlation of the number of outpatient physiotherapy sessions performed for each stroke type with "age" and "occupational therapy" (Student's *t*-test).

	TS	*N*	Median	Mean (SD)	*P*
Age	H	48	59.58	12.063	**0.04***
	I	89	65.90	12.038	
Outpatient physiotherapy	H	48	134.40	80.330	0.127
	I	87	114.03	58.433	
Outpatient physiotherapy with OT	–	96	138.19	69.355	–
Outpatient physiotherapy without OT	–	39	79.64	38.974	**0.001***

TS, type of stroke; H, hemorrhagic; I, ischemic; N, number of cases; OT, occupational therapy; SD, standard deviation; P, p-value of Student's t-test. The bold values are statically significant values (< 0.05). The symbol * is for the bold statically significant values.

TABLE 4 Correlation between the type of stroke and the different hospital physiotherapy variables (Mann–Whitney *U*-test).

	Type of stroke	*N*	Average range	*P*
Hospital physiotherapy	H	42	66.32	**0.01***
	I	65	46.04	
Early hospital physiotherapy	H	41	60.12	0.77
	I	65	49.32	
Waiting time in the room	H	41	51.68	0.824
	I	63	53.03	

H, hemorrhagic; I, ischemic; N, number of cases; P, Mann–Whitney U-test. The bold values are statically significant values (< 0.05). The symbol * is for the bold statically significant values.

of $p = 0.001$ (Table 3). A total of 70.8% of patients received outpatient occupational therapy in combination with PT (Table 1).

The correlation with the waiting days between the end of the hospital PT and the start of the outpatient PT was conducted with the Mann–Whitney *U*-test (Table 4).

There was a statistically significant difference between the number of hospital PT sessions received and the type of stroke, with a larger number of sessions being received by people with hemorrhagic stroke ($p = 0.01$).

TABLE 5 Correlations of "stroke localization" with "age," "outpatient physiotherapy," and "hospital physiotherapy" (Kruskal–Wallis test).

	Localization	*N*	Average range	*P*
Age	B	7	61.64	0.727
	R	63	71.62	
	I	67	67.31	
	Total	137		
Outpatient physiotherapy	B	7	74.00	0.299
	R	61	62.25	
	I	67	72.61	
	Total	135		
Hospital physiotherapy	B	4	75.63	0.133
	R	48	48.52	
	I	55	57.21	
	Total	107		

B, bilateral; R, right; L, left; N, number of cases; P, Kruskal–Wallis test.

TABLE 6 Correlation of "age" with the number of sessions of outpatient physiotherapy and the number of waiting days (Spearman's correlation coefficient).

Age	Outpatient physiotherapy	Waiting time in the room	*P*
<65	132.67 ± 75.423	41.17 ± 24.438	0.064
≥65	110.04 ± 56.914	48.77 ± 29.24	0.778

P, Spearman's correlation coefficient.

The correlation of "stroke localization" with "age," "outpatient PT," and "hospital PT" was analyzed using the Kruskal–Wallis *H*-test, obtaining no statistically significant differences in these correlations. The duration of both PT phases was longer for bilateral (massive) and left strokes (Table 5).

The variable "age" was divided into two subgroups (pwS < 65 years of age and pwS ≥ 65 years of age), and it was correlated with the number of sessions of outpatient PT, the number of waiting days from the end of the hospital PT, and the start of the outpatient PT treatment. To this end, Spearman's correlation coefficient (rho) was applied, obtaining no statistically significant differences between these variables (Table 6).

Discussion

At the descriptive level, the results are in agreement with those obtained in previous studies regarding the epidemiology and rate of stroke. The average age of the pwS (63.69 years), the greater prevalence of ischemic stroke (65%) over hemorrhagic stroke (35%), and the greater frequency in male patients (57.7%), except between the age group over 85 years, are in line with those reported in previous studies conducted in Spain (24, 25) and in nearby countries (26–28).

At the regional level, it is recommended to evaluate the pwS as soon as possible, preferably in the first 24–48 h (except in cases of severe complications), and prescribe the start of a PT treatment (29). In the hospital scope, the scientific literature (18, 30–35) highlights the physical and psychological benefits of early mobilization after suffering a CVA. Bernhardt et al. (35) analyzed 30 clinical practice guides, of which 22 recommended early PT (to be started in the first 48 h after the CVA), whereas the other eight advised very early PT (in the first 24 h after the CVA). There is no consensus on the optimum time to start the PT treatment after a stroke (36). The AVERT study (37) (A Very Early Rehabilitation Trial) shows negative results in pwS with severe affectation or with intracerebral hemorrhage subjected to early intensive mobilization, whereas Murie-Fernandez et al. (38) concluded that, for each day of delay in the start of the rehabilitation treatment, the functional prognosis of the person at discharge is worse. This corroborates the need to base this decision on the characteristics of each pwS and establish a patient profile that benefits especially from an early PT treatment. Thus, there is no consensus at the international level on the start of early PT after a stroke. Most of the clinical practice guides recommend beginning mobilization 24 h after the stroke event, as soon as the vital problems are under control (39), whereas important studies such as AVERT (40) do not associate very early mobilization with a significant reduction of post-stroke disability. In any case, the results of our study show an average of 9.91 days from the stroke event to the start of the hospital PT ("early PT"), which was slightly lower in the ischemic strokes (7 days); this could be related to the greater severity of the symptoms of the hemorrhagic cases and the consequent delay in the patient stabilization (41). These results are consistent with the waiting times mentioned in subsequent studies (42). Thus, we propose starting the PT treatment as early as possible, with a more direct referral to the PT service. There is a commitment on the part of such service to carry out the first PT assessment and treatment no later than 24–48 h after receiving the request.

The number of PT sessions conducted during the hospital stay was larger in the pwS affected by hemorrhagic stroke and in those who presented bilateral affectation (massive stroke). Since the hospital PT treatment is administered until the pwS is discharged, we presume that, as they are cases of greater clinical severity, the duration of the hospital stay is longer and, consequently, the duration of this phase of the PT treatment is also longer. Previous studies (43) have shown that the appearance of a greater number of medical complications in this type of person tends to prolong their hospital stay (43). Given the heterogeneity in the use of evaluations in CH, the functional state of the pwS upon discharge could not be reported in this study; therefore, we cannot conclude that a larger number of hospital PT sessions also entails a larger number of subsequent outpatient PT sessions for the recovery of the patient.

Regarding the duration of the PT treatment, there was also a slight increase in the number of PT sessions received in the room by the pwS affected by hemorrhagic strokes compared to ischemic strokes; this is in line with the results of the literature, which reports a better functional prognosis in the long term for hemorrhagic strokes (32) as the hemorrhage resolves, the brain compression decreases, and the neurological functions are recovered, which could justify the continuity of the PT treatment due to the slower but favorable evolution of the process. The recovery from ischemic strokes is, on the other hand, faster in terms of evolution in time (44), which is in line with the results of our study, showing that these pwS required a smaller number of outpatient PT sessions to recover.

Taking into account the differences with respect to the localization of the brain injury, the number of hospital and outpatient sessions performed with respect to the localization of the stroke was not significant. However, in both cases (hospital and outpatient PT), the average number of PT sessions conducted was slightly larger in the bilateral and left strokes. Previous studies have shown that left strokes present better functional results in terms of locomotion and posture recovery (45, 46), which could justify the larger number of PT sessions received and the decision to maintain them under treatment, given the good evolution of the process and the recovery potential.

The analyzed CH did not provide information about the PT techniques used in the subacute phase of the stroke, and the literature shows evidence of the effectiveness of task-oriented motor re-learning techniques over conventional PT (47) and the combined use of the new virtual and robotic therapies (48), which could shorten the treatment duration and improve the functional results.

Regardless of the stroke localization, there is evidence of an interdisciplinary program of PT and occupational therapy conducted in the hospital that produces better functional results (49). In our study, most of the persons in the outpatient phase also received an occupational therapy treatment at the same time, although in small groups and independent from the PT treatment.

In the organizational planning, the early inclusion of pwS under 65 years of age was already considered based on the hypothesis that, due to neuronal plasticity, the recovery capacity of the younger pwS would be greater if the PT treatment began earlier (13, 50). Our results do not show significant differences between the pwS <65 years and the number of outpatient PT sessions performed, although the resulting values are close to significance. These pwS carried out a larger number of PT sessions and their waiting time was slightly shorter. Due to the insufficient information provided by the analyzed CH about scales of functional valuation upon discharge from outpatient PT, we cannot draw objective conclusions about the greater recovery capacity of younger pwS.

The heterogeneity in the functional evaluations carried out during the PT treatment of the analyzed CH was the key limitation of this study since it hindered the establishment of objective conclusions regarding the functionality of the pwS at the start and end of the different PT phases.

As a future research line, it would be necessary to homogenize the existing functional scales for pwS and apply them unavoidably both in the initial PT evaluation and at the end of the treatment.

We can conclude that the PPP for the early start of the outpatient PT in our service is that of a young pwS, with left or bilateral hemorrhagic stroke. A more direct referral to the PT service could shorten the waiting times. The establishment of a definitive profile requires the homogenous valuation of the functional state at the beginning and end of the PT treatment, thus establishing the PPP that would benefit more from an early start and a larger number of sessions, with the latter aspect being justified by the greater recovery potential of such PPP. Future studies should

carry out homogeneous functional reviews that justify the efficient way to rehabilitate the PPP.

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 Institutional Research Ethics Committee of Virgen Macarena and Virgen del Rocio University Hospitals, of Seville, Spain, (protocol code TFG-ICT-2018-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MP-M, CL-M, IE-P, EM, DL-A, AG-M, and EP-P reviewed and edited the manuscript. AG-M funding acquisition. All authors approved the final version of the manuscript.

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Conflict of interest

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

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Innovative vision rehabilitation method for hemianopsia: Comparing pre- and post audio-luminous biofeedback training for ocular motility improving visual functions and quality of life

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Background: Homonymous hemianopsia (HH) corresponds to vision loss in one hemi-field secondary to retro-chiasmal injury. Patients with HH experience difficulties in scanning and orientation in their environment. Near vision daily activities such as reading can also be impaired. There is an unmet need for standardized vision rehabilitation protocols for HH. We investigated the effectiveness of biofeedback training (BT), used for vision rehabilitation in patients with central vision loss, in individuals with HH.

Methods: In this prospective pilot pre/post study, 12 participants, with HH consecutive to brain injury, performed 5 weekly BT sessions for 20min each under supervision using the Macular Integrity Assessment microperimeter. BT consisted of relocation of the retinal locus 1–4° toward the blind hemi-field. Outcomes measured post-BT were paracentral retinal sensitivity, visual acuity (near vision), fixation stability, contrast sensitivity, reading speed, and visual functioning questionnaire. Statistical analysis was performed using Bayesian paired t-tests.

Results: Paracentral retinal sensitivity significantly increased by 2.7±0.9dB in the treated eye in 9/11 of the participants. Significant improvements with medium-to-large effect size were observed for fixation stability (8/12 participants), contrast sensitivity (6/12 participants) and near vision visual acuity (10/12 participants). Reading speed increased by 32.5±32.4 words per minute in 10/11 participants. Quality of vision scores improved significantly with large effect size for visual ability, visual information and mobility.

Conclusion: BT led to encouraging improvements in visual functions and functional vision in individuals with HH. Further confirmation with larger trials is required.

KEYWORDS

biofeedback training - BT, hemianopia or hemianopsia, rehabilitation, vision, visual fields, microperimetry sensitivity, fixation stability, quality of life

Introduction

Patients with brain injury frequently suffer from homonymous hemianopsia (HH), defined as vision loss in one vertical hemi-field secondary to a retro-chiasmal lesion (1–4). In HH, impaired eye movements lead also to defective visual and spatial scanning and exploration. This defective scanning on the blind hemifield affects orientation and mobility, the ability to walk independently and as such, the quality of life (1–3). Moreover, because of the visual field loss, the subjective midline deviates affecting balance and contributing to an increase in risk of falling (5).

Central vision can also be affected in hemianopsia due to a parafoveal field loss with splitting of fixation and poor eye movements leading to reading deficit. Left-to-right readers with a right HH have particularly impaired reading abilities. For efficient reading, three to four letters to the left and seven to 11 letters to the right of fixation must be seen (1, 4, 6). Patients with right HH have trouble locating ensuing words, making systematic saccades to find those words. Additionally, there is prolonged fixation, disrupted saccadic amplitude, and an increased number of regressive saccades. Because parafoveal vision is used to obtain information about forthcoming words, patients with 3°–5° of macular sparing tend to have minimal impairment of reading (1, 4, 6).

Patients with HH naturally develop oculomotor strategies to compensate for visual field loss, however, these strategies are often suboptimal and oculomotor control is impaired (1). To scan the blind hemi-field, patients perform dismetric saccades with increased amplitude (7, 8). Fixation stability and landing accuracy decrease, affecting visual acuity (9, 10).

Biofeedback training (BT) is a compensatory rehabilitation technique that emerged three decades ago and has been used in various fields of medicine, including ophthalmology (11, 12). BT is one of the newest and more modern low vision rehabilitation techniques. By increasing the oculomotor control and relocating the visual fields through a change in the patient's locus of fixation, BT improves the visual acuity for distance, near vision, contrast sensitivity, retinal sensitivity, reading speed, and quality of life in many eye conditions. Mounting evidence has highlighted the benefits from BT in age-related macular degeneration, myopic degeneration, Stargardt's disease, glaucoma, and nystagmus (13–19). The studies show similar effectiveness using 4–10 sessions of BT, varying from 10 to 20 min each, although a minority of them followed the patients on a long-term basis (15). Our department has treated more than 350 individuals with low vision using BT with benefits sustained up to 5 years. However, BT had never been used for visual rehabilitation in hemianopsia before this study.

The goal of this study was to use BT in an innovative way. Using our experience from different pathologies, we proposed a BT protocol specific to HH with the automated MAIA microperimeter. One of the symptoms in hemianopia is the loss of parafoveal visual references, causing oculomotor dysfunction. We hypothesized that relocating the fixation locus of the patients to an area with a larger span would improve oculomotor control and increase visual performance. A retinal locus with higher sensitivity and larger visual span was used on the seeing hemi-retina, or blind hemifield. A maximum of 4° of fixation relocation was allowed, in order to keep the better visual acuity from the parafoveal retina. This method would eliminate the splitting of fixation from the hemianopsia while improving the oculomotor function. BT is a technique that primarily increases the fixation stability and oculomotor control, perpetuating the benefit from field relocation.

Materials and methods

Study design/participants

The study was designed as a prospective, pilot, interventional pre/post, case series. Twelve patients were recruited from the Low Vision Clinic at the Toronto Western Hospital, University of Toronto, Canada. Criteria for inclusion were diagnosis of hemianopsia based on visual fields, brain injury from various etiologies, age between 18 and 90 years old, and ability to follow the visual, auditory stimuli, and training instructions. Exclusion criteria were previous treatment for low vision rehabilitation, significant underlying ocular pathology not related to the hemianopsia physiopathology, and cognitive impairment that prevents an adequate test and training performance. Patients had one baseline visit 1 (V1), five BT visits (V2-6), 1 week follow up visit (V7) and 1 month follow up visit (V8).

Twelve patients (Table 1) with hemianopsia were treated with 5 BT sessions (100 min in total) over a 5-week period without adverse events. Age ranged from 40 to 90 years old (average 66.6 ± 15.3). 58% of the subjects were female. The time post-brain injury ranged from 2.5 to 36 months, average 12.3 ± 9.5 months. Only P5 had less than 5 months from the injury. Most of the patients (9) had a stroke. None of the patients had macular sparing as defined by a 4° parafoveal normal sensitivity. Eight patients had a left hemianopsia, three had a right hemianopsia, and P10 had a bitemporal hemianopsia. The eye ipsilateral to the blind hemi-field and, for P10, the eye with the best fixation stability, was treated. P7 was excluded for being unable to comply with the tests (Table 1) and paracentral retinal sensitivity could not be recorded in P8 due to dizziness.

Ethics statement

The study was approved by the University Health Network Research Ethics Board, reference number 20-5618 (Toronto, Canada) and registered at ClinicalTrials.gov (NCT05397873A). Data was collected from July 2021 to November 2022. Written informed consent was obtained from all patients.

Apparatus and measures

During V1, paracentral retinal sensitivity or PRS (average from the 20 points from the 2 central columns from microperimetry C 10-2 68 stimuli program) was assessed using the Macular Integrity Assessment (MAIA) microperimeter (Centervue, Padova, Italy). Fixation stability (FS) was calculated by the MAIA software as a 63% bivariate contour ellipse area (BCEA 63%). A standard LED fixation target consisting of a small red circle of about 0.76° diameter was presented for microperimetry and fixation tests. To account for learning effect, FS was measured two times and the first results were disregarded. Monocular Best Corrected Visual Acuity (BCVA) was obtained for distance with Early Treatment Diabetic Retinopathy

TABLE 1 Participants' demographic.

ID	Age range	Sex	Ethnicity	Cause	Side	Time from event
P1	50s	M	Black	Stroke	L	7 months
P2	40s	F	Caucasian	Stroke	L	12 months
P3	70s	M	Caucasian	Herpetic Encephalitis	L	7 months
P4	60s	F	Caucasian	Neurosurgery	R	5 months
P5	80s	M	Latino	Stroke	L	2.5 months
P6	90s	F	Caucasian	Stroke	R	24 months
P8	50s	F	Caucasian	Stroke	L	10 months
P9	80s	F	Caucasian	Stroke	L	36 months
P10	60s	M	Asian	Neurosurgery	B	18 months
P11	80s	F	Caucasian	Stroke	L	12 months
P12	50s	F	Caucasian	Stroke	R	10 months
P14	50s	M	Asian	Stroke	L	5 months

M, male; F, female; L, left; R, right, B, bitemporal.

Study (ETDRS) charts at 4 m and for near vision with the 100% contrast Colenbrander continuous print chart. Reading speed was measured using the Minnesota Low Vision Reading Test application (MNRead test, University of Minnesota) (20). Contrast sensitivity was obtained binocularly using the Vision Contrast Test System (VCTS) chart at 1 meter on the 1 cycle/degree (cpd) channel of spatial frequency (21). Quality of visual function estimates were obtained from the Veteran's Affair Low-Vision Visual Functioning Questionnaire 48 (VA-LV-VFQ 48) (22). At 1-week post-treatment, all the baseline tests (V1) were repeated. Retinal sensitivity using microperimetry was collected 1-month post-BT to better assess the stability of the potential improvements over time. The distance of the TRL from the initial PRL, measured in degrees, was calculated using the recorded microperimeter pictures from the tests.

Treatment

BT involved luminous stimulation with auditory feedback performed on the MAIA microperimeter, biofeedback module (Centervue, Padova, Italy; Figure 1). After the patient completed the microperimetry C10-2 test on the same device, the ophthalmologist analyzed the retinal sensitivity map report to determine the retinal trained locus to be used for BT (TRL). This locus should be located no more than 4° from the fovea, and toward the seeing hemifield, to bring the patient's fixation locus to a larger span area on the retina (Figure 2). The TRL was selected on the screen on top of the microperimetry C10-2 report. The eye ipsilateral to the hemianopsia was trained or, in cases of bitemporal hemianopsia, the eye with better fixation stability.

The BT session involved the presentation of a standard LED fixation point consisting of a small red circle of about 0.76° diameter on the display monitor. The participant was instructed to look at the LED target while listening to the audio feedback. The participant was asked to move the eye toward the TRL under the technician's scrutiny. The fixation of the patient was monitored in real time on the device's screen. The auditory feedback changed according to the position of the eye. As the patient was guided to move the eye toward the TRL, the auditory feedback (intermittent beep) would increase frequency progressively, until the TRL was reached, and the auditory feedback would change to a continuous pattern. At this moment, a luminous white dot appeared at the TRL to produce the bimodal stimulation. During this task, the participant would actively control the eye movements and repeat consecutively this fixation in order to exercise the oculomotor control toward and at the TRL.

From V2 to V6, BT was performed weekly for 5 weeks. Each BT session was 20 min long representing a total of 100 min. Pauses were allowed whenever needed.

Data

Data analysis was based on descriptive statistics including, a measure of central tendency (median) and dispersion (minimum, 25th, 75th percentile and maximum). Eventual missing data were discounted from baseline and outcomes measures. Statistical comparisons between populations were performed by Bayesian paired t-tests (strength of evidence for H1 and Cohen's d) using JASP software.

Results

After a 5-week BT treatment, very strong evidence for an increase in PRS was observed with large effect size in 9/11 patients, from 17.2 ± 5.06 dB [7.15, 12.9, 20.3, 21.0] pre-treatment to 18.3 ± 5.71 dB [6.25, 15.6, 23.4, 23.8, post-T > pre-T BF_{+0} = 65.5, error % = 8.14e-7, d = 1.15, 95%CI (0.37, 2.01)] after treatment in the treated eye, indicating a restoration of visual perception at the border of the blind hemifield (Figures 2A,B; Supplementary Figure 1A). Interestingly, the fellow eye also showed moderate evidence of PRS improvement with medium size effect in 9/11 patients, from 15.1 ± 5.4 dB [1.80, 13.6, 18.6, 22.1] to 18.3 ± 5.91 dB [1.30, 15.3, 20.5, 22.4, post-T > pre-T BF_{+0} = 4.01, error % = 2.10e-4, d = 0.60, 95%CI (0.08, 1.26)] after

treatment (Figure 2A; Supplementary Figure 1B). The stability of gaze fixation also improved with moderate evidence and medium size effect as BCEA 63% decreased from $0.20 \pm 0.39^{\circ 2}$ [0.00, 0.17, 0.52, 1.20] at baseline to $0.10 \pm 0.29^{\circ 2}$, [0.00, 0.10, 0.10, 1.00, post-T < pre-T $BF_{-0} = 6.79$, error % = 6.46e-4, d = 0.67, 95%CI (0.12, 1.32)] after treatment in 8/12 patients (Figures 2C,D; Supplementary Figure 1C). Although no differences were observed in best corrected visual acuity (BCVA) at far distance (ETDRS chart at 4 m – not shown) after

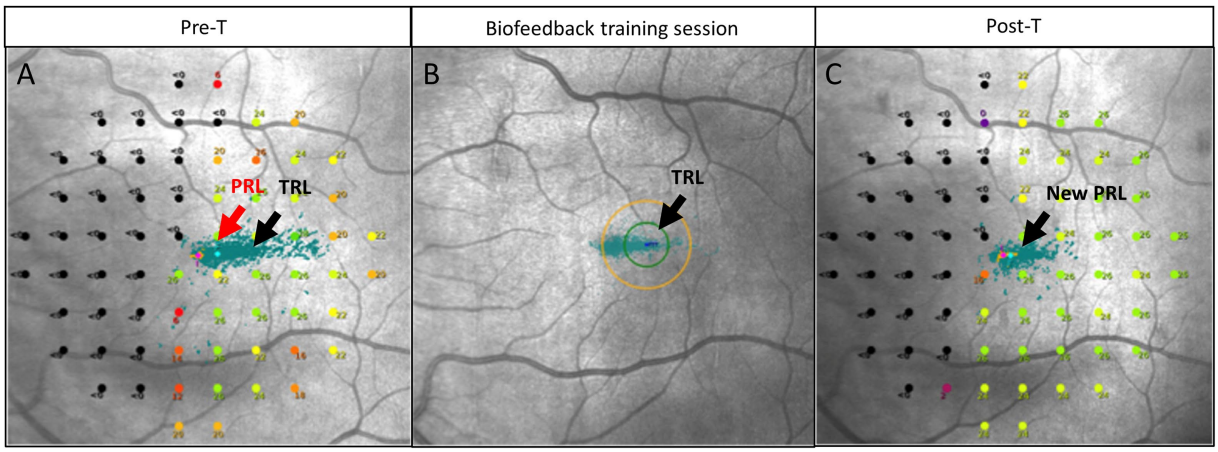

FIGURE 1
Principle of biofeedback training (BT). **(A)** Pre-BT microperimetry C10-2, left eye. Each green point is an attempt of fixation. Preferred retinal locus (PRL) center is located initially at a 22dB point, there is splitting of fixation. A trained retinal locus (TRL) was selected toward the seeing retina on a 25dB retinal point. **(B)** Biofeedback training session as reported by MAIA microperimeter: green dots—fixation attempts. Original PRL (on the left) has more fixation attempts (green dot), while BT training moves fixation points toward the TRL (on the right). **(C)** The center of the new PRL area is located at a 25dB retinal point. A temporal relocation occurred, and splitting of the fixation was mitigated. The microperimetry shown in C is a 2-year follow up for patient 2.

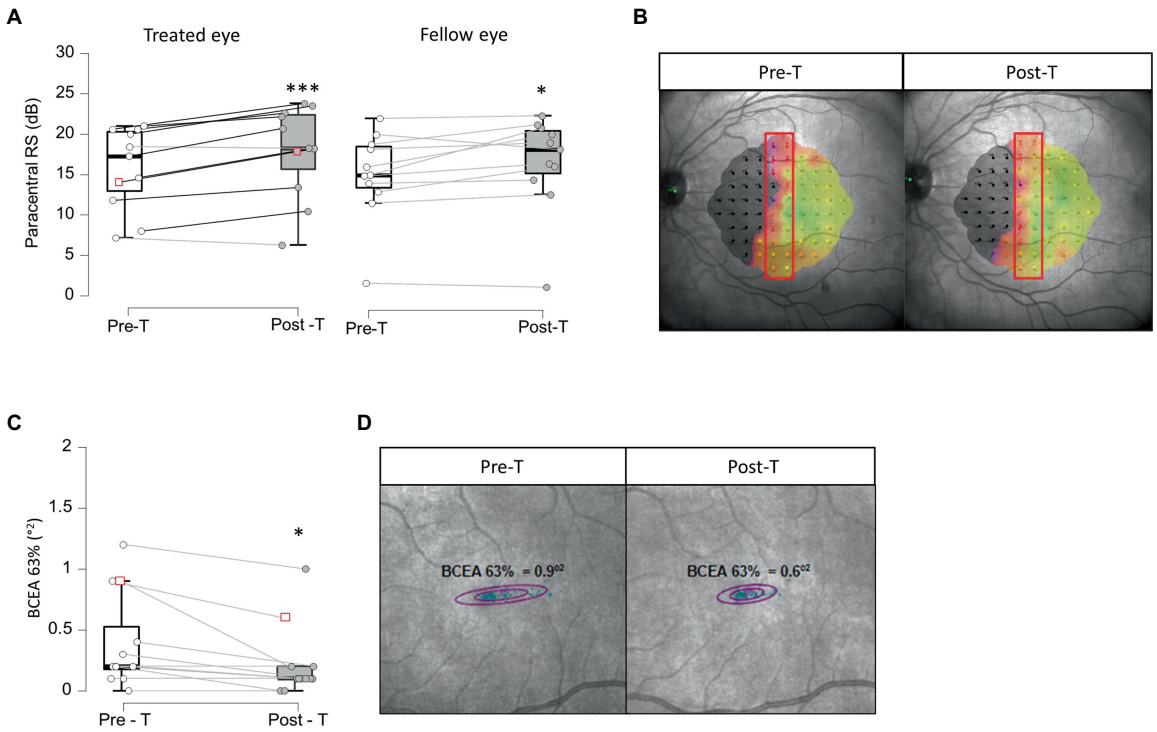

FIGURE 2
Paracentral retinal sensitivity and fixation stability. Panels **(A,B)** show paracentral retinal sensitivity pre-treatment (Pre-T) and post-treatment (Post-T) in treated and fellow eye in 11 patients **(A)**. Panel **(B)** represents an example of paracentral retinal sensitivity measures within red rectangle, using MAIA microperimeter before (Pre-T) and after (post-T) treatment in one patient, corresponding to red squares in **(A)**. *$BF_{+0} > 3$; ***$BF_{+0} > 10$ Panels **(C,D)** show fixation stability measured using the Best Contour Ellipse Area (BCEA) 63% pre- (Pre-T) and post-treatment (Post-T). Panel **(D)** represents an example of BCEA3% measured using MAIA microperimeter before (Pre-T) and after (post-T) treatment in one patient, corresponding to red squares in **(C)**. *$BF_{-0} > 3$.

treatment, very strong evidence for near distance BCVA (Colenbrander chart) improvement was observed in 10/12 patients, from 0.15 ± 0.29 logMar [−0.1, 0.0, 0.20, 1.00] to −0.05 ± 0.09 logMar [−0.10,-0.10, 0.02, 0.10, post-T < pre-T $BF_{-0} = 43.0$, error % = 1.54e-5, d = 1.00, 95%CI (0.30, 1.76)] after 5 weeks of BT (Figure 3A; Supplementary Figure 2A). Contrast sensitivity at 1 cycle/° also increased (moderate evidence, medium size effect) from 1.82 ± 0.18 logit [1.38, 1.64, 1.93, 1.93] at baseline to 1.91 ± 0.18 logit [1.64, 1.87, 1.93, 2.34, post-T > pre-T $BF_{+0} = 4.05$, error % = 1.59e^{-4}, d = 0.58, 95%CI (0.08, 1.20)] after BT in 6/12 patients (Figure 3B; Supplementary Figure 2B). Reading speed increased in 10/11 patients (P8 could not be assessed) from 87 ± 42.5 wpm [37.5, 75.5, 127, 181] to 112.0 ± 55.1 wpm [39.0, 80.5, 171, 202, post-T > pre-T $BF_{+0} = 3.41$, error % = 9.55e-5, d = 0.57, 95%CI (0.07, 1.22)] after treatment (Figure 3C; Supplementary Figure 2C).

Overall subjective quality of vision scores (Table 2; Figure 4; Supplementary Figure 3) reported by the patients increased from 1.49 ± 1.91 logit [−3.76, 0.35, 2.43, 5.82] at baseline to 2.51 ± 2.48 logit [−3.04, 1.19, 3.04, 13.0, post-T > pre-T $BF_{+0} = 1{,}289$, error % = 5.44e-6, d = 0.65, 95%CI (0.33, 0.98)] in 10/11 patients (P11 could not perform the test). Comparisons for individual sub-categories indicated significant improvement in all sub-sections from the VA-LV-VFQ 48 questionnaire (visual ability, reading, mobility, visual information, and visual motor) when comparing baseline and after treatment, however, a placebo effect cannot be excluded.

The PRL was trained to relocate 2.0 ± 0.4° toward the blind hemifield on the retina. Measures post-treatment indicated a relocation of the PRL 0.14 ± 0.5° within the blind hemifield (Figure 1).

Discussion

Our study showed significant improvement in paracentral retinal sensitivity, fixation stability, contrast sensitivity, near vision, reading speed, and subjective visual functioning. The treatment consisted of a weekly BT session (20 min) for 5 weeks with audio-luminous stimuli on the MAIA microperimeter. BT was delivered after the critical healing phase post brain-injury (exception for P5 treated 2.5 months post-stroke).

Strong and moderate evidence for increased PRS within the central 4° horizontal and 20° vertical of the new PRL were observed in the treated and fellow eyes, respectively. PRS measured by automated microperimetry (MAIA C10-2 program) is controlled for the loss of fixation, therefore, such improvement of the PRS with medium to large effect size strongly suggests visual field relocation at the border of the blind hemi-field. As the seeing hemi-retina is relocated to the center of the new test, the MAIA would capture the PRS from a better retinal area, representing a better use of the visual functions.

The recovery of visual perception at the border of the scotoma has been observed in individuals with hemianopsia using field restitution rehabilitation approaches, although it requires significantly longer duration of stimulation, typically for several months, representing hundreds of hours of stimulation (23, 24). Other compensatory approaches such as oculomotor training typically takes place over 1-h daily sessions for 1 month, requiring strong commitment (2). Here, visual field relocation, improved fixation stability, improved visual functions, and increased quality of life were observed after 5 weeks, representing a total of 100 min of static luminous stimulation with auditory feedback.

The fast functional visual improvements when compared to the traditional compensatory therapies might be the consequence of the combination of auditory biofeedback and visual stimulation, reinforcing the training effect of new PRL relocation through multisensory processing (25).

Fixation stability significantly improved in accordance with the expected effect of BT which trains the patients to use a new PRL through oculomotor control for activities of daily living (12). Similar improvements of fixation stability are observed in individuals with macular degeneration and PRL relocation through BT (12, 14, 15, 19).

Contrast sensitivity at 1 cycle/° also improved. This could be the consequence of the improvements observed in paracentral fields sensitivity and fixation stability. Such increase in contrast sensitivity was observed in other studies using high-contrast visual stimulation (26, 27).

Parafoveal retinal sensitivity, fixation stability and contrast sensitivity are essential features for proper reading (28). Accordingly, improvement in these three features led to an increase in left-to-right reading speed in 83% (10/12) of our patients with hemianopsia regardless of the side affected (left or right HH). Patients with right

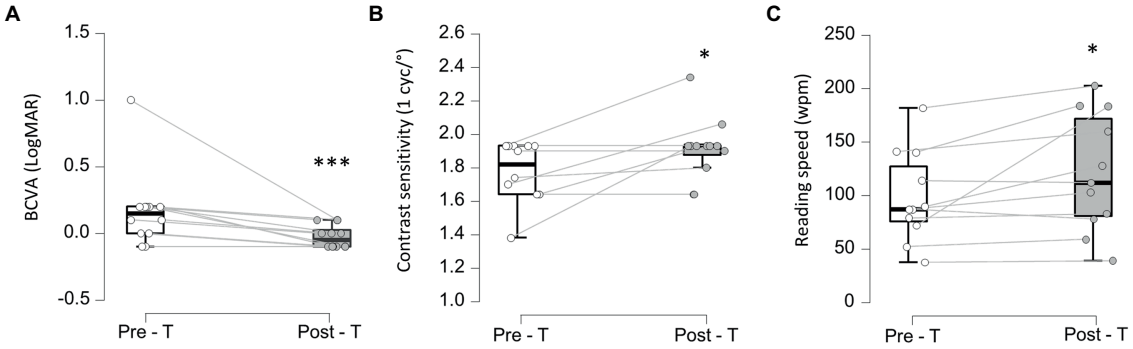

FIGURE 3
Visual acuity, contrast sensitivity and reding speed. **(A-C)** Pre (Pre-T) and post-treatment (Post-T) measures of visual acuity using Best Corrected Visual Acuity (BCVA) **(A)** ***$BF_{-0} > 10$, contrast sensitivity at 1cyc/° **(B)** and reading speed (in words per minute—wpm) **(C)** *$BF_{+0} > 3$.

TABLE 2 LV-VA-VFQ-48 sub-group scores.

Subsections		Median	Min	Q1	Q3	Max	BF_{+0}	Error %	d
Reading	Pre-T	2.99	−1.23	1.13	3.32	5.82	4.61	3.43×10^{-4}	0.63
	Post-T	3.35	1.41	2.56	5.52	13			
Visual ability	Pre-T	1.78	−2.37	0.5	2.36	3.24	245	1/∞	1.44
	Post-T	2.20	−0.62	1.40	3.21	3.51			
Visual information	Pre-T	2	−1.54	1.25	2.40	3.29	9.15	8.36×10^{-6}	0.91
	Post-T	2.81	0	2.12	3.04	3.56			
Mobility	Pre-T	1.18	−3.76	−0.44	1.61	2.81	52.1	1.87×10^{-4}	1.10
	Post-T	1.51	−3.04	0.37	2.55	3.12			
Visuo-motor	Pre-T	1.42	−3.04	0.20	2.19	2.65	4.22	2.56×10^{-4}	0.61
	Post-T	2.02	−1.96	0.72	2.60	2.65			

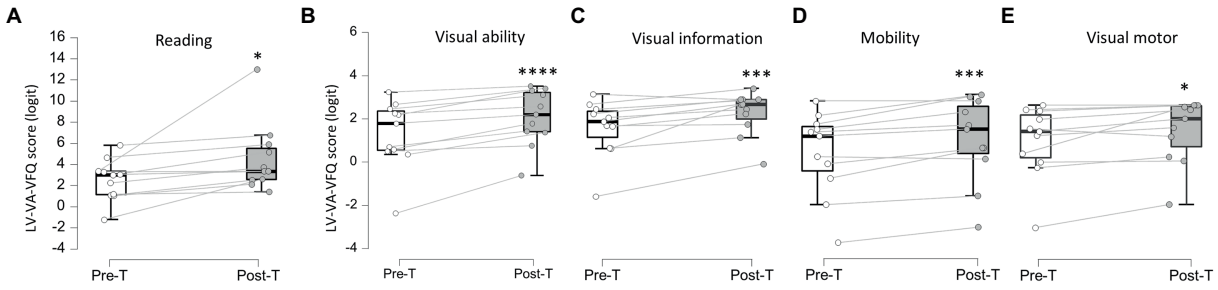

FIGURE 4
Veteran's Affair Low-Vision Visual Functioning Questionnaire 48 sub-categories scores. **(A–E)** Pre (Pre-T) and post-treatment (Post-T) measures of subjective self-assessment of reading **(A)**, visual ability **(B)**, visual information **(C)**, mobility **(D)**, and visual motor **(E)**. *$BF_{+0} > 3$; ***$BF_{+0} > 10$; ****$BF_{+0} > 100$.

hemianopsia (right-sided field loss) have difficulties in shifting their gaze systematically from left to right and show poor sentence tracking whereas patients with left hemianopsia have issues finding the beginning of a new line in right-to-left reading. Our results suggest that such eye movements are improved after BT and hence BT is probably the mechanism which enhances fixation stability and results in better visual functions post treatment.

Overall subjective patient-reported visual function strongly improved, corroborating the results observed with visual function and functional vision outcomes. More specifically, the visual ability and visual mobility subgroups showed the highest effect size, suggesting that the patients show improved navigation and orientation. Consistent with the medium size of improvement in reading speed, the patient-reported score of reading ability also moderately increased after BT.

Our results are unlikely due to a learning/adaptation effect of the visual tests as baseline and after treatment assessments at the clinic were separated by a minimum of 5 weeks, above the learning effect time window shown to last for up to 1 week (29). Audiovisual stimulation with BT efficiently improved oculomotor control toward pre-designated targets. Improved oculomotor control resulted in better fixation stability of the eyes. BT allowed relocation of parafoveal visual fields, enlarging the central vision. Larger paracentral fields, better fixation stability and an increased contrast sensitivity translate into improved reading but also better navigation and orientation, and consequently, increased quality of visual function.

The audiovisual sensory BT is a therapy used in low vision for more than 10 years, showing good results for near and distance vision in individuals with macular degeneration and other low vision conditions (13–19). A limitation of this study was the small number of participants. As a safe and cost-efficient rehabilitation technique and following validation with larger studies, BT could provide a relevant visual rehabilitation for patients with hemianopsia.

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 Health Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MMi is the first author, current clinical fellow seeing the patients and contributing to the manuscript preparation. YP worked for 2

years as a clinical fellow seeing patients for the project, obtaining consents and questionnaires. AS worked as a technician and optometrist assessing the patients and obtaining consents and questionnaires. MMa is an optometrist and occupational therapist and was involved in the design of the study and recruitment of patients. SM is the professor involved in the design of the study and manuscript confection. MR is the co-senior author involved in design, statistical analysis, and manuscript preparation. MD-N idealized the study, was the principal investigator supervising and participating in all activities, including manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1151736/full#supplementary-material

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Combined multidisciplinary in/outpatient rehabilitation delays definite nursing home admission in advanced Parkinson's disease patients

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Introduction: Advanced Parkinson's disease (aPD) patients have a high risk on definite nursing home admission. We analyzed the effectiveness of an in-and outpatient multidisciplinary rehabilitation, focusing on activities of daily living (ADL) and delaying definite nursing home admission.

Methods: This study included 24 aPD patients, who received a 6-week inpatient multidisciplinary rehabilitation program, including optimization of pharmacotherapy, which was followed by an individualized outpatient support program during 2years (intervention group). A non-randomized matched control group (n=19), received care as usual. Primary endpoints consisted of the Amsterdam Linear Disability Scale (ALDS) and percentage of patients being able to live independently at home after 2years. Secondary endpoints included changes in medication (LEDD), motor performance (SCOPA-SPES), cognition (SCOPA-COG), hallucinations (NPI) and depression (BDI).

Results: Overall, 83% of patients were able to return home after the 6-week inpatient intervention, and 65% still lived at home at 2years follow-up. Median ALDS scores after 2years in the intervention group were significantly better, compared to the control group (p=0.002). All secondary endpoints had improved significantly vs. baseline directly after the 6-week inpatient rehabilitation, which had disappeared at 2years follow-up, with the exception of the daily dose of medication, which was significantly higher in the intervention group.

Conclusion: This 2-year follow-up study showed that a combined multidisciplinary in/outpatient rehabilitation program for aPD patients, was able to stabilize ADL functions, and finally delayed definite nursing home admissions in 65% of treated patients.

Trial registration: filenumber M10.091051; ABR code NL32699.042.10.

KEYWORDS

Parkinson's disease, multidisciplinary, rehabilitation, ADL (activities of daily life), nursing home

Introduction

Parkinson's disease (PD) has an enormous impact on quality of life (1–3). Many patients lose the ability to live independently at home (3–6). Important reasons for nursing home admission include cognitive deterioration, hallucinations, older age and the loss of activities of daily life (7–12). PD patients in nursing homes are the most expensive group to treat, increasing the overall costs by approximately 4 times the costs of living at home (13). No intervention in aPD patients thus far has shown any delay or prevention of nursing home admission.

This study investigated whether a combined multidisciplinary in/outpatient rehabilitation program, focusing on ADL functioning, was able to delay definite nursing home admission. For this purpose, we performed a non-randomized controlled trial during 2 years, to analyze the short-and long-term effectiveness of a 6-week inpatient rehabilitation program, followed by a multidisciplinary support program during 2 years in aPD patients, who were on the brink of losing their independence.

Materials and methods

Participants

Recruitment of patients for this prospective, controlled, multicenter trial took place at the outpatient departments of 2 hospitals (Martini hospital/MZH and the University Medical Centre Groningen/UMCG) in the northern part and at seven different nursing homes in the southern part of the Netherlands. Inclusion criteria were: (a) diagnosis of PD according to the UK Brain Bank Criteria (14); and (b) combination of motor-, cognitive-and behavioral problems, interfering with independent living at home, necessitating direct nursing home admission. Exclusion criteria included: (a) presence of atypical Parkinsonism, (b) inability or unwillingness to give informed consent; and (c) unstable general medical conditions, requiring intensive or invasive treatment. We included two groups of aPD patients (Table 1). All of them were not able to live independently at home at the moment of inclusion. The first group consisted of 24 aPD patients, who received an in/outpatient rehabilitation program. The second group consisted of 19 aPD patients, serving as matched controls, who had been admitted to a nursing home, receiving care as usual. Data of controls were selected from a group of nursing home patients in the Southern part of the Netherlands, who had been admitted to a nursing home since 0–3 months. The controls were selected from a larger population of nursing home patients with aPD, that participated in an already completed quality of care study in Dutch nursing homes (15, 16). To avoid selection bias, patients in the intervention group were included sequentially, based on the following order of referral. The ethics committees of the University Medical Center Groningen and University Medical Center St. Radboud gave informed consent for the study.

TABLE 1 Demographics at baseline.

	Intervention PfP group (n=24)	Control group (n=19)
Patients characteristics		
Men (n/%)	13 (54%)	7 (37%)
Age (years)	70.0 (65.25–77.0)	76.0 (70.0–83.0)
Disease duration (years)	8.0 (4.5–11.0)	9.0 (5.0–12.0)
Hoehn and Yahr stage		
IV (n/%)	15 (62.5%)	13 (68.4%)
V (n/%)	9 (37.5%)	6 (31.6%)
Daily LEDD** (mg)	1097.5 (568.75–1743.75)	687.5 (400–1,000)
Probable PD dementia (n/%)[#]	13 (54.2%)	14 (73.6%)
Visual hallucinations (n/%)	10 (41.7%)	3 (15.8%)*
Depression (n/%)[##]	6 (25%)	6 (31.6%)
Primary outcome		
ALDS score	59.3 (41.2)	69.3(16.0)*
Secondary outcomes		
SCOPA-SPES score	23.5 (16.5–29.25)	27.0 (22.0–36.0)
SCOPA-COG score	22.0(14.0–26.75)	15.0 (11.0–20.0)*
NPI score	2.0 (1.0–6.0)	2.0 (1.0–3.0)
BDI score	11.0 (9.75–15.0)	12.0 (11.0–14.0)

Data reflect median scores, with percentages or the Interquartile Range between brackets. Both groups did not show significant differences at baseline (Mann–Whitney test). *Except for ALDS scores (p = 0.022) at baseline, which were higher in the controls (corresponding with better performance), cognition (p = 0.013) and presence of hallucinations (p = 0.031). **LEDD, levodopa-equivalent daily doses.
[#]SCOPA-COG < 22.
[##]BDI > 14.

Treatment programs of both groups

The rehabilitation program consisted of 2 parts, Phase I and II (Figure 1; flowchart). Phase I; the inpatient program during 6 weeks was delivered at the rehabilitation unit of the Parkinson expertise center in Groningen (Point for Parkinson, PfP). The inpatient program consisted of 1 week of baseline observations, including the assessment of motor-, cognitive-and behavioral scales. Thereafter, a medical-and allied health treatment plan was performed during 5 weeks. During this inpatient period 2–3 h physiotherapy, 1 h speech therapy, 1–2 h occupational therapy, 2–4 h of professional coaching, 2 h of social work and 0.5 h dietary support a week were provided, with minimal interindividual variations (Supplementary Table S1).

Their individualized treatment plan, was initiated by the allied health professionals of PfP in phase I, focusing on the presented signs and specific symptoms of each patient. These treatments were provided, according to the national guidelines on allied therapies, and handed over to allied health professionals, trained by the Dutch ParkinsonNet (17, 18), in their own environment during the rest of the follow-up period during phase II (17). The medication adjustments in the intervention group strictly followed the Dutch multidisciplinary guideline on PD, focusing on optimal dosing of motor symptoms, the implementation of advanced therapies if necessary, and adequate treatment of non-motor symptoms (19, 20). Medication adjustments (Supplementary Table S2) took place based on predefined objectives, like improvement of walking or reduction of visual hallucinations. Patients were weekly evaluated by the complete multidisciplinary team, including a neurologist and a specialist elderly care with special training in treating aPD patients, Parkinson nurses, physiotherapists, social workers, speech therapist, occupational therapist and dietician. All dopaminergic medication was converted into levodopa-equivalent-daily doses (LEDD) (19, 21).

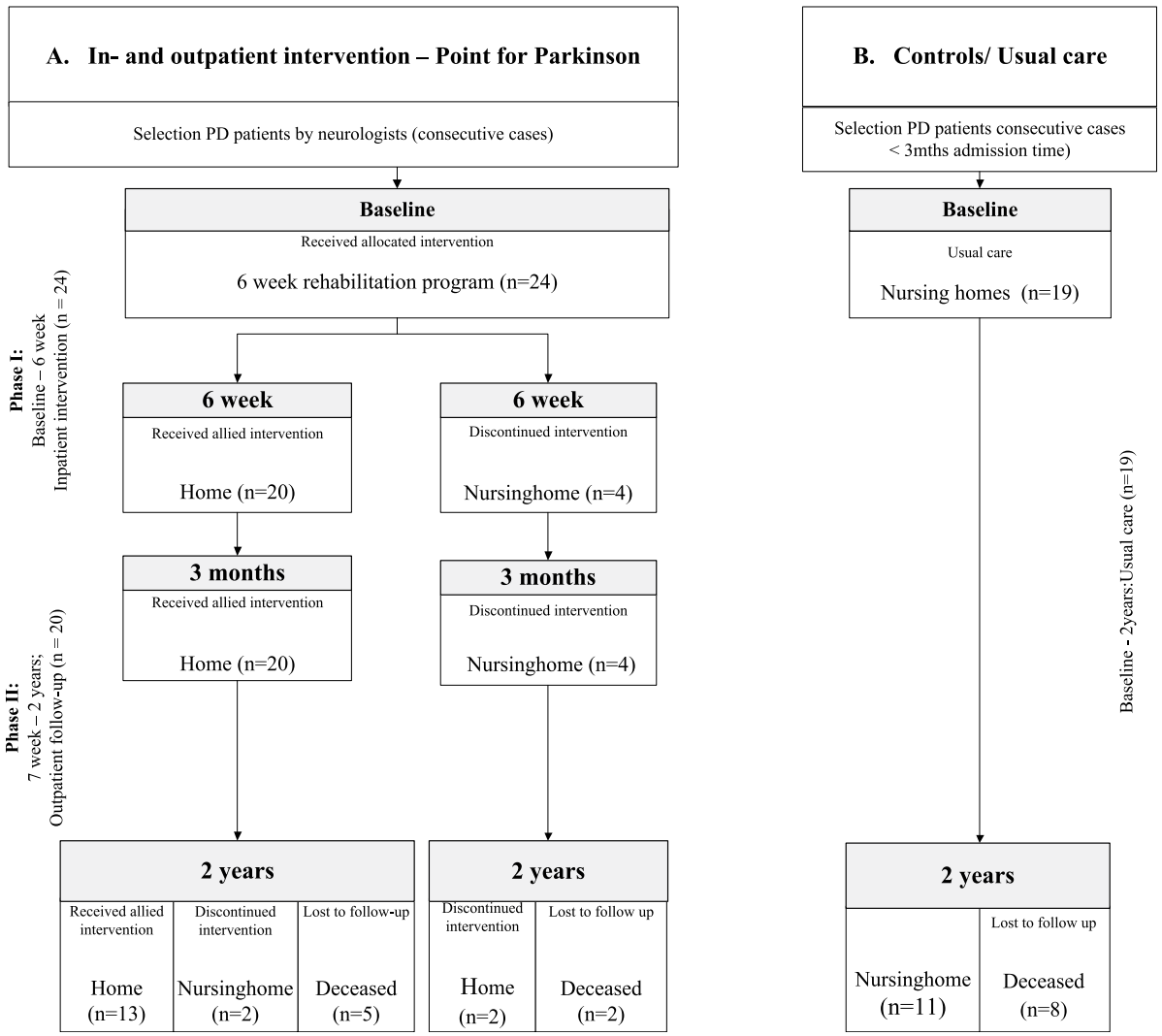

FIGURE 1
Flowchart of the study divided into: Phase I. The inpatient intervention program at the Groningen expertise center (Point for Parkinson, PfP); Phase II. The outpatient follow-up program (Parkinson specialist/neurologist PfP and ParkinsonNet allied health professionals). **(A)** Intervention Group; who received an inpatient intervention program at the expertise center Point for Parkinson Groningen. **(B)** Control Group; who were directly admitted to a nursing home and received care as usual.

The control group received care as usual. Care as usual included adjustments of medication regimens, if considered appropriate by the specialist elderly care (according to the Dutch multidisciplinary guidelines elderly care-Verenso), as well as allied health interventions, mostly on a regular basis, with a focus on retaining functions. Standard care in nursing homes in the Netherlands includes in most cases physiotherapy in 88% of patients, during 0.5–1 h per week and 26.3% follow speech therapy (22, 23). If a patient is admitted to a nursing home, treatment by the neurologist often ends. Neurologists are still involved in the nursing home patients in only 42% of cases.

Outcome measurements

Primary endpoints

We defined two primary endpoints. The first one was the difference between both groups in the change of the Amsterdam Linear Disability Scale (ALDS) scores between baseline and 24 months. In total 26 items of the ALDS, were selected, hierarchically ordered from simple to more complex. The ALDS is calculated as a logistic regression coefficient, expressed in thetas, which can be transformed linearly into values between 10 and 90, with higher scores indicating better functional ability. ALDS has shown adequate clinometric properties in patients with PD (24, 25) and can be used as a reliable indicator of the functional status of aPD patients in nursing homes as well as in an outpatient setting (26). The other primary endpoint, directly related to the ALDS, was the percentage of patients, discharged from the nursing home setting, living independently in both groups after 2 years.

Secondary endpoints

The first secondary endpoint was the change in LEDD during the 2 year follow-up in both groups. Motor performance was assessed using the Short Parkinson's Evaluation Scale (SCOPA-SPES). The SCOPA-SPES is a reliable and valid instrument to assess motor functions (27, 28). The SCOPA-SPES is a 21-item scale with 3

sub-groups, being Motor Evaluation, ADL, and Motor complications. Higher scores on the SCOPA-SPES reflect more severe motor impairments.

The cognitive status of all patients was assessed with the SCOPA-COG, a short, reliable, and valid instrument that examines 4 cognitive domains: memory, attention, executive functioning and visuospatial functioning (29, 30).

The Neuropsychiatric Inventory Questionnaire (NPI-Q) (30, 31). The NPI-Q contains 12 neuropsychiatric symptoms, measuring the presence of items (yes/no), the severity by a 3-point scale and the impact of the symptoms by a 6-point scale, with a maximum overall score of 36. All secondary endpoints analyzed the difference in change over 24 months between both groups.

Mood changes were measured using the Beck Depression Scale (BDI), which is the most valid instrument to measure depression in Parkinson's disease (31–34). This 21-item questionnaire has a 4-point scale, whereby a total score of >14 indicates depression in a PD population (32).

Behavioral and neuropsychiatric disturbances were evaluated using the Neuropsychiatric (35, 36).

In order to get an impression of the acute and subacute effects of the inpatient intervention, all primary and secondary endpoints were also evaluated at 6 and 12 weeks.

Statistical analysis

Previous Dutch data suggested an average yearly decline of 1.3 point in ALDS in patients with PD (37) To detect this difference with 80% power and an α of 5%, assuming a standard deviation of 8.9 (24) and a correlation of 0.75 between the measurements, a sample size of at least 19 patients for both groups was calculated. The type 1 probability failure testing this null hypothesis is 0.05. Assuming a drop-out of up to 25% in the intervention group, we aimed to include 24 patients. Based on these data, we postulated that a change in ALDS score of ≥3 points would represent a clinically relevant difference at 2 years.

SPSS 23 was used to perform the statistical analyses. Regression analysis and analysis of covariance were performed to correct for the difference of the ALDS and SCOPA-COG scores at baseline, whereby control patients had a significant better ALDS score at baseline compared to the intervention patients, whereas intervention patients performed better on SCOPA-COG at baseline. The Mann–Whitney test was used to calculate the between-group differences of baseline vs. 2-year follow-up scores. The Wilcoxon test and Friedman test were used to calculate the changes in endpoint scores over time. Given the small group sizes, 95% confidence intervals (CI) were established also using bootstrapping ($n = 1{,}000$ bootstraps). To avoid selection bias, patients in the intervention group were included sequentially (consecutive cases), based on the following order of referral. The known variables, like increasing age, functional impairment, Parkinson's disease dementia (PDD) and hallucinations, were interrogated as potential confounders. Besides these variables also PD medication and disease duration were tagged as potential confounders.

The protocol was approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen (UMCG), using the checklist with TREND criteria (filenumber M10.091051; ABR code NL32699.042.10). The principal investigator TvL was responsible for the integrity of the design, the conduct and analysis of the study.

Role of the funding source

The sponsors of this study had no involvement in the study-design, data collection, data analysis and interpretation, neither in writing the final report. Final responsibility for submitting the publication was taken by BRB and TvL.

Results

Overall, 43 PD patients were included; 24 patients in the intervention group and 19 patients in the control group with care as usual (Figure 1). The mean duration of admission of patients in the inpatient program was 42 days (SD 10.79).

Primary outcomes

Amsterdam Linear Disability Scale scores of the patients in the intervention group significantly improved directly after the inpatient intervention (6 weeks), but slightly worsened thereafter over 2 years, resulting in final scores which were comparable to baseline (Supplementary Table S3). Sub-analysis of the intervention group showed a significant difference (37.8 points; $p = 0.030$, 95%CI) in baseline ALDS scores between patients who could return home (higher scores) and those who were admitted to a nursing home (Supplementary Figure S1). Both groups improved on their ALDS scores, however only the group who went home showed a significant improvement (7.5 points. $p = 0.000$, 95%CI).

Amsterdam Linear Disability Scale scores of the intervention group returned again to baseline scores after 2 years (Table 2). On the contrary, the ALDS scores worsened significantly over 2 years in the control group; with 40 points ($p = 0.017$, 95%CI) after 2 years (Figure 2). Regression analysis and analysis of covariance were performed to correct for the difference in ALDS scores between both groups at baseline (controls had better ALDS scores), but both analyses showed a significant worsening of scores in the control group ($p = 0.002$) compared to intervention group.

Overall 20 out of 24 patients from the intervention group could return home after the 6-week inpatient program (83.3%). All 20 patients still lived independently at 3 months follow-up, and 13 patients (65%) even lived still independently at home after 2 years follow-up. All control patients remained in the nursing home throughout the follow-up period. After 2 years, seven patients in the intervention group and eight patients in the control group had died.

Secondary endpoints

The median LEDD of the intervention group increased significantly with 495 mg ($p = 0.002$, 95%CI) at the end of the intervention. LEDD in the control group increased non-significantly with 141.5 mg ($p = 0.144$, 95%CI). Subcutaneous infusion of apomorphine was initiated in 3 patients in the intervention group, and the dose of already existing apomorphine infusion was increased in 2 patients (mean 506.25 mg LEDD). Overall dopaminergic medication increased in 75% ($n = 18$) of patients by a median LEDD of 495.00 mg, whereas in only 4 patients (17%) dopaminergic medication was decreased and in 2 patients (8%) their original baseline dose was continued in the intervention group. The level of cholinesterase inhibitors, atypical antipsychotics and tricyclic antidepressants also

TABLE 2 Primary and secondary endpoints of patients in the rehabilitation-and control group.

Test score	Intervention group (*n*=24)			Control group (*n*=19)			Between group differences at 2years
	Baseline median (IQR)	2years median (IQR)	Value of *p**	Baseline median (IQR)	2years median (IQR)	Value of *p**	Value of *p***
Primary outcomes							
ALDS	59.28 (31.09–72.29)	62.61 (34.87–71.99)	0.140	69.33 59.9–75.17	29.33 (18.29–54.72)##	0.017	**0.002**
Patients living independently at home (*n*, %)	–	13 (65%)		–	0(0%)		
Secondary outcomes							
LEDD (mg)	1097.5 (568,75-1743,75)	1592.5 (1000.0–2105.0)	0.002	678.5 (400–932.5)	820 (400–1,000)	0.144	**0.042**
SCOPA-SPES	23.50 (16.5–29.25)	24.00 (20.0–35.0)	0.462	27.00 (22.0–36.0)	33.00 (29.0–37.0)	0.306	0.141
Subitems							
Motor evaluation	9.00 (6.25–13.5)	12.00 (7.0–15.0)	0.786	11.00 (9.0–17.0)	16.00 (13.0–19.0)##	0.15	**0.034**
ADL	10.50 (9.0–14.0)	11.0 (8.0–17.0)	0.495	12.00 (9.0–17.0)	16.00 (12.0–17.0)	0.203	0.157
Motor complications	2.00 (0.0–3.75)	4.00 (3.0–5.0)	0.68	2.00 (1.0–3.0)	2.00 (0.0–2.0)	0.216	**0.041**
SCOPA-COG	22.00 (14.0–26.75)	20.00 (11.0–27.0)	0.753	15.00 (11.0–20.0)	9.00 (1.0–17.75)##	0.042	0.062
Subitems							
Memory	6.00 (4.0–9.0)	5.00 (5.0–7.0)	0.073	5.00 (4.0–7.0)	3.00 (0.0–6.50)	0.216	0.125
Attention	3.00 (1.5–4.0)	2.00 (1.0–4.0)	0.336	3.00 (2.0–4.0)	2.00 (0.0–3.25)	0.066	0.509
Executive functioning	9.00 (4.25–10.0)	9.00 (4.0–11.0)	0.248	5.00 (3.0–6.0)	2.50 (1.0–4.75)##	0.167	**0.021**
Visuospatial functioning	4.00 (3.0–5.0)	3.00 (1.0–7.0)	0.339	3.00 (1.0–4.0)	0.50 (0.0–4.25)	0.084	0.168
NPI	2.00 (1.0–6.0)	0.50 (0.0–1.25)#	0.048	2.00 (1.0–3.0)	0.0 (0.0–8.00)	0.31	0.488
Hallucinations (*n*/%)	10(42%)	5 (38%)	0.753	3 (16%)	5 (45%)	0.18	0.391
Depression (*n*/%)	7 (29%)	1 (8%)	0.157	9 (47%)	4 (36%)	0.564	0.339
Delusions(*n*/%)	2 (8.3%)	0	0.317	0	2 (18%)	0.317	0.083
BDI	11(9.75–15.0)	12(11.0–14.0)	0.18	12(11.0–14.0)	11.5 (7.5–14.5)	0.345	0.685

Scores are median scores and range IQR25-IQR75, 95% CI.
#Suggest improvement over time.
##Suggest worsening over time.
*Wilcoxon.
**Mann–Whitney.
Bold values: significant between group differences at 2 years follow-up.

showed a significant difference between both groups (Supplementary Table S2).

During phase II, physiotherapy was applied significantly more frequent, compared to baseline, with an increase of 29.2% ($p=0.025$). The other allied health therapies in phase II were not significantly increased vs. baseline; [speech therapy 13.3%, ($p=0.317$), occupational therapy 15.8% ($p=0.083$), social work 5% ($p=0.317$) and dietary support 5% ($p=0.317$)].

The SCOPA-SPES scores in the intervention group worsened 0.5 points, whereas the control group worsened 5 points over 2 years, which however was not significantly different (Table 2).

Sub-analysis of the intervention data showed a significant improvement of the SCOPA-SPES after 6 weeks, which worsened again during 2 years follow-up (Supplementary Table S3). The motor complication scores, being part of the total SCOPA-SPES, showed the longest improvement, lasting up to at least 3 months.

The SCOPA-COG scores in the intervention group did not change significantly over 2 years (Table 2). However, the control group showed a SCOPA-COG decrease of 6 points ($p=0.042$, 95%CI). The most important cognitive change between both groups was related to worsening of the executive functioning ($p=0.021$) in the control group.

Regression analysis and analysis of covariance were performed to correct for the difference in SCOPA-COG scores between both groups at baseline, but both groups showed the same significant worsening. After joining the intervention program sub-analysis showed that the median score of the SCOPA-COG improved significantly with 6 points ($p=0.000$, 95%CI), which remained stable in phase II at 3 months (27.5; IQR 20.25–30.75).

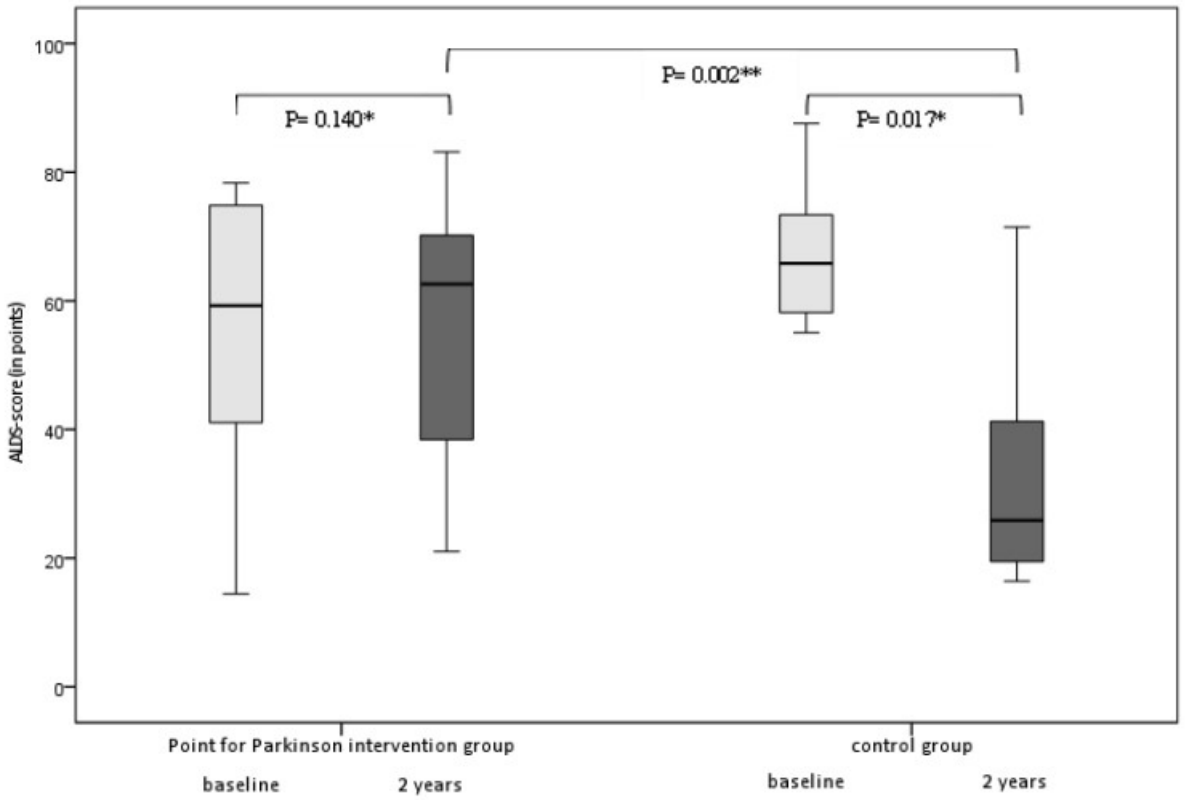

FIGURE 2
Box plots of median changes in primary outcome (ALDS scores/min-max range) between the intervention group and the control group at baseline (between group differences at 2years p=0.002 95% CI). *Wilcoxon, **Mann–Whitney *U*.

NPI scores improved significantly ($p = 0.001$) after phase I in the intervention group (Supplementary Table S2), and this improvement was still significantly different vs. baseline at 3 months ($p = 0.046$). Especially the occurrence of hallucinations decreased significantly from 42 to 25% of the patients in the intervention group ($p = 0.014$). This difference had disappeared at 2 years follow-up.

BDI scores had improved significantly in the intervention group after phase I (Supplementary Table S2), which difference also had disappeared after 2 years follow-up (Table 2).

Discussion

This study describes the positive outcomes of a long-term, controlled trial on the efficacy of an in/outpatient, multidisciplinary Parkinson rehabilitation program, including medication optimization. Importantly, only aPD patients were included, who were not longer able to live independently at home at the time of inclusion. Our data indicate that a multidisciplinary intervention, is able to keep these aPD patients stable for at least 2 years, as shown by the functional ALDS scores, which was not the case in the controls with care as usual. Moreover, the controls experienced a significant decrease in their functional capability, which is in line with previous data showing that PD patients in a nursing home with moderate cognitive impairment showed deterioration of MDS-ADL scores of 1.78 points in 6 months (38). Post-hoc analysis of the baseline ALDS scores of treated patients indicated that returning home was correlated to higher baseline ALDS scores (Supplementary Figure S1).

Our study reports for the first time that multidisciplinary rehabilitation of aPD patients is able to postpone definite nursing home admission by at least 2 years in 65% of cases. None of the control patients left the nursing home during the same period.

An important difference between both groups was the level of dopaminergic stimulation. The intervention group showed a significant increase in LEDD, including initiation or optimization of continuous infusion therapies in some patients. This suggests that optimal pharmacotherapy offers important advantages on the short-and long-term. The pharmacotherapy for PD patients in nursing homes is suboptimal, with 44% of PD patients being most of the time 'off', and low LEDDs, varying from 400 to 500 mg/day, while patients had already PD for at least 7 years (10, 39). In our study the mean LEDD at baseline of the intervention group was 1097.5 mg, but still 75% of included patients were considered to be underdosed.

The other secondary endpoints showed that the effect of the inpatient rehabilitation (phase I) was most optimal directly thereafter, which decreased over time during phase II, resulting in comparable outcomes at 2 years follow-up, except for the NPI, which improved significantly in the intervention group, despite a higher LEDD in the intervention group, which could have increased hallucinations, but that did not happen (40–42). The increased dosages of apomorphine, CHEI's and clozapine in our study are the most likely explanation for this finding (43–47). This is an important result, because visual hallucinations are the strongest predictor of definite placement in nursing homes (9, 11, 12). The intervention program also included a small group without the need to change their LEDD. These patients

also improved on their motor-and ADL scores, stressing the importance of allied therapies and other disciplines involved in our rehabilitation program. These findings strengthen the evidence of the effect of allied therapies within a multidisciplinary rehabilitation treatment (without medication adjustments) on patients with early stage PD on ADL functioning and QoL (48, 49).

Improvement of the cognition is very likely due to optimization of medication. Suppletion of the cholinergic deficit with rivastigmine, eventually in combination with optimization of the levodopa dose. In 54% of the PD patients rivastigmine was added to their medication regimen during the treatment. Overall 87% of the PD patients showed improved scores (SCOPA-COG) with an average of 6 points. This is in line with other studies, which found improvement of cognition after optimized treatment as well (45–47).

This study also has some limitations. Both arms included relatively small numbers of patients, although this was based on our power calculations before study onset. The fact that this small sample already resulted in significantly positive outcomes supports the strength of our rehabilitation concept. We performed bootstrapping to provide a more representative outcome, to control for the relatively small sample size. However, the outcomes after bootstrapping were not significantly different from the original data.

At 2 years follow-up, seven patients in the intervention group (29.2%) and eight patients in the control group (42.1%) had died. This means that the loss-to-follow-up is a potential threat to validity and might cause significant bias (50). A chi-square test was performed to control for these differences and no dissimilarities were found (0.7816; $p = 0.3766$) between the intervention and control group. The differences in ALDS-and SCOPA-COG scores at baseline might also have impacted the effect size. However, regression analysis with adjustment for these baseline values and analysis of covariance with adjustment for the baseline values gave exactly the same output, suggesting there was no serious influence on the effect size.

Another limitation is the lack of QoL data in our control group. This would have offered an extra possibility to discuss the observed functional improvements in this study. Living longer at home and greater independence in activities of daily living provide better QoL in late-stage Parkinson, as was shown previously (3).

Finally, neither patients nor the assessors were blinded with respect to the intervention. This might have influenced the final outcomes. However, the most important finding, being the percentage of patients returning home after the intervention, and still staying at home after 2 years in 65% of cases, cannot be explained by this open assessments, which is also the case for the LEDD changes, which are the result of a particular vision on optimal treatment of aPD, instead of assessment bias. Therefore, the stabilization in the rehabilitation group and the clear worsening in the control group can be considered as real and important effects of our rehabilitation program.

Our findings potentially have large implications. If in/outpatient aPD rehabilitation, with a focus on optimization of pharmacotherapy, is able to stabilize advanced PD patients and delay nursing home admission, many more advanced PD patients should be offered similar programs. This would not only improve their independence but would also significantly save costs of nursing home admission (around 90.000 Euro per patient per year in the Netherlands). A Norwegian study showed that costs arising from nursing home placement were 5 times higher for PD patients compared to controls (51) For exact cost-effectiveness of this particular concept further research is necessary. The costs of the control group are related especially to the costs of institutional care. The costs of the intervention group exist of the inpatient intervention/rehabilitation period and the outpatient support program. The inpatient program costs are estimated on 300 Euro per day, which makes around 12.500 Euro for 6 weeks. The costs of the outpatient program are based on a questionnaire covering the health-care costs during the previous 3 months, including medical care, allied health care, home care nursing as well domestic informal care, and even hospital admissions, if needed. These costs summed up to 4.000 Euro/3 months, which means a yearly cost of 16.000 Euro/patient in the intervention group. If it is hypothesized that those costs were kept at the same level during the 2 year follow-up, this would mean an overall cost of the intervention group of 44.500 Euro vs. 180.000 Euro of the nursing home group. This means that not only the QoL is improved by our intervention, but that the prevention of definite nursing home admission also implicates a huge financial benefit of almost 70.000 Euro per patient per year.

The most important message of our study is the huge benefit of intensive rehabilitation for advanced PD patients. We have shown the impact on living independently at their own houses, which is a significant contribution to their quality of life. Therefore, in every country neurologists should take responsibility to create places where advanced PD patients are rehabilitated, in order to prevent definite nursing home admission. The place where this rehabilitation should take place will differ between countries, and may vary between hospital settings (which is mostly too expensive), rehabilitation centers or, as in our case, specialized nursing homes, creating a setting without time–pressure, but offering a stimulating atmosphere, created by an educated multidisciplinary PD team. Without these rehabilitation options, advanced PD patients will have a reduced quality of life at high costs, because our study also shows the huge financial benefit of delaying definite nursing home admission.

However, before this approach can be recommended to all advanced PD patients or even be more widely used in chronic patients on the brink of nursing home admission, our data have to be confirmed in larger samples, preferably in other clinics, and in other countries, in order to validate our PD rehabilitation concept.

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 Trial registration: filenumber M10.091051; ABR code NL32699.042.10. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ES-O and TL contributed to the research design. ES-O wrote the first draft of the manuscript. TL and BB were responsible for revisions. ES-O and NW were responsible for data collection. JV was responsible

for statistics. All authors made a substantial, intellectual contribution to the work read and approved the final manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1128891/full#supplementary-material

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Effects of 12 weeks of Tai Chi on neuromuscular responses and postural control in elderly patients with sarcopenia: a randomized controlled trial

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Objective: To explore the effect of 12 weeks of Tai Chi on neuromuscular responses and postural control in elderly patients with sarcopenia.

Methods: One hundred and twenty-four elderly patients with sarcopenia from ZheJiang Hospital and surrounding communities were selected, however, 64 were later disqualified. Sixty elderly patients with sarcopenia were randomly assigned to the Tai Chi group (n=30) and the control group (n=30). Both groups received 45-min health education sessions once every 2 weeks for 12 weeks, and the Tai Chi group engaged in 40-min simplified eight-style Tai Chi exercise sessions 3 times per week for 12 weeks. Two assessors who had received professional training and were unaware of the intervention allocation assessed the subjects within 3 days prior to the intervention and within 3 days after completion of the intervention. They chose the unstable platform provided by the dynamic stability test module in ProKin 254 to evaluate the patient's postural control ability. Meanwhile, surface EMG was utilized to assess the neuromuscular response during this period.

Results: After 12 weeks of intervention, the Tai Chi group showed a significant decrease in neuromuscular response times of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius and overall stability index (OSI) compared to before the intervention (p <0.05), while there was no significant difference in the control group for these indicators before and after intervention (p> 0.05). In addition, these indicators in the Tai Chi group were significantly lower than those in the control group (p <0.05). The changes in neuromuscular response times of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius were positively correlated with the changes in OSI (p<0.05) in the Tai Chi group, but there were no significant correlations between changes in neuromuscular response times of the aforementioned muscles and changes in OSI in the control group (p<0.05).

Conclusion: Twelve-weeks of Tai Chi exercise can improve the neuromuscular response of the lower extremities in elderly patients with sarcopenia, shorten their neuromuscular response time when balance is endangered, enhance their dynamic posture control ability, and ultimately reduce the risk of falls.

KEYWORDS
Tai Chi, neuromuscular responses, postural control, elderly patients, sarcopenia

Introduction

Sarcopenia is a clinical syndrome characterized by a progressive and widespread loss of skeletal muscle mass and/or muscle strength related to the aging process (1). As reported by the Asian Working Group for Sarcopenia, nearly 1/3 of people aged 65 years and older suffer from sarcopenia, and the prevalence is as high as 50–60% in people aged 80 years and older (2). It is predicted that over the course of the next 40 years, up to 200 million people in mainland China will suffer from this illness (3). Sarcopenia causes a decrease in muscle mass and muscle strength, which reduces mobility in elderly individuals and is one of the main physiological factors contributing to falls in elderly individuals (4). Regardless of whether falls cause physical or psychological damage to older adults, they can limit the daily mobility and functional activities of older adults and exacerbate the loss of skeletal muscle mass and muscle strength, thus further limiting their ability to perform daily activities and ultimately leading to a reduced quality of life and even death (5, 6). It has been reported that the annual probability of falls in the general elderly population over 60 years of age is 20.7% (7), while the incidence of falls in the elderly population with sarcopenia is two to three times higher than that of the general elderly population (8). In addition, studies have shown that the mortality rate of elderly people with sarcopenia due to falls is one to five times higher than that of normal elderly people (9). In conclusion, elderly patients with sarcopenia face serious fall risks and accidental injuries from falls.

Regular exercise has been indicated to improve physical and mental health (such as reducing anxiety and depression and boosting self-confidence); reduce the risk of developing diseases (such as heart disease, diabetes, and stroke) and mortality; increase social participation, integration, and adaptation; and prevent falls and fall-related injuries. In particular, Battaglia et al. demonstrated that the adaptation of the body, such as increased support surface and equal redistribution of body weight on both feet, resulting from a 5-week dynamic balance training protocol, may be enough to improve static balance in elderly women (10). Won et al. found that regular exercise can enhance the subjective well-being, life satisfaction, leisure satisfaction, and exercise satisfaction of older adults and improve their quality of life (11). Similarly, Korniloff et al. found that exercise can reduce the risk of depression in older people, and the frequency of exercise is negatively correlated with the incidence of depression (12). Exercise is the most economical and effective way to prevent and improve sarcopenia in the elderly in the long term. However, resistance exercises are often characterized by high intensity and fast pace, making it difficult for elderly individuals with sarcopenia to complete them. Additionally, high-intensity resistance exercises can easily induce cardiovascular and cerebrovascular diseases. Although aerobic exercise can improve the cardiorespiratory function and activity level of elderly individuals, there is still controversy about the impact of aerobic exercise on muscle mass and muscle strength in elderly individuals (13). Therefore, it is imperative to find appropriate clinical interventions to reduce the risk of falls and accidental injuries from falls in elderly people with sarcopenia.

Fall prevention is not only related to acute proprioception and adequate muscle strength but also depends on the neuromuscular response, that is, the timely activation of the appropriate postural response to control the body's center of gravity once displacement occurs (14). Neuromuscular response is also considered to be one of the most important factors contributing to falls (15). Older adults exhibit greater deficits in neuromuscular responses, leading to a potentially slower correction of postural disturbances, ultimately increasing their incidence of falls, which is more pronounced in elderly patients with sarcopenia (16). In particular, for the aged population, exercise intervention is a powerful approach to enhance neuromuscular function (15). However, there is no clear consensus on appropriate exercise interventions for sarcopenia. The gentle, beautiful motions of Tai Chi, a traditional Chinese workout regimen, are what make it so popular. In China, Tai Chi practice is widespread and has higher compliance rates in older persons than simple resistance exercise (17). Studies have revealed that those who practice Tai Chi have greater muscle strength, balance, coordination, and concentration abilities than control groups (18–21). These qualities help to improve physical function and avoid falls in older adults. The processes by which Tai Chi elicits these improvements are yet unknown, although Tai Chi is recognized as a useful method for improving balance and reducing falls. One study showed that older adults who regularly participated in Tai Chi had more sensitive neuromuscular responses than sedentary controls and responded more quickly to surprise ankle inversion perturbations, which facilitated the timely correction of postural problems to avoid falls (22). However, no studies have elucidated the potential mechanisms by which Tai Chi improves the dynamic stability of elderly patients with sarcopenia, especially the association with neuromuscular responses. Therefore, this study examined the effects of 12 weeks of regular Tai Chi practice on neuromuscular responses in elderly patients with sarcopenia and further investigated the mechanisms by which Tai Chi practice improves their postural control. In this study, we hypothesize that 12 weeks of Tai Chi exercise can improve the neuromuscular reactions and dynamic postural control ability of elderly patients with sarcopenia and that there is a certain correlation between the degrees of improvement in the two.

Methods

This study was designed as a parallel randomized controlled trial. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Shanghai Fourth People's Hospital (No. SYLL2023008). We registered the study in the Chinese Clinical Trial Registry (No. ChiCTR2200063921).

Participants

Participants were recruited in the Outpatient Department of ZheJiang Hospital and surrounding communities through posters, oral presentations, Internet advertisements, and WeChat platforms from March 2021 to September 2022. From the study of Xu et al. (22), the reaction time of the tibialis anterior muscle was 81.91 ± 8.20 ms in older adults with Taijiquan intervention and 88.52 ± 6.67 ms in those without specific exercise intervention. The sample size was calculated by analysis using PASS software (power = 0.86; α = 0.05). The minimum sample size needed was 25, and considering a 15% shedding rate, the sample size required for each group in this study was 30. Inclusion criteria were as follows: (1) met the diagnostic criteria for sarcopenia (Asian Working Group for Sarcopenia, AWGS) (2); (2) male or female participants aged 60 to 80 years; (3) had a history of falling during the last 2 years and met the cutoff time of 15.96 s for the Timed Up & Go (TUG) test to check for recurrent falls; (4) were able to walk independently without the help of an aid, such as a cane; and (5) agreed to a random assignment to receive an intervention for 12 weeks and to sign an informed consent form. Exclusion criteria were as follows: (1) sprains, fractures, severe joint deformities or other traumatic injuries that cause immobility; (2) severe cardiovascular or cerebrovascular diseases, skeletal muscular system diseases or neurological diseases; (3) speech, hearing, cognitive or vestibular dysfunction; (4) history of regular exercise within the last 1 year; and (5) taking part in additional forms of exercise during the research period.

Initially, 124 participants were selected, however, 64 were later disqualified. In particular, 43 participants did not meet the inclusion requirements, and 21 people were unable to finish the entire study for a variety of reasons. The remaining 60 participants met the qualifying requirements and completed the informed consent form (Figure 1).

Randomization and blinding

A total of 60 eligible participants were randomly assigned to either the Tai Chi group (n = 30) or the control group (n = 30). An independent researcher who was not involved in baseline data collection, clinical interventions, outcome evaluations, data gathering, or statistical analysis used the SAS Statistics program version 9.4 (SAS Institute Inc. Cary, NC, United States) to generate random sequences.

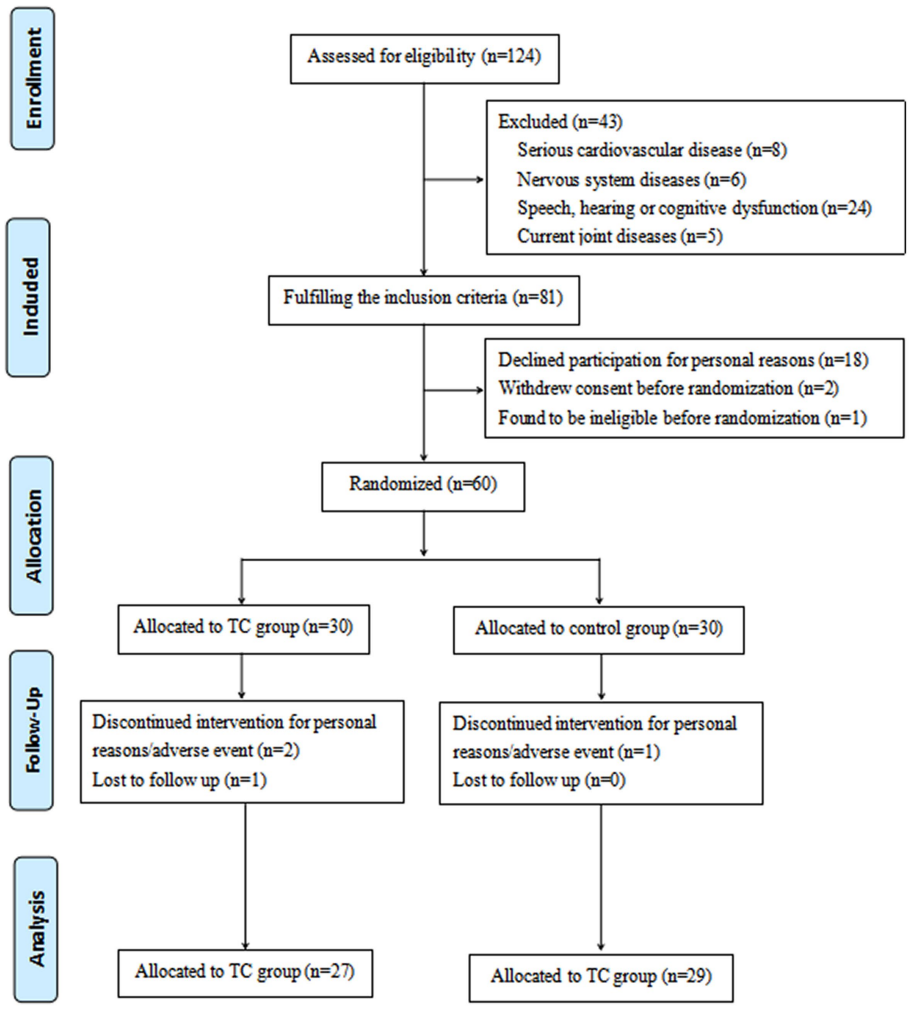

FIGURE 1
CONSORT diagram of the eligibility, exclusion and randomization scheme.

Assignments were enclosed in sequentially numbered, opaque-sealed envelopes to hide the participant allocation. Clinicians strictly followed the aforementioned inclusion and exclusion criteria when deciding whether subjects were eligible to participate in the study. The eligible number of patients was sent to the recruiters by the researchers, who also obtained a sealed, opaque packet with information about the intervention, allocation, and randomization. Then, they gave the envelope to the therapist or clinician. Notably, group allocations were not disclosed to the researchers in charge of recruiting subjects. The clinical intervener opened the envelope and learned about the intervention plan that was given to the participants. The participants, clinician, and therapist could not be blinded after being assigned to the clinical intervention due to its nature. Prior to the completion of all data analyses, the outcome assessors and data statisticians did not know the treatment allocation.

Interventions

The control group

Starting at the beginning of the study, participants in the control group received 45-min health education sessions once every 2 weeks for 12 weeks. Health education was conducted by a clinician to educate the participants regarding sarcopenia, including the etiology, pathogenesis, clinical manifestations, hazards to elderly individuals, and prevention and treatment measures of sarcopenia. Participants in the control group maintained their prestudy routine during the experimental period and did not participate in any planned training activities, such as brisk walking or resistance training.

The Tai Chi group

The Tai Chi group engaged in a 40-min simplified eight-style Tai Chi exercise session based on the provided health education. The simplified eight-style Tai Chi exercise procedures included (1) brachial rewinding, (2) left- and right-knee kyphosis steps, (3) left and right mustang mane, (4) cloud hand, (5) left and right Golden Rooster, (6) right and left foot pedal, (7) right- and left-wing fingertips, and (8) crossing hands. Simplified eight-style Tai Chi is composed of slow, fluid, and rhythmic motions that highlight the practitioner's attention on trunk rotation, weight shifting, coordination, and maintenance of lower limb postural stability. To prevent overly rigorous activities around the knee joints, changes were made that concentrated on decreasing and avoiding sustained unilateral weight bearing, dynamic rotation of the knee joints, and excessive knee flexion (i.e., low stance). The training program started with simple standing postures that emphasized proper body alignment, body mass centering, weight shifting in multiple directions, and easy knee flexion and extension with minimal resistance. The difficulty level of the exercises gradually increased over time.

The protocol comprised three distinct phases, wherein the first phase (weeks 1–2) emphasized basic Tai Chi preparatory movement exercises such as weight shifting, knee flexion, push-off with toes, meditation, rhythmic breathing, and Tai Chi, with 4 repetitions of 5 min with 3 min of recovery between repetitions. The second phase (weeks 3–4) centered on mastering the forms and associated movements, with 5/6 repetitions of 4 min with 2 min of recovery between repetitions. The third phase (weeks 5–12) focused on practicing and reinforcing the precision and sequence of the forms by varying the practice configuration, such as changing directions, 7/8 repetitions of 3 min with 1 min of recovery between repetitions.

An experienced Tai Chi coach instructed and supervised patients with sarcopenia to maintain the consistency of the practice time and the fundamental correctness of the action rhythm. Each tai chi session included three components: a 5-min warm-up, a 30-min tai chi exercise routine, and a 5-min cool-down. There were 36 sessions held three times per week over the course of 12 weeks.

Patients were encouraged to participate even if they experienced slight fatigue throughout the entire training process. If a patient's fatigue was obvious during a training session, as measured by a Borg's CR-10 scale score of >4 points, we advised the patient to rest or stop training and resume once the fatigue had been relieved.

Outcome measurements

Two assessors who had received professional training and were unaware of the intervention allocation assessed the subjects within 3 days prior to the intervention and within 3 days after completion of the intervention.

Referring to the designs reported in other related studies (23, 24), we simulated ankle inversion using the movable platform offered by the dynamic stability test module in ProKin 254 (TecnoBody, Italy). The foot platform on this device can tilt up to 15° from horizontal on all sides. The tilting's onset and terminating signals could be collected simultaneously with the EMG signals.

First, the tests were explained to the participants, after which the equipment was calibrated for each person's age, height, and body mass. The test subjects were instructed to stand on the platform in bare feet, evenly distributing their weight between the two feet and arms crossed against chest. The axis of rotation of the platform was just medial to between the two feet. To familiarize the subjects to the dynamic stability testing procedure, they were given two practice runs on the movable platform.

Then, the placement of the EMG electrodes above the center of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius of the right leg was confirmed by manual testing and voluntary contractions. After the subject stood on the platform, the researcher turned on the dynamic stability test without the subject's knowledge to make the platform movable, and the researcher simultaneously randomly pressed a plane on the platform to cause a sudden perturbation of the subject's ankle joint. Subjects were required to regain balance through lower limb control and remain on the movable platform for 20 s. At the end of the test, we obtained the overall stability index (OSI) of each subject by ProKin 254, and the EMG activity of the right leg muscles was collected.

Subjects who shifted their feet on the platform or held the bar with both hands during the test were considered to have failed the test and needed to retest. At least three qualified EMG data sets were collected for each subject. Rest periods of approximately 2 min in length were provided between trials to counteract the risk of subject fatigue.

Overall stability index

The OSI reflects the subject's postural control, with larger values indicating poorer postural control and higher fall risk (25).

EMG (neuromuscular response time)

The surface EMG signals of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius muscles of

TABLE 1 Baseline demographic and clinical characteristic of the participants.

Demographic characteristic	Tai Chi group (n=27)	Control group (n=29)	t/χ^2	p
Age (year)	69.70 ± 5.05	72.14 ± 4.79	−1.852	0.07
Gender			1.220	0.269
Male	17	14		
Female	10	15		
Height (cm)	163.11 ± 6.79	162.24 ± 5.14	0.540	0.591
Weight (kg)	55.08 ± 2.57	54.53 ± 1.85	−0.599	0.549
BMI (kg/m^2)	20.75 ± 1.23	20.74 ± 0.80	0.037	0.970
Education			1.259	0.739
Bachelor or above	3	5		
High school	7	8		
Middle school	5	7		
Primary school	12	9		
Number of fall			0.386	0.534
>2 times per year	9	12		
<2 times per year	18	17		
Fall injury	8	11	0.430	0.512
TUGT (second)	20.63 ± 3.31	19.11 ± 2.52	−1.600	0.110

TABLE 2 Comparison of reaction time at baseline and 12-week follow-up among the two groups (mean±standard deviations).

Outcome variable	Tai Chi group (n=27)	Control group (n=29)
Rectus femoris		
Baseline	142.75 ± 8.41	141.03 ± 7.00
After 12-week intervention	143.47 ± 7.17	126.25 ± 7.58[ab]
Semitendinosus		
Baseline	138.07 ± 5.56	137.36 ± 7.19
After 12-week intervention	137.14 ± 4.17	127.10 ± 7.54[ab]
Gastrocnemius		
Baseline	151.04 ± 6.55	150.28 ± 5.87
After 12-week intervention	152.30 ± 5.73	137.36 ± 6.26[ab]
Anterior tibialis		
Baseline	135.40 ± 6.34	134.17 ± 5.52
After 12-week intervention	136.64 ± 6.28	121.28 ± 5.81[ab]

[a]Denotes a difference significant at $p < 0.05$ when compared with pretest values; [b]denotes a difference significant at $p < 0.05$ when compared with the control group.

the right leg of each individual were collected using a Bagnoli-8 EMG system (Delsys, United States). LabVIEW Software (National Instruments, United States) was used to sample the raw EMG signals at 1000 Hz, and the results were saved on a computer for off-line data reduction.

A similar procedure to that used by Xu et al. (22) and Li et al. (26) was used for EMG data reduction. EMG software was used to measure the raw EMG signals. The period in milliseconds (1 sample = 1 ms) between the initiation of the movable platform and the first rising response of EMG signals from baseline to certain activity is referred to as the neuromuscular response time. A tiny artifact occasionally appeared in the EMG signal when the electric motor operating the movable platform started. The earliest reflex activity would start 45 ms after the movable platform opened; therefore, everything that happened before that was disregarded. The same researcher analyzed the data from the right leg.

Statistical analysis

Statistical analysis was carried out using SPSS Statistics, version 22.0 (SPSS Inc., Chicago, IL, United States). The intention-to-treat principle was used for all assigned individuals with data to analyze the results. If the distribution of the variables was normal or skewed, continuous variables were expressed as the mean standard deviation (SD) or medians (25th to 75th centiles). The Mann–Whitney test was used for further analysis of categorical data. Repeated-measures ANOVA was used to evaluate variables with multiple measurements. To clarify the relationship between neuromuscular response and postural control ability, we calculated Pearson's or Spearman's correlation coefficients (r) between 12-week changes in the response time of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius muscles of the right leg and OSI. Statistical significance was determined when a result had a corresponding p-value <0.05.

Results

At 12 weeks, 56 of the 60 eligible individuals had finished the assessment. After several weeks of exercise, a total of 3 participants in the Tai Chi group and 1 participant in the control group dropped out, and contact was lost. After 12 weeks, participants in the Tai Chi group and control group completed 90 and 96.7%, respectively, of the total planned exercise sessions (Figure 1). As far as the baseline comparison allowed, there were no differences between the two participant groups (Table 1).

Within-group comparisons revealed that in the Tai Chi group, there was a significant reduction in OSI and response time of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius after 12 weeks of intervention compared to baseline ($p < 0.05$), but there were no significant prepost differences in the above indicators in the control group ($p > 0.05$). Between-group comparisons demonstrated no significant baseline differences between the Tai Chi and control groups for OSI or response time of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius ($p > 0.05$), but the Tai Chi group had significantly lower levels of these indicators than the control group after treatment ($p < 0.05$) (Tables 2, 3).

In the Tai Chi group, significantly positive correlations were observed between the changes in OSI and the changes in response time of the rectus femoris ($r = 0.682$, $p < 0.001$), semitendinosus ($r = 0.488$, $p = 0.007$), anterior tibialis ($r = 0.757$, $p < 0.001$), and gastrocnemius ($r = 0.767$, $p < 0.001$). Furthermore, no significant correlations were observed between changes in OSI and response times in the control group ($p > 0.05$) (Table 4).

TABLE 3 Comparison of OSI at baseline and 12-week follow-up among the two groups (mean±standard deviations).

Outcome variable	Tai Chi group (n=27)	Control group (n=29)
Baseline	4.65 ± 0.42	4.80 ± 0.29
12-week	4.76 ± 0.35	4.00 ± 0.24[ab]

[a]Denotes a difference significant at $p < 0.05$ when compared with pretest values; [b]denotes a difference significant at $p < 0.05$ when compared with the control group.

TABLE 4 Correlations of changes in reaction time with changes in OSI among Tai Chi Group (n=27) and control group (n=29).

	OSI	
	r	p
Reaction time (rectus femoris)		
Control group	−0.142	0.480
Tai Chi group	0.682	0.000
Reaction time (semitendinosus)		
Control group	0.121	0.547
Tai Chi group	0.488	0.007
Reaction time (anterior tibialis)		
Control group	−0.015	0.940
Tai Chi group	0.757	0.000
Reaction time (gastrocnemius)		
Control group	0.193	0.334
Tai Chi group	0.767	0.000

Discussion

Our 12-week Tai Chi training protocol resulted in a significant reduction in neuromuscular response time for the right lower limb muscles of the rectus femoris, semitendinosus, gastrocnemius, and anterior tibialis in elderly patients with sarcopenia. Additionally, the patients' dynamic posture control ability was also significantly improved. Sorock et al. believe that the deterioration of neuromuscular function related to age or disease is the root cause of increased risk of falls in the elderly (27). There is currently research indicating that elderly individuals have longer neuromuscular response times in their lower limbs than younger individuals (28–30). Regarding the differences between fallers and nonfallers, Studenski et al. found that fallers have a 7–10 ms longer neuromuscular response time as well and believe that excessively delayed neuromuscular responses can lead to inadequate postural adjustments in situations of falling (31). Therefore, observing a shortened neuromuscular response time and improved performance on dynamic balance tests in our study indicates that our 12-week Tai Chi training protocol has a positive effect on improving postural control and reducing the risk of falls in elderly patients with sarcopenia. Furthermore, our study found a positive correlation between the degree of improvement in neuromuscular response and dynamic posture control ability, which further reflects the potential role of enhanced neuromuscular response as a factor in improving posture control and reducing the risk of falls in elderly patients with sarcopenia through Tai Chi exercise.

Tai Chi is a graceful, slow, continuous movement form that demands that exercisers always maintain flexion of the hip and knee and dorsiflexion of the ankle during exercise. Sun et al. found that after 1 year of Tai Chi exercise in elderly women, the neuromuscular response times of the rectus femoris, semitendinosus, and gastrocnemius muscles were significantly shortened (32). Similarly, DQ also demonstrated that long-term Tai Chi exercise has a positive effect on the neuromuscular response of the lower limbs (22). However, there are currently no studies reporting the effect of Tai Chi on neuromuscular response in elderly patients with sarcopenia. Possible reasons include the following: (1) each movement of Tai Chi requires accuracy, fluidity, and naturalness, but Tai Chi involves much single-leg support and significant weight shifting movements, which can be difficult for elderly patients with sarcopenia to complete; and (2) traditional Tai Chi training typically consists of 24 movements, which can be time-consuming and may pose a challenge for elderly patients with sarcopenia to complete the entire sequence. Taking into account the above reasons, we have adopted the simplified eight-style Tai Chi exercise, which reduces and avoids continuous single-leg weight-bearing, dynamic rotation of the knee joint, and excessive flexion of the knee joint, and have developed a progressive training plan. From the results of our study, the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius muscles of the patients in the Tai Chi group showed faster responses than those of the patients in the control group after 12 weeks of intervention, and further comparison of dynamic posture control ability revealed that the OSI in the Tai Chi group was better than that in the control group after 12 weeks of intervention. This is related to the ability of Tai Chi to improve neuromuscular responses in elderly patients with sarcopenia. First, long-term Tai Chi exercise can frequently stimulate joint proprioceptors, promote and consolidate the process of proprioceptive transmission, and strengthen the neuromuscular response ability, and when the body is disturbed by the outside world, it can quickly perceive changes in body space position and maintain balance. Second, in Tai Chi, participants always maintain a squatting position with flexed hips and bent knees with their own body weight, providing the resistance to keep the lower limb muscles in a state similar to a constant isometric muscle action. This improves the central nervous system excitation time, which is conducive to neuromuscular response ability.

When an organism is subjected to external environmental disturbances, the central nervous system takes the lead in producing preprogrammed posture responses, including feedforward control, feedback control, and voluntary movement control, which sequentially activate posture muscle activity, action muscle activity, and the coordination between the two, thereby quickly and effectively maintaining body center of gravity stability and limb spatial positioning and preventing imbalance and falls. To some extent, the neuromuscular response ability in elderly people can represent their posture control ability. After sudden ankle perturbation, the loaded leg displayed flexion of the hip and knee and dorsiflexion of the ankle (26). Obviously, this is accomplished by contracting the anterior tibialis, gastrocnemius, hamstrings and quadriceps muscles. This activation strategy appears to have two goals: to increase stability and to minimize the load on the inverting foot. Therefore, in this study, we reflected the patient's posture control capability by analyzing the neuromuscular response ability of the aforementioned four muscles.

A previous study on upright subject posture reactions typically employed the classic trap-door test using ankle inversion devices with a 30° tilted trapdoor to induce ankle inversion, combined with surface electromyography measures of muscle activation timing, activation duration, and muscle activation level (23, 33, 34). However, for elderly patients with sarcopenia, the 30° tilted angle is often too large, and they may have difficulty completing the test or even fall during the test. Moreover, this ankle inversion device cannot objectively reflect the patient's overall postural control during testing. Finally, in daily life, patient falls are caused not only by ankle inversion but also by ankle eversion, ankle dorsiflexion, and ankle plantarflexion in other directions. In our study, we chose the unstable platform provided by the dynamic stability test module in ProKin 254 to observe the pose response. ProKin254, as a new type of balance testing device, utilizes computerized numerical assessment to provide accurate quantitative scores, which can comprehensively, in detail, and objectively evaluate the posture control ability of the subjects. The dynamic stability test module in Prokin254 enables the platform to tilt in various directions to simulate scenarios of patients falling in different directions. Meanwhile, considering the particulars of elderly patients with sarcopenia, the tilting angle was decreased to 15° to prevent falls during the test. In this study, we used Prokin254 to assess the postural control ability of subjects under sudden ankle disturbance and real-time evaluation of the neuromuscular response ability of the rectus femoris, semitendinosus, anterior tibialis, and gastrocnemius and explored the potential correlation between the two. The results showed that the degree of improvement in neuromuscular response time in the Tai Chi group was significantly positively correlated with the degree of improvement in postural control ability, suggesting that Tai Chi may improve postural control ability and reduce the risk of falls in elderly patients with sarcopenia by improving neuromuscular response ability.

Conclusion

Our Tai Chi training protocol simplifies the training movements, reduces the training difficulty, and gradually increases the workload. This training protocol is feasible, safe, and repeatable for elderly patients with sarcopenia. Twelve-weeks of Tai Chi exercise can improve the neuromuscular response of the lower extremities in elderly patients with sarcopenia, shorten their neuromuscular response time when balance is endangered, and enhance their dynamic posture control ability. The application of this protocol in communities may favor a reduction in fall risk and promote socialization among elderly patients with sarcopenia. In the future, we plan to conduct multicenter, large-sample size studies to further validate the conclusion of this study, thus promoting the promotion and application of this protocol among elderly patients with sarcopenia.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Zhejiang Hospital (No. 2021-135 K). The patients/participants provided their written informed consent to participate in this study.

Author contributions

DH designed the clinical trial, analyzed the data, and wrote the publication. XK, WS, JF, and AZ carried out the experiment's feasibility analysis, were in charge of the article's quality control and review, and were in charge of the article's general management and supervision. HZ, RZ, and FL were responsible for data gathering and trial evaluation. CJ provided support for language polishing and guidance for final revisions of the article. All authors reviewed and approved the article's submission.

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Conflict of interest

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

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Effects of community ambulation training with 3D-printed ankle–foot orthosis on gait and functional improvements: a case series of three stroke survivors

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Introduction: Many of the patients using ankle–foot orthoses (AFOs) experience poor fit, pain, discomfort, dislike of the aesthetics of the device, and excessive range of motion restrictions, which diminish the use of AFOs. Although 3D-printed ankle–foot orthoses (3D-AFOs) affect patient satisfaction and overall gait functions such as ankle moment, joint range of motion (ROM), and temporal-spatial parameters, the material properties and manufacturing process of 3D-AFOs are still diverse; the clinical effects of community ambulation using 3D-AFOs and satisfaction in patients with stroke are poorly understood.

Case description: Case 1: A 30-year-old man, with a history of right basal ganglia hemorrhage, presented with marked foot drop and genu recurvatum. Case 2: A 58-year-old man, with a history of multifocal scattered infarction, presented with an asymmetrical gait pattern due to abnormal pelvic movement. Case 3: A 47-year-old man, with a history of right putamen hemorrhage, presented with recent poor balance and a prominent asymmetrical gait pattern due to increased ankle spasticity and tremor. All patients could walk independently with AFOs.

Interventions and outcomes: Gait was assessed under three walking (even, uneven, and stair ascent/descent) and four AFO (no shoes, only shoes, shoes with AFOs, and shoes with 3D-AFOs) conditions. After 4 weeks of community ambulation training with 3D-AFO or AFO, the patients were followed up. Spatiotemporal parameters; joint kinematics; muscle efficiency; clinical evaluations including impairments, limitations, and participation; and patient satisfaction with wearing 3D-AFO were evaluated.

Results and conclusion: 3D-AFOs were suitable for community ambulation of patients with chronic stroke and effective on step length, stride width, symmetry, ankle range of motion, and muscle efficiency during even surface walking and stair ascent in patients with chronic stroke. The 4-week community ambulation training with 3D-AFOs did not promote patient participation; however, it increased ankle muscle strength, balance, gait symmetry, and gait endurance and reduced depression among patients with a history of stroke. The participants were satisfied with 3D-AFO's thinness, lightweight, comfortable feeling with wearing shoes, and gait adjustability.

KEYWORDS

stroke, gait, stair, 3D printing, ankle-foot-orthosis (AFO), community

1. Introduction

Mobility is limited in most stroke survivors, and the restoration of gait ability is a major task in their rehabilitation (1). Walking difficulties in patients with stroke can be managed using ankle–foot orthoses (AFOs), which stabilize the foot and ankle. Customized AFOs are often prescribed to prevent foot drop causing serious falls, alleviate chronic pain associated with joint deformity, and control the ground reaction force during the stance phase of gait to reduce fatigue (2). However, many AFO users experience poor fit, pain, discomfort, and dislike of the aesthetics of the device; moreover, the design options are limited (3). Although many patients with stroke have an insufficient level of physical function that may cause increased fear of community ambulation, which further leads to depression, they often intentionally avoid AFOs (4).

3D-printed ankle–foot orthoses (3D-AFOs) can be personalized based on individual biomechanical requirements to provide improved function, better fit, and enhanced aesthetics (2). Some recent studies reported that 3D-AFOs affect patient satisfaction and overall gait functions such as ankle moment, joint range of motion (ROM), and temporal-spatial parameters (5–7). The size, thickness, weight, durability, easy usability, walking efficiency, and adjustability should be considered while fabricating 3D-AFOs (2). However, the material properties and physical features of 3D-AFOs are still diverse, and studies on their clinical effects and patient satisfaction are limited (2). Furthermore, only a few studies reported long-term effects of wearing 3D-AFOs (7, 8), and no studies compared the effects of community ambulation with conventional AFOs in patients with stroke.

Community ambulation is an important skill for stroke survivors that incorporates both mobility and social aspects (9). Approximately one-third of stroke survivors with ankle–foot impairment were unable to walk outdoors independently (9, 10). Patients with ankle–foot impairment commonly have limited ability to walk confidently in public venues including uneven terrains, stairways, and slopes, which is closely linked to their participation in community ambulation. Nevertheless, no studies reported whether the use of AFOs in a community environment increases social participation and gait function of patients with stroke.

Herein, we report the effects of community ambulation with 3D-AFOs on gait kinematics, muscle efficiency, and social participation of three patients with chronic stroke after 4-week training.

2. Methods

2.1. Case presentation

Case 1: A 30-year-old male university student had a history of right basal ganglia hemorrhage with 10 months 12 days duration at the first day of participation. He could walk with AFO on level ground under supervision or stand-by help from one person. He was very motivated to go back to school and meet his friends. The patient had good balance (47 on the Berg balance scale, BBS), slight spasticity diagnosed on the basis of resistance to passive stretch of ankle plantar flexor at rest (1/5 on the modified Ashworth scale, MAS) (11), and proprioceptive dysfunction (Supplementary Table 1). During observational gait analysis, the patient presented with marked foot drop during the swing phase of walking and plantarflexion during the stance phase with appreciable genu recurvatum.

Case 2: A 58-year-old male high school teacher had a history of multifocal scattered infarction 24.5 months ago. He used the prescribed AFO only during level walking and stair ambulation. He was planning to return to work 3 months later. The patient had poor muscle strength (1/5 of the ankle dorsiflexor based on manual muscle test, MMT) (12) and mild spasticity (1/5 on MAS) without any observable proprioceptive dysfunction. He had good balance (45 on BBS) and hemiplegic asymmetrical gait pattern due to abnormal pelvic movement and stiff ankle during walking.

Case 3: A 47-year-old male white-collar worker had a history of right putamen hemorrhage 21.2 months ago. He always had to use the prescribed AFO and cane due to deteriorated ankle spasticity during walking. He was planning to return to the countryside house after discharge. The patient had poor muscle strength (2/5 on MMT), marked spasticity (1+/5 on MAS), and observable proprioceptive dysfunction. He presented with poor balance (43 on BBS) and a prominent asymmetrical gait pattern (weight bearing was biased toward the non-paretic side) due to increased ankle spasticity and tremor. He could walk independently with both AFO and cane at his own slow speed.

This study was approved by the Institutional Review Board of the National Rehabilitation Center, Seoul, South Korea (IRB No. NRC-2021-01-002) and registered for clinical research (No. KCT0007195) prior to the study. All participants provided written informed consent before study enrollment. This study's design was a case series, retrospective study based on single-center trials. All participants were assessed on gait function in four AFO conditions and functional ability and reassessed on functional ability at the end of the 4-week intervention period.

2.2. Procedure for manufacturing 3D-printed ankle–foot orthosis

The initial aim of manufacturing 3D-AFO was to provide a personalized orthosis with improved fit and convenience. The process was divided into three steps (Figure 1): 1) 3D scanning (13): A portable 3D scanner (EinScan Pro 2x, SHINING 3D, San Leandro, United States) captured the hemiparetic areas of the lower limb to generate the initial AFO design. The images were obtained with the patient lying supine, and the target leg was supported by a tripod. The high-resolution image file was remeshing through MeshLab to obtain a smooth curved surface. 2) 3D designing: Unwanted surfaces for 3D printing, such as the medial and lateral malleolus, heel of the foot, and forefoot, were removed from the images using the 3D system's Geomagic Freeform Plus program and phantom haptic device. 3) 3D printing: The designed AFO model was printed in Z-FLEX filament, which is a thermoplastic polyester elastomer with excellent interlayer adhesion and precision of dimensional tolerance, using a 3D printer (Zortrax M300 plus, Olsztyn, Poland). Finally, unnecessary supports of the printed AFO were removed, the center line was cut

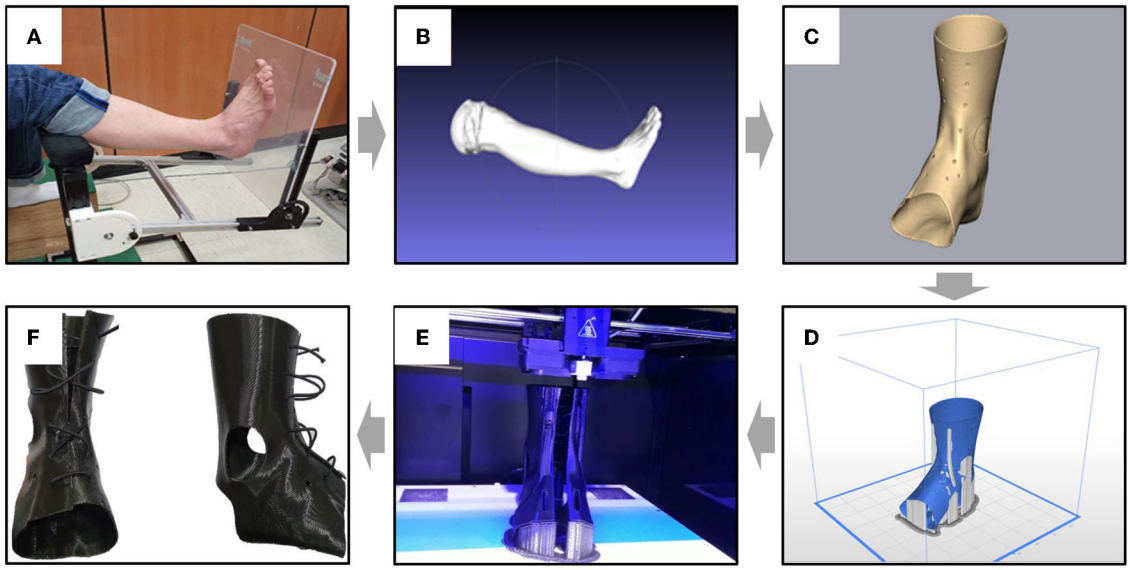

FIGURE 1
Manufacturing process of customized 3D-printed ankle–foot orthosis (3D-AFO). The process is as follows: **(A)** ankle–foot scanning, **(B)** remeshing from high-resolution image to smooth curved surface, **(C)** individual AFO design with a haptic device, **(D)** 3D printing simulation with print condition setting (infill density: 70%, nozzle thickness: 0.1 mm, layer thickness: 0.19 mm), **(E)** design model output using a 3D printer, and **(F)** final prototype of 3D-AFO.

off, and the length of the band connecting the hole along the center line was adjusted with a boa dial.

2.3. Training

After baseline assessments, the patients performed gait training with 3D-AFO (cases 1 and 2) or conventional AFO (case 3) in various community settings (Figure 2). The intervention program consisted of gait training on even/uneven terrains, curbs, and slopes for 20 min, followed by stair ambulation for 20 min at a progressive walking level per week. The training was performed for 40 min per session for a total of 20 sessions for 4 weeks.

2.4. Assessments

The gait was evaluated under three walking (even, uneven, and stair ascent/descent) and four AFO (barefoot, only shoes, shoes with AFOs, and shoes with 3D-AFOs) conditions before and after the intervention (14). To compare differences in gait kinematics according to AFO conditions, all subjects underwent the same gait assessment process with four conditions, i.e., bare foot, shoe, conventional AFO, and 3D-AFO, under three walking conditions at the initial evaluation, i.e., on even and uneven surface and stair. After the sufficient walking adaptation periods, the patients performed a minimum of three trials under each randomized condition, and a minimum of three steps per trial were recorded. The participants did not take the AFOs and shoes off until all gait assessments were completed. For walking on even and uneven surfaces, the patients walked on a 1.5 × 10 m walkway covered with industrial carpeting at a comfortable speed. The uneven surface was created using randomly arranged triangular wooden prisms (H 1.5 cm × W 3.5 cm × L 6–12 cm) placed under a 1.5 × 10 m strip of industrial carpeting with a surface texture identical to that of the even surface. During the stair (17.5 cm riser, 30 cm tread, and 90 cm width) ascent and descent, handrails were present for safety, but they were lightly gripped to prevent weight shift. As footdrop or increased ankle muscle tone could seriously affect the patients' safety, barefoot stair walking was not performed.

To capture kinematic data, 20 reflective markers were placed on each side of the lower limbs. A 12-camera motion capture system (VICON, UK), sampled at 100 Hz, was used. Motion data were low-pass filtered at 6 Hz with a fourth-order Butterworth filter. Surface electromyography (EMG; Delsys Trigno Wireless EMG, Delsys, USA) was performed at 2,000 Hz on each side of the quadriceps (rectus femoris, Q), hamstring (biceps femoris, H), tibialis anterior (TA), and medial gastrocnemius (MG) muscles. The EMG data were processed using a 20–400 Hz band-pass filter and rectification and normalized by maximum voluntary isometric contraction.

Since stroke is the third leading cause of disability in developed countries and the sixth leading cause throughout the world (15), it was one of the first health conditions to receive attention that consider the international classification of functioning, disability, and health (ICF). The ICF model represents a new paradigm with a broader biopsychosocial approach that considers not only the health condition but all factors that can exert a positive or negative influence on functioning (16). Therefore, physical impairments, activity limitations, and social participation according to the ICF model were assessed before and after the training. For the physical

FIGURE 2
Community gait training consisting of walking on even and uneven terrains, obstacles, slopes, curves, and stairs. The subjects were trained to walk on the ramp **(A, C)** and stairs **(B, G)** for at least 1 week in an indoor environment. After that, for the remaining 3 weeks, the training of walking on uneven surfaces **(D–F)**, climbing the slope **(H)**, and going down the slope **(I)** was gradually increased in the outdoor community environment.

impairments, MVIC of paretic ankle muscles was measured using a portable manual muscle strength tester (Lafayette, USA, 2018). The isometric strength of the ankle dorsiflexors, plantar flexors, invertors, and evertors was measured for 5 s, and the maximum value was recorded. For the activity limitations, Fugl–Meyer lower extremity (FM-L), BBS, and a 6-min walking test were performed. The motor domain of FM-L includes measurements of movement, coordination, and reflex action of the hip, knee, and ankle (17). The domain is rated on a 3-point ordinal scale (0 = cannot be performed, 1 = partially performed, and 2 = fully performed). The maximum possible score of the motor domain of FM-L is 34, corresponding to full sensorimotor recovery. BBS was used as a clinical test of a subject's static and dynamic balance (18). The test comprised a set of 14 simple balance-related tasks, ranging from standing up from a sitting position to standing on one foot. The 6-min walking test is commonly used as a measure of walking endurance and a significant predictor of community ambulation and integration in individuals with stroke (19). For social participation, the stroke impact scale, fall efficacy scale, and Beck Depression Inventory were considered. The stroke impact scale participation domain, which includes selected items from the hand function, activity of daily living/instrumental activity of daily living, and mobility domains, can be used as stand-alone scales to assess social and physical function (20). The fall efficacy scale was applied to ascertain a person's level of confidence in performing activities of daily living (21). It is a self-reported questionnaire and contains 10 items, with each scored on a scale of 0–10, and the total summed scores range from 0 to 100. A high score indicates high confidence in performing activities of daily living without falling. The Beck Depression Inventory is a 21-item questionnaire commonly used in research on post-stroke depression (22).

Patient satisfaction with wearing 3D-AFO was investigated using the system usability scale (SUS) and open-ended questions (23).

2.5. Data analysis

All the motion and EMG data were exported using Visual 3D software (C-Motion, USA). We analyzed spatiotemporal parameters, joint kinematics, and integrated EMGs and calculated the ankle muscles co-contraction index (CI), which indicates muscle efficiency wherein the antagonist and agonist muscles (i.e., tibialis anterior and medial gastrocnemius) were activated in stance and swing phases (24):

$$CI = \frac{\int_{t1}^{t_2} EMG_{TA}\,(t)\,dt}{\int_{t_1}^{t_2} [EMG_{TA} + EMG_{MG}]\,(t)\,dt} \times 100.$$

The data were averaged and compared among three walking and four AFO conditions.

3. Results

3.1. Initial effect

As a result of initial gait assessments of the three participants, the walking speed and step length increased more in 3D-AFO conditions, followed by AFO and only shoes (Figure 3 and Supplementary Table 2) conditions. Stride width increased more in the 3D-AFO condition than in the AFO condition. Among all the AFO conditions, 3D-AFO showed the most symmetrical gait. The ankle and thigh muscle CI increased more in the only shoes and AFO conditions than in the 3D-AFO conditions. The ankle ROM increased the most in the only shoes condition, followed by the 3D-AFO and AFO conditions; the increase was more on the even surface than on the uneven surface (Supplementary Figures 1, 2). The knee and hip ROM showed the most increase in the AFO condition. During stair ascents, walking speed increased in the AFO and 3D-AFO conditions compared to that in the only shoes condition. 3D-AFO showed the most symmetrical stance time among other conditions. During stair descents, the only shoes condition showed the most increased walking speed and symmetrical cycle time (Supplementary Table 3).

3.2. Long-term effects

Patients trained with 3D-AFO acquired increased walking speed (difference value; case 1: 0.1 m/s, case 2: 0.04 m/s) and step length (case 1: 0.2 m, case 2: 0.15 m). However, there was no difference in the stride width with an improvement in the symmetry of the cycle and stance time and decreased symmetry of the step length. Patients trained with AFO showed no difference in walking speed, decreased step length (case 3: −0.01 m), increased stride width (case 3: 0.02 m), and decreased gait symmetry. All patients experienced improvements in their physical impairments (elicited by the strength of ankle dorsiflexor) and activity limitations (elicited by the Fugl–Meyer assessment of lower extremity, Berg balance scale, and 6-min walking test); however, social participation did not increase (elicited by the stroke impact scale and fall efficacy scale). All participants showed decreased Beck Depression Inventory scores after 4 weeks (Figure 4).

3.3. Patient satisfaction

The average SUS score was 69 (SD: 5.2), and 60% of the respondents reported a score of 71 or higher. A SUS score of >70 indicates good products (23). In the interview using open-ended questions, the respondents were satisfied with the use of 3D-AFO in terms of its weight, thinness, better fit, enhanced aesthetics, safety (stability), and improved functions. Furthermore, they revealed that 3D-AFO was more convenient on uneven surfaces, ramps, and stairs when compared with conventional AFO or only shoes. However, they felt uncomfortable due to the difficulty of wearing the 3D-AFO by themselves.

4. Discussion

We investigated the effects of 3D-AFO use on gait kinematics and physical functions of patients with stroke. All the participants had increased step length, stride width, and symmetry; the muscle efficiencies of Q/H and TA/MG were improved during the stance and swing phases, respectively. In particular, stair ambulation with 3D-AFO allowed increased ankle ROM and symmetrical gait when compared with AFO use; this improvement was more effective during the 4-week community ambulation training. This study is unique in that it compared the effects of 3D-AFO, including muscle efficiency and individual satisfaction, in community ambulation.

3D printing technology is advantageous as it maximizes the design freedom to optimize the stiffness properties of AFO (7, 8, 25). The greater AFO stiffness generally results in reduced peak joint angle of ankle plantar flexion and dorsiflexion and increased dorsiflexion at initial contact and total ROM; (5, 26) it also increases the peak ankle dorsiflexion moment and decreases peak knee extension (6). A study that compared different 3D-AFO stiffnesses using various materials reported no significant differences in temporal-spatial parameters and ankle angles, but a difference was noted in the ankle ROM over the whole gait cycle (27). This study also showed increased ankle ROM during stair ascent as well as gait on an even surface. Another study reported that the selective adjusting orthotic stiffness of 3D-AFO can produce stance phase stability, mitigation of toe drag, reduction in steppage gait, and an improvement in symmetry and muscle efficiency (28). In our patients, the step length, stride width, symmetry, and muscle efficiency increased more with 3D-AFO than with conventional AFO, which indicates that a decrease in AFO stiffness helps the user to improve the biomechanical gait function. However, in patients with excessive ankle spasticity that could seriously interfere with gait, walking with AFO was more effective than walking with 3D-AFO. The use of stiff AFO is often accompanied by reduced activity in the paretic ankle muscles and disuse atrophy, causing long-term dependence (29). A previous study compared the muscle activity under different AFO conditions and demonstrated a decrease in CI, which indicates increased muscle efficiency when using dynamic AFO compared with solid AFO (30). Similarly, the stance CI of Q/H and swing CI of TA/MG in 3D-AFO conditions in this study were decreased compared to those of the only shoes and conventional AFO conditions. The TA muscle activity did not differ significantly between the AFO and no orthosis conditions as shown in a previous study (31). Although a few studies have reported muscle efficiency in different AFO stiffnesses, the current study suggests that variations in 3D-AFO stiffness can affect the wearer's biomechanical function and muscle efficiency.

Community environments require adaptations of the lower limb to successfully navigate rough terrain or to ascend and descend slopes and stairs (32). In particular, stair ambulation, which requires higher muscular strength, coordination, and balance (33, 34), is the best predictor of physical activity levels in community-dwelling people with stroke; (33) it requires greater ROM and ankle joint power than level ground walking (35). Although AFO use has the advantage of preventing trips and falls resulting from foot drop and controlling the ground reaction force to reduce

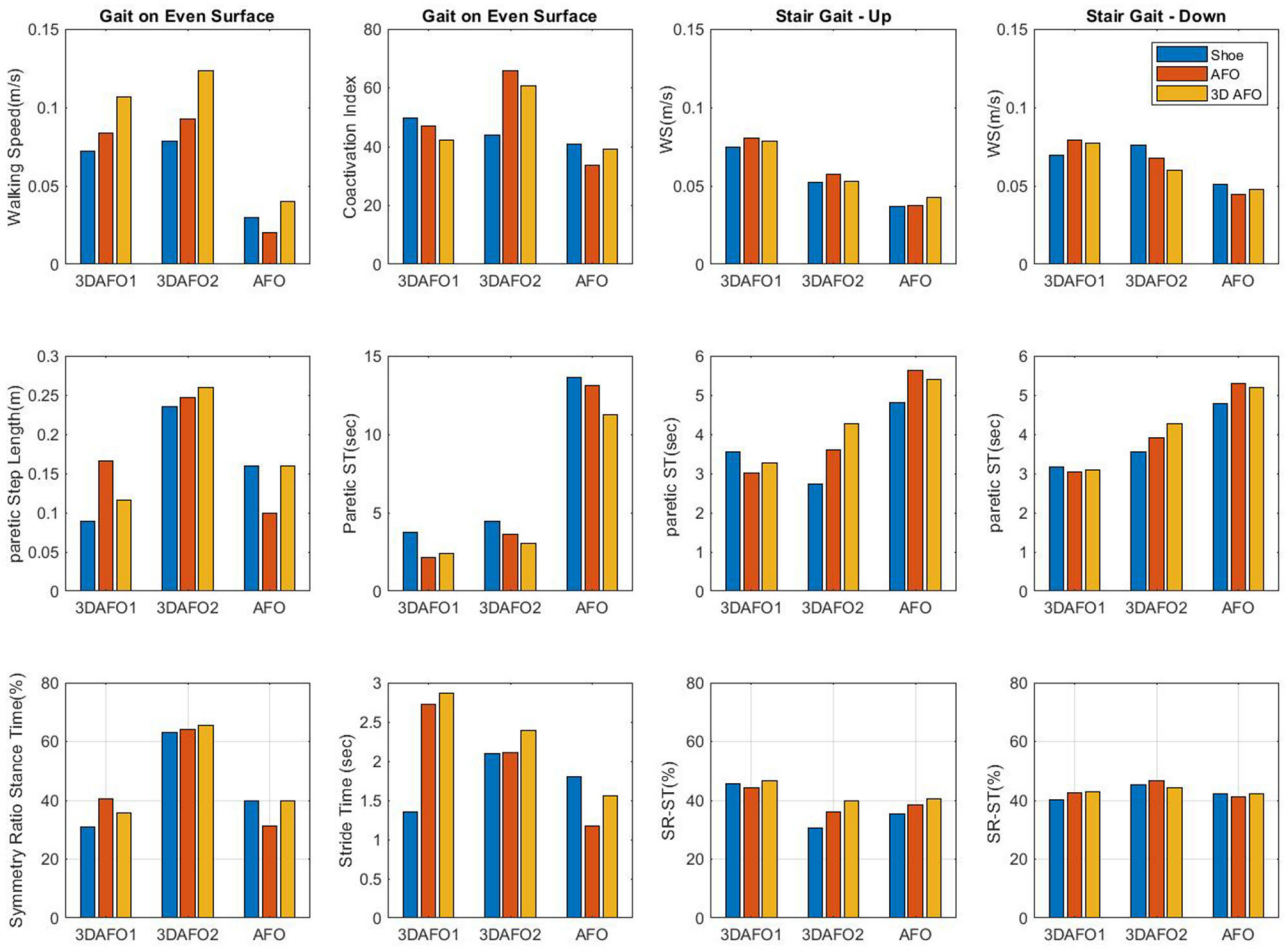

FIGURE 3
Comparison of spatiotemporal gait kinematics in different AFO (ankle–foot orthosis) conditions. AFO, ankle–foot orthosis; 3D-AFO, three-dimensional-printed ankle–foot orthosis; CI, co-contraction index; Q, quadriceps; H, hamstrings; TA, tibialis anterior; GCM, gastrocnemius.

fatigue during stair ambulation (2), it commonly increases the risk of fall because of the limited ankle ROM that does not allow control of the upper part of the lower limb both in stair ascent and decent. Nevertheless, prescribing AFO is recommended for the majority of stroke patients. The meta-analysis of 434 stroke patients reported immediate or short-term effectiveness on walking speed, cadence, step length, stride length, timed up and go test, functional ambulation category score, sagittal plane angle at initial contact, and knee sagittal angle at toe-off ($p < 0.05$) (36). However, this study, differing from previous studies, was mainly focused on the effects of AFO in a simulated community environment such as uneven walkway and stair gait in comparison with its long-term training effect. In the present study, the ankle ROM was more limited in both the AFO conditions than in the only shoes condition; it was limited more with conventional AFO than with 3D-AFO during stair ambulation. During stair ascent, 3D-AFO would have helped to generate an appropriate ankle ROM, allowing the tibia to progress over the foot; (37) active ankle plantar flexion and increased power generation during trailing limb push-up (38) resulted in increased ankle torque and knee extensor moment (39). Conversely, the only shoes condition showed a tendency to decrease the stance time, swing time, and cycle time and increase the symmetry of cycle time during stair descent. Controlled ankle dorsiflexion and power absorption, which are critical for weight acceptance during stair descent, are more feasible in the only shoes condition (37). Nevertheless, 3D-AFO indicated the most symmetric stance time among the other three conditions during stair ascents and more symmetric stance time when compared with AFO condition during stair descent. This indicates that 3D-AFO may be more useful in community environments including uneven terrain, stairways, and slopes; therefore, it is closely linked to social participation.

Satisfaction with AFO wear often has a significant impact on the user's physical function. The users require improved size, weight, adjustability, and durability as well as overall biomechanical function of their AFOs (3). Although the safety and effectiveness of AFO are considered the most important, some individuals, especially adolescents, prioritize the aesthetic and psychological factors (2, 3). A participant of this study, who was planning to return to school as a teacher, was obsessed with the symmetrical gait pattern without an outstanding conventional AFO wear. Another participant complained that conventional AFO was

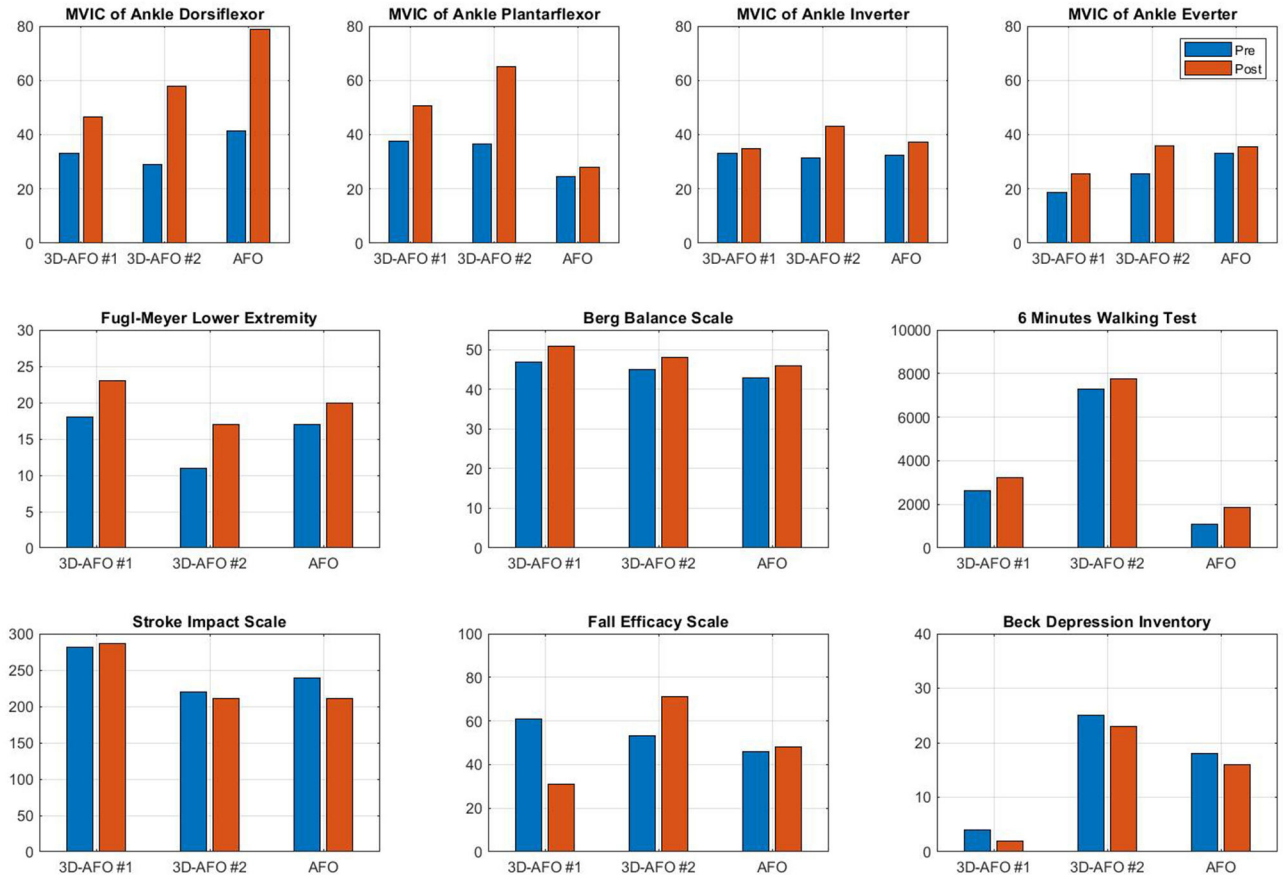

FIGURE 4
Effects of 4 weeks of gait training with AFO on maximum voluntary isometric contraction force of ankle muscles, Fugl–Meyer assessment of lower extremity, the Berg balance scale, the 6-min walking test, the stroke impact scale, the fall efficacy scale, and the Beck Depression Inventory. Pre, pre-test; Post, post-test; FU, follow-up.

bulky, requiring different sizes for both shoes, which led to the development of pain, blisters, and calluses. The participants were satisfied with 3D-AFO's thinness, light weight, and comfortable feeling with wearing shoes. Conversely, they also gave feedback on decreased durability of 3D-AFO when used continuously for more than 2 months; patients with hemiparesis found difficulty in wearing it alone. Nevertheless, all the participants were satisfied with the usability of 3D-AFO when they returned to the community and their colleagues. However, social participation did not improve among our study participants. The flexibility of 3D printing material, i.e., thermoplastic polyurethane, allowed more range of motion of the ankle joint in 3D-AFO, which enabled more comfortable walking in a community environment where ramps and stair climbing were often unavoidable. In addition, this study deduced that the function of AFO in the community is not only in the enhancement of biomechanical function but also in the aesthetic and psychological factors, and better fit would be a critical factor to stroke survivors.

This study has some limitations. First, there may be baseline functional differences between the participants that might have affected the outcomes. Second, the number of participants wearing 3D-AFO or AFO during the 4-week training and their initial gait functions were different. Therefore, the intensity of community ambulation training such as the number of stairs going up and down and walking distance were not equal for all patients. Third, actual AFO stiffness was not measured. Fourth, the effect of wearing 3D-AFO in this study was applied to only three stroke patients, so it cannot be generalized to all stroke patients. Further studies are required to investigate the effect of 3D-AFO and its stiffness on a larger number of patients with chronic stroke while considering the age, gender, footwear, and lifestyle of the users.

5. Conclusion

The participants were satisfied with 3D-AFO use. 3D-AFO was particularly effective in increasing the step length, stride width, symmetry, ankle ROM, and muscle efficiency during gait on even surfaces and stair ascent. After the 4-week training, the patients who trained with 3D-AFO showed an increase in ankle strength, balance, gait endurance, and gait symmetry and a reduction in depression; however, their social participation did not improve.

6. Patient perspectives

Case 1: The patient and his caregiver revealed that the 3D-AFO was especially helpful while walking on ramps and climbing stairs. However, when he wanted to walk faster on the treadmill, the AFO

could hold the paretic ankle more firmly than the 3D-AFO. He was very satisfied with the 3D-AFO and reported its continuous use after returning home.

Case 2: At the end of the training, his improved gait function stood out conspicuously, but his gait speed slowed slightly because he was paying attention to an excessively symmetrical gait pattern. He was satisfied not only with the effectiveness but also with the aesthetics of the 3D-AFO and the ease of wearing it with shoes.

Case 3: The patient's ankle spasticity worsened especially while standing and walking. He liked the better fit and flexibility of the 3D-AFO but preferred to wear conventional AFO, which is more stable and robust.

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 Institutional Review Board at National Rehabilitation Center on February 2nd, 2021 (IRB No. NRC-2021-01-002). 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

J-EC, K-JS, and HK contributed to the study design. J-EC and K-JS contributed to the project administration. SH acquired the data. J-EC and SH performed the data analysis. J-EC contributed to writing—original draft preparation and implementation of evaluations and interventions. K-JS contributed to the fabrication of 3D-AFO and the implementation of evaluations. K-JS, SH, and HK were involved in writing, reviewing, and editing. HK contributed to funding acquisition and contributed to the conception and methodology. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1138807/full#supplementary-material

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A scoping review of scientific concepts concerning motor recovery after stroke as employed in clinical trials

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The scientific literature on poststroke rehabilitation is remarkably vast. Over the last decades, dozens of rehabilitation approaches have been investigated. However, sometimes it is challenging to trace new experimental interventions back to some of the known models of motor control and sensorimotor learning. This scoping review aimed to investigate motor control models' diffusion among the literature on motor recovery after stroke. We performed a literature search on Medline, Cochrane, Web of Science, Embase, and Scopus databases. The last search was conducted in September 2023. This scoping review included full-text articles published in English in peer-reviewed journals that provided rehabilitation interventions based on motor control or motor learning frameworks for at least one individual with stroke. For each study, we identified the theoretical framework the authors used to design the experimental treatment. To this aim, we used a previously proposed classification of the known models of motor control, dividing them into the following categories: neuroanatomy, robotics, self-organization, and ecological context. In total, 2,185 studies were originally considered in this scoping review. After the screening process, we included and analyzed 45 studies: 20 studies were randomized controlled trials, 12 were case series, 4 were case reports, 8 were observational longitudinal pilot studies, and 1 was an uncontrolled trial. Only 10 studies explicitly declared the reference theoretical model. Considering their classification, 21 studies referred to the robotics motor control model, 12 to the self-organization model, 8 to the neuroanatomy model, and 4 to the ecological model. Our results showed that most of the rehabilitative interventions purposed in stroke rehabilitation have no clear theoretical bases on motor control and motor learning models. We suggest this is an issue that deserves attention when designing new experimental interventions in stroke rehabilitation.

KEYWORDS

motor control, motor learning, stroke, neurological rehabilitation, motor disorders, treatment outcome

1 Introduction

Motor recovery after a stroke is a crucial aim in neurological rehabilitation. The incidence of stroke is estimated at over 13.7 million new cases per year globally (1). Motor impairment after a stroke can be related to different aspects of movement, such as control, learning, planning, and execution (2). Moreover, sensation deficits may affect motor control causing inaccurate feedback and affecting both motor planning and voluntary motor output (3). Although stroke is one of the most treated events in rehabilitation due to the long-term sequelae, there is no consensus on the optimal motor recovery strategy but only a consensus that physiotherapy is beneficial and that intensive repetitive and task-oriented training may foster neuroplasticity and maximize functional recovery (4, 5). However, although of paramount importance, this evidence recommends some treatment features but fails to help clinicians in selecting the most effective approaches and exercises.

Even when it comes to choosing the outcome measures to assess the effect of the rehabilitation, there is no shared definitive consensus. Recently, a Delphi study was conducted with this aim (6). From 119 assessment tools the authors found in the literature, they recommended a core set of nine to be used in clinical practice. Noteworthy, the authors underlined that this selection was meant to concern only clinical settings, and it was not useful to solve research issues in stroke motor rehabilitation (6).

Although recently there has been increasing interest in some crucial aspects of rehabilitation intervention such as the optimal feedback to be provided (7, 8), most of the interventions proposed in the last decades came from the pragmatic application of new evidence from different fields of knowledge. An example is the tremendous impact that neurophysiological advancements in the study of neural plasticity have had in the field of rehabilitation after stroke (3). A recent literature review highlighted the role of motor learning mechanisms, identifying clusters of principles and phenomena that play a key role in shaping recovery patterns in neurological diseases (9). Although this is an active field of study, it was suggested that some inertial factors may hamper its translation into clinical practice (10), resulting in the intervention being proposed more by the personal beliefs of the practitioners than driven by scientific hypothesis (10). The modest translation of scientific evidence into clinical settings also emerged from a recent review of the driven principles used during the design of robotic devices for neurological rehabilitation (11). Specifically, the authors suggested that often a theoretical reference was used to interpret the results a-posteriori, instead of being the theoretical background the research question was built on (11). In contrast, it would be expected that a theoretical frame drove the rehabilitative proposals and that the results of interventional studies could eventually be used to improve the reference theories.

In a neurorehabilitation framework, the concept of recovery may have different meanings. Following motor system damage, recovery could stem from a combination of innate biological processes and adaptive behavioral restitution or compensation (12). Behavioral restitution refers to the process of reverting to more typical patterns of motor control involving the affected effector (i.e., the body part interacting with the environment). Conversely, compensation denotes the patient's capacity to achieve a goal by substituting a novel approach instead of relying on their pre-stroke behavioral patterns (13). For compensation processes, motor learning is required, and conversely, neural repair could not be necessary (14). In any case, the use of compensations can be maladaptive and acceptable only in severe deficits when there is very little chance of recovery.

These considerations support the importance of investigating the link between the physiological evidence on motor control and sensorimotor learning and the rehabilitation approaches that the literature has proposed in the past years. This topic is vast and complex since decades of scientific research have developed several scientific theories aiming to describe how humans control their movements (15–18). However, their impact on rehabilitation practice has been surprisingly overlooked. At the state of the art, there is no compelling evidence of the superiority of one theoretical framework over the others; instead, different models have been proven to effectively capture different aspects of human motor behavior (19–21). When dealing with this topic, the first issue is a taxonomy problem. Turvey and Fonseca, in a previous study, reviewed the existing motor control models and classified them into four categories considering if they are inspired by neuroanatomy, robotics, self-organization, or ecological realities (21). In the present review, we refer to this classification assuming it is comprehensive and suitable to be applied in stroke rehabilitation.

This scoping review aims to investigate motor control models' diffusion among the literature on motor recovery after stroke. The review will examine the literature on motor rehabilitation after stroke searching for hypothesis-driven training.

This study will try to answer the following questions:

- Is motor rehabilitation after stroke driven by and based on scientific motor control and learning models?
- Are the models explicitly declared when experimental treatments are proposed in the literature?
- Can the interventions be classified even when there are no explicitly declared principles?

2 Materials and methods

The proposed scoping review was conducted in accordance with the JBI methodology for scoping review (22), and Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (23) was adopted as a guideline for the reporting.

2.1 Eligibility criteria

To ensure that the review included studies relevant to motor rehabilitation interventions after stroke, we used the population-concept-context (PCC) framework. The eligibility criteria included patients with stroke and specific concepts related to motor control, motor learning, and theories/approaches. The criteria also included the context of motor rehabilitation, which ensured that the review only included studies that involved interventions aimed at improving motor function after stroke.

2.2 Type of source

This scoping review considered various experimental study designs, including randomized controlled trials, non-randomized controlled trials, case series, and individual case reports. Systematic reviews and meta-analyses were not included as they typically involve the synthesis of existing studies rather than original data collection. Additionally, text, opinion papers, and letters were not deemed appropriate or useful to meet the objectives of this scoping review as they do not typically involve empirical data collection or analysis.

2.3 Search strategy

The following bibliographic databases were searched: MEDLINE, Cochrane, Web of Science, Embase, and Scopus. The search strategies were drafted by an experienced researcher and further refined through the snowballing approach and team discussion. Searching terms were identified based on the selected PCC framework. Thus, we selected studies that involved neurological patients with strokes, and concept of motor control and motor learning theories/approaches, motor rehabilitation and related motor outcome. We also included additional search terms to ensure that we covered all relevant studies. The identified search terms were searched within the titles, abstracts, and keywords of the articles. The databases that allow controlled vocabularies (e.g., medical subject headings and Emtree) were searched with terms belonging to controlled and not controlled vocabularies. No limitation was applied for the publication year. The final search strategy for each searched database can be found in Supplementary Table 1. The last search was conducted in September 2023, including the articles published up to the end of August 2023.

Once retrieved, the database search results were exported into EndNote, and duplicates were removed. After removing duplicates, the title and abstract of each retrieved article were checked by three independent researchers, and articles related to stroke and motor control or motor learning were selected for the full-text read. Conflicts underwent group discussion until a consensus was reached. Articles selected for the full text were read and assessed by two independent researchers with a group discussion resolving any disagreements. This process ensured that we included only studies that met our inclusion criteria. The study selection process is depicted in Figure 1.

2.4 Inclusion criteria

This scoping review includes full-text articles published in English in peer-reviewed journals that present rehabilitation interventions based on motor control or motor learning principles for at least one individual with stroke.

2.5 Exclusion criteria

Articles not written in English, book chapters, review papers, article commentaries, conference abstracts or posters, and articles not included in the selected databases were excluded from this review. No exclusion criteria were applied for the study design to allow the identification of all the treatments based on motor control and motor learning principles.

2.6 Data extraction

From each included study, information concerning the study aims, the used outcome measures, and the declared motor control or motor learning theoretical frameworks were extracted. When a reference theoretical framework for the rehabilitation intervention was not clearly stated, it was reported as "not declared." The reported bibliographic references related to the declared theoretical framework were also extracted. The findings from the included studies were synthesized through a narrative synthesis, presenting a comprehensive overview of the different motor rehabilitation interventions after stroke. The narrative synthesis helped to identify the scientific motor control and learning models that drive these interventions, the extent to which these models are explicitly declared, and how the interventions can be classified even when there are no declared principles.

For this reason, we categorized all included articles into four frameworks of motor control models in accordance with an influential study on this topic by Turvey and Fonseca (24). The authors suggested that motor control theories and models previously proposed may be classified according to their source of inspiration: neuroanatomy, robotics, self-organization, and ecological realities.

Models referring to the neuroanatomic category consider movement control essentially as a neural task. In this view, movement emerges as a combination of motor programs stored in the central nervous system (CNS) that selects and adapts them to perform a specific task. The subject acts as an executive system, and the cortical and spinal systems are used as a keyboard to play them. Neuromotor treatments based on this framework aim to rebuild motor programs lost after the brain lesion through the systematic repetition of specific movements. The learned motor programs are then assembled to explicitly construct the action.

Over the last decades, the development of robotics and the associated control systems inspired a series of human motor control theories that, in Turvey's and Fonseca's classification, fall into the category of robotics. These models suggest that the body is not a mere executor of neural commands. Instead, the physical properties of the limbs play a significant role in motor control. According to this perspective, when the CNS plans a movement, it explicitly computes the kinematics and dynamics of that movement, defining its trajectory and mapping through inverse kinetic and kinematics into motor torque and muscle activation. To do so, it can be hypothesized that the CNS shall have, at some level, knowledge of the physical laws involved in the body's mechanics. Internal models allow the CNS to perform these computations through the prediction of movement's consequences (forward model) or the analytic definition of the motor command

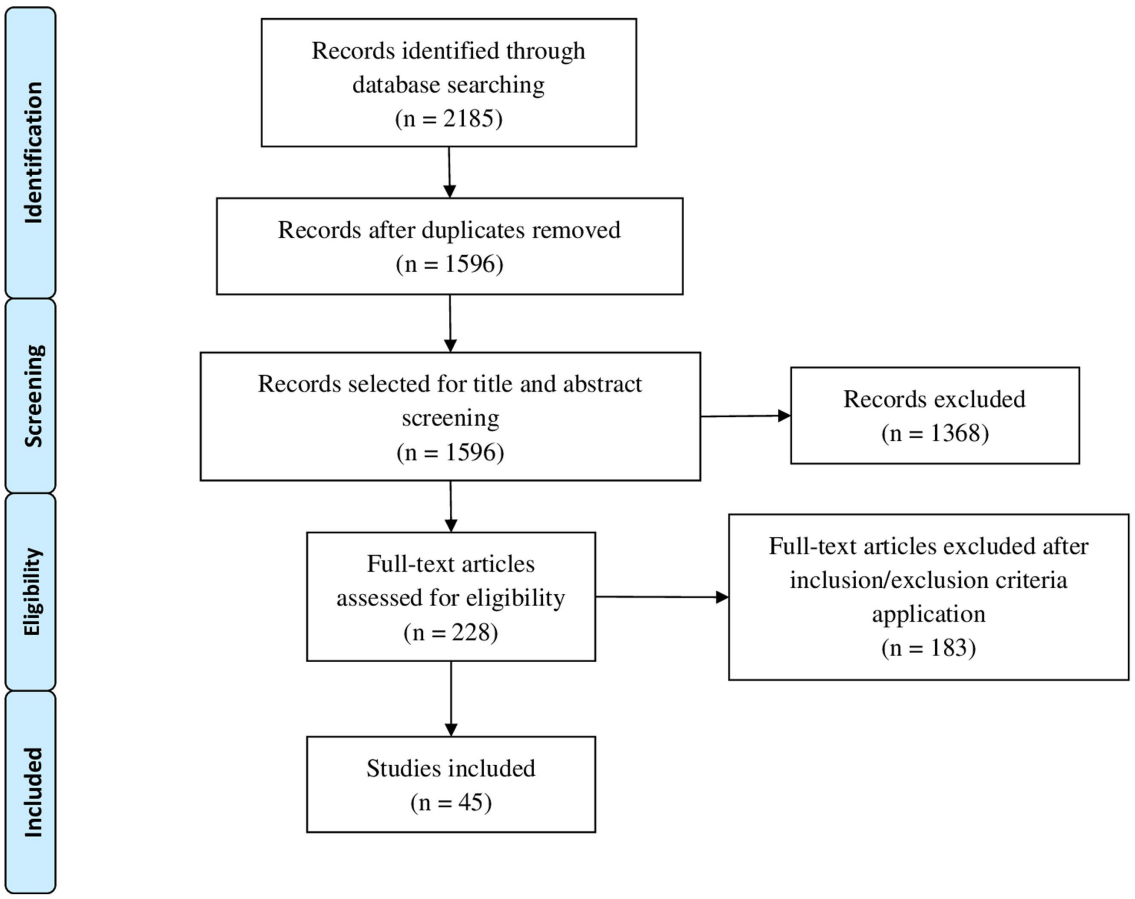

FIGURE 1
PRISMA flowchart of the study's selection process.

needed to perform a desired trajectory (inverse model) (16, 18). Noteworthy there is neurophysiological evidence that does not support the inverse model representation in the cerebellum (25).

Therefore, we included in this category neuromotor treatments that involve motor learning through external feedback chosen by the therapist (augmented feedback) and training that provides online feedback on the movement's execution focusing explicitly on trajectories and applied forces. Augmented feedback can be delivered without providing explicit information, but this was not implemented in the articles included in our study. These treatments can also include physical constraints to movement (e.g., planar robots for upper limbs). These first two models suggest a hierarchical ordering of neuroanatomical structures and processes of control.

Another framework of motor control models included theories inspired by the self-organization concept. In this view, motor control emerges from and is influenced by the dynamic interaction between three systems: the CNS, the body, and the environment. In the context of motor learning, the system is left free to act and the only feedback that modulates learning is the achievement of the goal of the action. In this category, we included interventions that leave the system free to move until converging on a solution. In this perspective, the training of a neuromotor task has no constraints, the therapist does not manipulate the feedback, and the subject has more freedom of action during the execution of the exercise.

Recently, a series of theories proposed that movements and postures are controlled and coordinated to realize functionally specific acts based on the perception of affordances (26). The action is seen as intrinsically related to the environment and the context in which it is performed. The treatments that fall into this category (ecological) include a careful choice of the task to perform and the constraints to apply so that when the subject is engaged in the specific task, the desired motor behavior emerges from the biomechanical and informational constraints exchanged with the environment. Task and context become tools for bringing out motor behavior. The treatment is controlled by the therapist who prepares tasks and contexts to bring out the absent and/or desired motor action.

In the first model, the speculation was made that one can pinpoint both the anatomical regions being controlled and the origins of this control. In the progression from the first and last models, the 'what' and 'where' of control become increasingly less concrete and less expressible in anatomical terms.

To allocate studies into different categories, we referred to the background theoretical framework declared in the included studies. When this was not mentioned explicitly, we referred to the intervention used in the single studies following the criteria previously described. To highlight these different classification procedures, when reporting the results of this process in Supplementary Table 2, we divided between studies in which the theoretical framework was

explicitly declared and studies in which it was not. For the studies in which the theoretical framework was explicitly declared, we evaluated the coherence between methods and the theoretical model declared. For all the included studies, we also analyzed the coherence between the aims and the outcome measures declared. For each of these two topics examined, we assigned a green dot if coherence was total and a yellow one if partial.

3 Results

Figure 1 shows the flowchart of the study selection process. Forty-five studies were eventually included in our review and analyzed. The synoptic table with the overview of the studies is available in Supplementary Table 3. From a methodological perspective, 20 (44.4%) were randomized controlled trials, 12 studies (26.7%) were case series, 4 (8.9%) were case reports, 8 (17.8%) were observational longitudinal pilot studies, and 1 (2.2%) was uncontrolled trial. The number of included patients varies between 50 (22) and 1 (26–29), with a greater prevalence of studies with more than 20 patients included (23) (51.1%). Only 1 study (a case report) refers to a child affected by hemiplegia poststroke (29) because childhood stroke is a rare event. From the intervention identification perspective, 27 studies had specific training for upper limb motor recovery, both considering reaching function and hand dexterity (30–32), 12 studies had lower limb and gait training, 3 studies had balance training, 2 studies had functional activities, and 1 study investigated the effect of PRISMA adaptation measure for recovery of spatial neglect (33).

As reported in Supplementary Tables 2, 3, most of the included studies (77.8%) did not explicitly mention a specific theoretical framework as the background of their proposed intervention (34). The robotics framework was most frequently used with 21 studies (46.7%) explicitly or implicitly basing their intervention on this model. Twelve studies (26.7%) referred to the self-organization framework, 8 (17.8%) to the neuroanatomy, and only 4 (8.9%) to the ecological one. Considering the studies that declared the theoretical framework they referred to, the coherence between the methods applied and the theoretical framework was good in 8 out of 10 studies (80.0%) and partial in 2 out of 10 studies (20.0%) (34, 35). Moreover, the coherence between the aims and the outcome measures was good in 42 out of 45 studies (93.3%) and partial in 3 out of 45 studies (6.7%) (28, 34, 36).

4 Discussion

This scoping review investigated whether and how rehabilitation interventions in patients with stroke motor sequelae were based on motor control and sensorimotor learning models. We included studies that explicitly or implicitly referred to theoretical frameworks of motor control and learning. Of the 1,596 records that entered the screening process, only 45 fulfilled the inclusion criteria and were included in the review. Of these, only 10 (22.2%) explicitly described the rationale of their proposed intervention referring to a specific motor control and learning model.

As for the studies that explicitly declared the theoretical framework they designed their treatment on, we found an overall good agreement between the declared framework and the proposed interventions. In two studies, a partial agreement was found. In detail, Dipietro et al. (35) designed a training based on robot-assisted pointing tasks to investigate whether improvement in accuracy and smoothness in such tasks resulted in improved smoothness in an untrained movement. The background described in the study conceived upper limb movements as built from the combination of simpler submovements (37). We reported partial coherence between the aim and reported rationale because if the authors assumed that upper limb movement could be conceived as a combination of simpler submovements, it is hard for the reader to understand how improvements in a specific task (i.e., robot-assisted pointing task) would generalize in a different task (i.e., circular movements). Reinkensmeyer et al. (34) proposed and evaluated a new model by comparing two groups performing therapeutic activities with and without a robotic device. However, the non-robotic-assisted treatment description was limited, preventing correctly understanding the highlighted motor learning components that were applied to it. Furthermore, although the new model could be categorized in the self-organization category (as it proposed that the learning occurs based on knowledge-of-result feedback and is linked neither to the level of assistance provided nor to the range and speed of practiced movement), the proposed training did not match the assumptions of this category. Indeed, the augmented feedback was provided during the robotic-assisted training, and the subject could not freely explore all the movement possibilities.

In light of the vast literature on rehabilitation in patients with stroke, the scant number of studies that explicitly declared their theoretical frameworks suggested that this information plays little role in describing the proposed intervention. In other words, there are several clinical rehabilitation trials in which it is difficult, if not impossible, to find any theoretical reference on the selected treatment. Noteworthy, this does not mean that in most interventional studies, the rationale of interventions is not declared but rather that the interventions are not reported to be designed on the known motor control and sensorimotor learning models. Although it can be seen as a minor issue, this is a crucial flaw that may significantly affect the quality of the research on neurorehabilitation.

First, this may foster the conduction of several clinical trials with limited clinical impact. Improving our understanding of crucial aspects associated with motor learning (e.g., optimal dose, principles of applications, and feedback manipulation) should be encouraged before focusing on the comparison of the effect of different interventions (e.g., when comparing experimental treatments to conventional physical therapy) (38). Designing experimental interventions based only on previous trials, without a clearly described theoretical background, makes it difficult to interpret and translate their results, eventually failing to improve the clinical practice. It is important to underline that the progression of knowledge in neurophysiology, especially on neuroplasticity mechanisms, allowed us to understand some characteristics that neurorehabilitation intervention should have to foster experience-dependent plasticity and functional motor recovery (3). As an example, there is a shared agreement that repetitive task-oriented and engaging practices may foster stroke patients' recovery. Some of these principles helped to introduce some rehabilitation techniques that showed a strong level of evidence (e.g., constraint-induced movement therapy) (39). However, although all the rehabilitation interventions should follow these principles irrespective of the theoretical framework they are based on, we argue that it is the

theoretical models of motor learning and motor control that inspire and define the actual design of exercises (e.g., choosing feedback modalities and adding perturbations or facilitations).

Second, and arguably most importantly, overlooking these aspects has led the literature to focus more on the device used than the treatment itself (11). This was particularly apparent in the context of robotic devices for rehabilitation. Indeed, when a new technology is ready and in fashion, it could happen that, without a clear scientific hypothesis, the development of new solutions might be confined to pragmatism and the personal feelings of practitioners (10).

In the current scoping review, a classification system for the theoretical models underlying the rehabilitation treatments for people with stroke was proposed based on the one presented by Fonseca et al. (24). This classification system could represent a valid tool for researchers in the field of motor rehabilitation, providing a reference to describe the foundation principles for rehabilitation treatment proposals. Moreover, the possibility to classify the treatments according to their theoretical framework (even when it is not explicitly declared) laid the basis for future meta-analyses to assess the efficacy of a theoretical approach instead of specific treatments. This opportunity gains value in light of the results of the proposed interventions: all the analyzed studies reported rehabilitative success and revealed their functional efficacy but also highlighted the lack of a valid and effective theoretical framework explaining the participants' improvements after such different treatments. Identifying a theoretical framework appears mandatory for conducting further steps in the knowledge of the motor recovery process.

Among the four models proposed in the classification system, the most used was the robotics model. This model dues its name to the fact that it was inspired by the studies of control systems for robotic devices, and it was not surprising that most of these studies investigated robot-assisted training. The predominance of the robotics model in the current review reflects the wide impact that robotic devices have had on neurorehabilitation research. Indeed, robotics is one of the augmenting techniques aiming to exploit the enriched environment for providing augmented feedback, information, and repetitions to patients. The concept of augmented modalities involves the notion that enriching the external environment in which animals or subjects interact can result in significant modifications to their own functional systems both at a central level (e.g., CNS) and a peripheral level (e.g., muscles) (40, 41).

On the other hand, the least used reference model was the ecological framework. This model refers to selecting specific tasks and contexts to facilitate the emergence of the desired motor behavior. It is rarely considered because of the obvious difficulty in standardizing the interventions investigated in research in the rehabilitation field. Indeed, the ecological model imposes a high individualization of the selected tasks and contexts. Therefore, the same conditions can lead to different motor behaviors in different people, complicating the achievement of the replicability required in clinical trials.

Finally, the agreement between the objectives and outcome measures in the included studies was investigated and found adequate in 37 out of 40 studies (92.5%). This result highlighted the researchers' attention to selecting appropriate measurements that answer their research questions. We did not find this agreement in three studies. The measurement used by Reinkensmeyer et al. (34) partially agreed with their study's aim. The authors intended to prove the similar effect of robotic and non-robotic treatments. However, they assessed the outcome measures in a task that was a part of the robotic training, implying the participants enrolled in the robotic training could have been facilitated in the task performance. Furthermore, in the studies of Smedes and da Silva (28) and Tretriluxana et al. (36), the aims stated the intention to investigate the feasibility of the proposed treatments, but no feasibility measures were collected. This result was satisfactory as using adequate outcome measures was essential in producing high-quality research. However, when an intervention is aimed at activating motor learning processes, appropriate measures of motor learning are required to be collected. Although the in-depth analysis of the used outcome measures goes beyond the scope of the current review, a recent literature review suggested that selecting an adequate motor learning measure should be based on the treatment focus and that this approach is currently lacking (42).

This scoping review underlined that most of the interventions proposed in stroke motor rehabilitation research had no declared motor control or learning models as theoretical scientific frameworks. This aspect highlighted that, in stroke rehabilitation, the authors usually stress the efficacy of the proposed intervention more than the theoretical model used. The presentation of rehabilitation interventions not based on solid and explicit theoretical models could provide pragmatic procedures but is insufficient to understand the mechanism underlying the rehabilitation processes, restraining the growth of rehabilitation as a scientific discipline. Future rehabilitative trials should be driven by solid scientific hypotheses on motor control and learning principles to promote rehabilitation as a scientific-driven process.

Author contributions

MF, ARo, NV, BC, SF, AG, DM, GP, ARi, SS, EC, NS, SB, PK, and MP contributed to devising and planning the study. MF, ARo, NV, BC, SF, AG, DM, GP, ARi, SS, PK, and MP screened abstracts, full texts, and contributed to the data extraction. MF, ARo, NV, PK, GP, and MP wrote the first draft of the study. SF, SS, MF, ARo, AG, GP, EC, NS, SB, and NV revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1221656/full#supplementary-material

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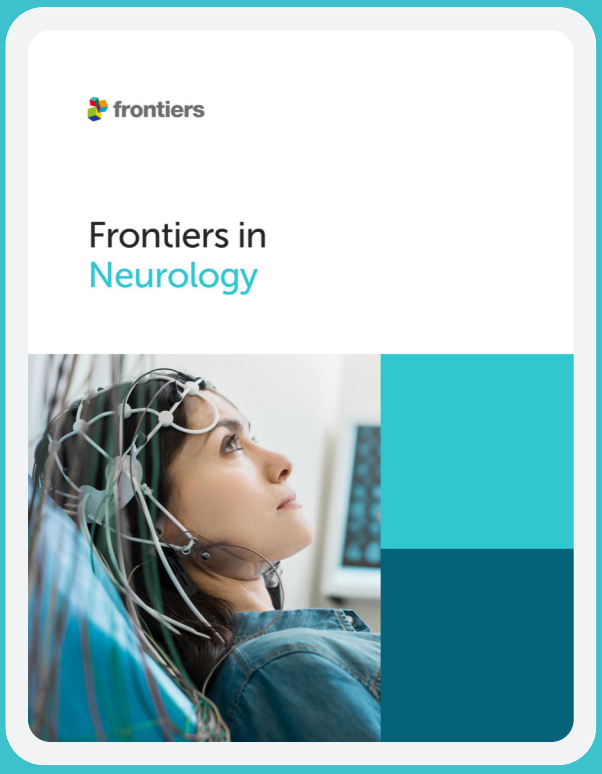

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