NEUROPSYCHOLOGICAL AND COGNITIVE-BEHAVIORAL ASSESSMENT OF NEURODEGENERATIVE DISEASE AND REHABILITATION USING NEW TECHNOLOGIES AND VIRTUAL REALITY

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EDITORIAL
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Editorial: Neuropsychological and Cognitive-Behavioral Assessment of Neurodegenerative Disease and Rehabilitation Using New Technologies and Virtual Reality

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Editorial on the Research Topic

Neuropsychological and Cognitive-Behavioral Assessment of Neurodegenerative Disease and Rehabilitation Using New Technologies and Virtual Reality

Neurodegenerative diseases are characterized by a progressive degeneration of the nervous system and as a consequence, of the brain function (Batista and Pereira, 2016). Such degeneration may affect body movement and brain function, causing an important and progressive decline of the cognitive functions such as memory, thinking, behavior, language, calculation, learning, and emotion capacity (Chekani et al., 2016). The life expectancy of patients presenting neurodegenerative diseases, and the incidence of these has increased over the years, representing one of the most important medical and socio-economic problems of our time (Batista and Pereira, 2016). The rehabilitation process of these patients is long and the assessment periods and follow-up are time consuming for both patients and clinicians. In this regard, the development of new technologies in the last two decades had led to the introduction of different technological devices to enhance the clinical outcomes of conventional clinical interventions, and to facilitate clinical assessments to the clinicians (Moccia et al., 2021). Some of these technological solutions for rehabilitation includes virtual reality, robotic device, non-invasive brain stimulation systems such as transcranial direct current stimulation (TDCS), transcranial magnetic stimulation (TMS), functional electrostimulation techniques, or brain computer interfaces (BCI) (Weiss et al., 2014; Matamala-Gomez et al., 2018; Tamburin et al., 2019). The combination of different technologies for rehabilitation can pave the way to a more holistic rehabilitation intervention for neurological patients presenting multiple deficits because of their clinical condition.

The present Research Topic "Neuropsychological and Cognitive-Behavioral Assessment of Neurodegenerative Disease and Rehabilitation Using New Technologies and Virtual Reality" includes 12 high-quality manuscripts that offer an interesting scenario on these technological advances, as well as new features and approaches for the assessment and rehabilitation of patients with neurodegenerative disorders. Some studies pertained the field of motor and cognitive rehabilitation by using different technologies and approaches. For instance, Chew et al. investigated the effects of priming with tDCS prior to Motor imagery (MI)-BCI training in forty-two patients with chronic stroke presenting moderate to severe upper extremity paresis. The patients were randomized to receive 10 sessions of twenty-min 1 mA real or sham-tDCS before MI-BCI. Results showed that both the real- and sham-tDCS groups improved significantly in UE function with MI-BCI training, with gains continuing up to 4 weeks post-intervention, which were greater in extent in the real-tDCS group.

Cao et al. investigated the sequence effect (SE), which is the reduction in amplitude of step-to-step function which leads to the freezing of gait (FOG) effect in patients with Parkinson's disease (PD), when approaching a destination. Further, the authors also explored the effects of different types of visual cues on destination SE. Thirty-five patients with PD were divided into a freezing group and a non-freezing group. Patients underwent three different conditions while walking: (1) without cues (no-cue condition), (2) wearable laser lights (laser condition), and (3) transverse strips placed on the floor (strip condition). The results from this study showed that patients with PD presenting FOG showed greater destination SE in the no-cue and laser conditions when compared to the patients with PD without FOG. Further, the destination SE was alleviated only by using the transverse strips on the floor. In contrast, transverse strips and wearable laser lights increased the step length. In this line, van der Ham et al. examined technology acceptance for cognitive rehabilitation in a sample of healthcare providers involved in cognitive rehabilitation by using an adapted version of the Technology Acceptance Model (TAM) questionnaire. Results indicated a generally favorable attitude toward the use of digital cognitive rehabilitation and positive responses toward the TAM constructs. This study is interesting as it may stimulate further implementation of digital technologies in cognitive rehabilitation. Similarly, Bottiroli et al. investigated whether Smart Aging, a serious game (SG) platform that generates a 3D virtual reality environment in which users perform a set of screening tasks designed to allow evaluation of global cognition, could differentiate between different types and levels of cognitive impairment in patients with neurodegenerative disease. Ninety-one subjects were involved in this study: healthy older adults (HCs, $n = 23$), patients with single-domain amnesic mild cognitive impairment (aMCI, $n = 23$), patients with single-domain executive Parkinson's disease MCI (PD-MCI, $n = 20$), and patients with mild Alzheimer's disease (mild AD, $n = 25$). Results highlighted significant between-group differences in all the Smart Aging indices, suggesting the validity of this platform as a screening tool for the detection of cognitive impairment in patients with neurodegenerative diseases.

Di Tella et al. aimed at identifying the significant predictors of ecological memory amelioration after the Human Empowerment Aging and Disability (HEAD) virtual rehabilitation program for chronic neurological diseases. The study showed that residual level of cognitive and/or motor functioning is a significant predictor of the treatment success, and an intrinsic relationship between motor and cognitive functions showing the beneficial effects of physical activity on cognitive functions and vice versa. Furthermore, in the manuscript from Pavlidou and Walther the authors proposed that VR can be utilized to restore and improve motor functioning in patients with schizophrenia through VR-mediated motor-cognitive interventions. In this regard, Iosa et al. developed a virtual reality task for upper limb motor rehabilitation, which allows patients, by moving their hand on a virtual canvas, to have the illusion of painting some art masterpieces. The authors conducted two studies, one with 20 healthy subjects, and another with four patients with stroke which performed the experimental task and a control one in which they simply colored the virtual canvas. The results showed that the art condition was performed by healthy subjects with shorter trajectories and with a lower perception of physical demand. The patients with stroke treated with artistic stimuli showed a reduction in the erroneous movements performed orthogonally to the canvas. This study can be relevant for the design of future motor rehabilitation trainings with virtual reality. Mancuso et al. proposed the integration of (i) virtual reality, which immerses the user in a controlled, ecological, and safe environment; and (ii) non-invasive brain stimulation, i.e., transcranial magnetic or electric brain stimulation, which has emerged as a promising cognitive treatment for MCI and Alzheimer's dementia, to cognitive rehabilitation as well as to provide a multimodal stimulation that could enhance cognitive training, resulting in a more efficient rehabilitation. Finally, Burke and Rooney considered the role of VR as a viable platform for the clinical utility of dual-task assessments in an opinion article. The authors highlighted some of the cognitive and neuropsychological considerations to be made when using VR for dual-task assessments in neurodegenerative and neurological conditions.

Robotics are also widely used for motor and cognitive rehabilitation purposes. In this field, Kang et al. aimed at investigating the effect of a Smart Glove Training (SGT) for upper-extremity rehabilitation in patients with sub-acute stroke. The authors conducted a randomized control trial enrolling 23 patients with sub-acute stroke and observed a decrease in upper-extremity impairment after a 2-week of smart glove training period. Similarly, Aprile et al. used a robotic motor/cognitive rehabilitation program in order to enhance cognition in patients with stroke. In this pilot study, patients received an upper limb rehabilitation program consisting in a set of three robots and one sensor-based device comprising both motor and cognitive exercises. Patients underwent 30 rehabilitation sessions, each session lasting 45 minutes, 5 days a week. Results showed that patients improved in all the investigated cognitive domains, as measured by the selected cognitive assessment scales, suggesting that robotic technology can be used to combine motor and cognitive exercises in a unique treatment session. Further, some perspective and opinion articles proposed interesting suggestions and considerations for the future use of VR in the field of assessment and rehabilitation. In particular, Burke and Rooney considered the role of VR as a viable platform for the clinical utility of dual-task assessments. The authors highlighted some of the cognitive and neuropsychological considerations necessary when using VR for dual-task assessments in neurodegenerative and neurological conditions. Mancuso et al. provided a brief review of current evidence regarding the benefits of non-invasive technologies (VR and TMS) on MCI cognitive rehabilitation. They also proposed an integrated intervention approach consisting of VR-based cognitive training and neural stimulation by means of TMS that should act on both a neural-cognitive and behavioral-cognitive, resulting in a more efficient rehabilitation for MCI. Finally, Han et al. introduced a protocol for a randomized controlled trial consisting in the use a novel therapy – known as Remote Ischemic Conditioning (RIC) therapy (designed to protect vital organs from severe lethal ischemic injury by blockage of transient sublethal blood flow to non-vital organs) combined with an exercise (E) therapy — for acute ischemic stroke patients. Overall, this Research Topic aimed to integrate some of the novel information regarding the use of newly developed technologies, robotics, and virtual reality systems for neuropsychological assessment and rehabilitation applied to patients with neurodegenerative diseases. We would like that the manuscripts of this research Topic should — at least in part — shed light on the understanding on how to apply such new technologies to the treatment, monitoring or assessment of neurological patients.

AUTHOR CONTRIBUTIONS

MM-G and SB drafted the manuscript. SS, DB, FS, and AC critically revised the manuscript for important intellectual content. All authors conceived, designed the manuscript, and approved the final version of the manuscript.

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Transverse Strips Instead of Wearable Laser Lights Alleviate the Sequence Effect Toward a Destination in Parkinson's Disease Patients With Freezing of Gait

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Background: The sequence effect (SE), referring to step-to-step reduction in amplitude, is considered to lead to freezing of gait (FOG) in Parkinson's disease (PD). Visual cues may alleviate SE and help reduce freezing episodes. FOG patients show significant SE prior to turning or toward a doorway, but the SE toward a destination has not been clearly studied.

Objectives: To examine the SE when approaching a destination in PD patients with FOG, and to further explore the effects of different types of visual cues on destination SE.

Methods: Thirty-five PD patients were divided into a freezing (PD+FOG, $n = 15$) group and a non-freezing (PD–FOG, $n = 20$) group. Walking trials were tested under three conditions, including without cues (no-cue condition), with wearable laser lights (laser condition), and with transverse strips placed on the floor (strip condition). Kinematic data was recorded by a portable Inertial Measurement Unit (IMU) system. The destination SE and some key gait parameters were evaluated.

Results: The PD+FOG group showed greater destination SE in the no-cue and laser conditions when compared to the PD–FOG group. There were no significant differences in the strip condition when comparing destination SE of the two groups. The destination SE was alleviated only by using the transverse strips on the floor. In contrast, transverse strips and wearable laser lights could increase the step length.

Conclusions: The significant destination SE may explain why FOG patients are prone to freezing when heading toward their destination. Visual cues using transverse strips on the floor may be a more effective strategy for FOG rehabilitation in PD patients.

Keywords: Parkinson's disease, freezing of gait, sequence effect, destination, visual cues, transverse strips, laser lights, rehabilitation

INTRODUCTION

Freezing of gait (FOG), defined as "a brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk" (1), is a debilitating symptom in Parkinson's disease (PD). The incidence and severity of FOG increase as the disease progresses (2). FOG is dramatically influenced by environmental factors and tends to occur when turning, passing through a doorway or approaching a destination (3). In addition, medication state (off or on L-dopa condition), cognitive overload and negative emotions (anxiety or depression) can also precipitate FOG (4–7). Due to its paroxysmal and unpredictable features, FOG can easily cause falls and increase the risk of fractures, thus further causing worse prognosis and increasing the burden on families and society (8, 9).

However, the pathophysiology of FOG remains unclear (4). The progressively decreasing step length has been reported in steps prior to freezing (10). The phenomenon of gradual step to step reduction is termed sequence effect (SE), which may attribute to the inability of basal ganglia (BG) to provide timing cues and is believed to cause FOG in PD patients (11, 12). Based on the defects of BG function and gait-control system, the concept of dual requirement of background step length reduction (manifestation of gait hypokinesia) and presence of SE can explain most of the freezing phenomenon in PD (13). Chee et al. reported that FOG episodes were induced more frequently through voluntarily diminishing step length if a significant SE was co-existent in the PD patient (14). Particularly, motor blocks will not occur in the absence of SE during walking (13).

The severity of SE is influenced by environmental factors and varies between individuals, therefore the SE can be much greater under some circumstances (13). For example, it has been shown that prior to turning, the SE in PD patients with FOG was significantly greater than that in healthy people and PD patients without FOG, although all groups perform progressive step-to-step reduction (15). These could partly explain why turning induces freezing episodes in PD. Another study explored the gait changes of participants when they walked through a variable-width doorway. PD group had greater gait changes and their step length decreased significantly when approaching the narrow doorway (16). If the SE attended, it could result in a motor block. In fact, destination freezing is also one of common types of FOG in PD patients (3). Although reducing step length is an expectable reaction to the approaching destination, SE toward a destination has not been directly demonstrated in PD patients.

The treatment of FOG still poses a clinical challenge (17, 18). Therefore, alleviating the SE may provide a new therapeutic option for FOG in PD. Iansek et al. investigated the SE in FOG patients and found that the SE was eliminated by using visual cues, but it did not respond to L-dopa or attention strategies (11). In that study, they chose transverse white strips on the floor as visual cues. However, it remains unclear whether other types of visual cues (e.g., wearable laser lights) could alleviate SE in a similar way.

The purpose of this study is to compare the SE toward a destination between PD patients with and without FOG and evaluate the effects of two types of visual cues (transverse strips on the floor and wearable laser lights) on the destination SE and some key gait parameters.

MATERIALS AND METHODS

Participants

A total of 35 participants with idiopathic PD were recruited from the Movement Disorders Clinic at Tongren Hospital, Shanghai Jiao Tong University School of Medicine, including 15 patients with FOG (the PD+FOG group) and 20 patients without FOG (the PD–FOG group). All participants were diagnosed in terms of the MDS Clinical Diagnostic Criteria for Parkinson's Disease. Participants were included if they could independently walk a 10-m distance for several times, with periodical rest. Exclusion criteria included any additional brain parenchyma injuries (e.g., stroke, hydrocephalus, brain tumors or traumatic brain injury), ophthalmic or orthopedic conditions that might affect gait, and cognitive deficits that cannot complete the experiment. PD patients were identified experiencing FOG, if they scored 1 "I have experienced such a feeling or episode over the past month" on Part I question of New Freezing of Gait Questionnaire (NFOG-Q) (19) or if they were detected freezing in the outpatient clinic.

This study was approved by the Medical Ethics Committee of TongRen Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from all patients prior to testing.

Clinical Assessments

In the dopaminergic "on" state, demographic data (e.g., age, gender, height and disease duration) of each subject was collected, and clinical assessments were evaluated. Motor performance was assessed with Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Cognitive and affective conditions were evaluated with Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment-Basic (MoCA-B) Chinese Version and Geriatric Depression Scale (GDS). Subjective severity of FOG was assessed using the NFOG-Q. The other clinical variables included the Hoehn and Yahr (H&Y) scale for evaluating disease severity and 39-item Parkinson's Disease Questionnaire (PDQ-39) for assessing quality of life.

Equipment and Gait Protocol

To measure spatiotemporal gait parameters, a portable Inertial Measurement Unit (IMU) system (GYENNO Science, Shenzhen, China) was applied, with 10 inertial sensors placed on each subject's lower back, chest, and bilateral feet, ankles, thighs and wrists by elastic belts. Each sensor collected spatiotemporal gait information in real time while the participants were walking, and transmitted the information to the host computer via a Bluetooth link for further processing and storage. IMU-based measurements can measure the fundamental gait parameters with sufficient accuracy in both healthy subjects and PD patients (20). The gait assessments were conducted in a hall with enough

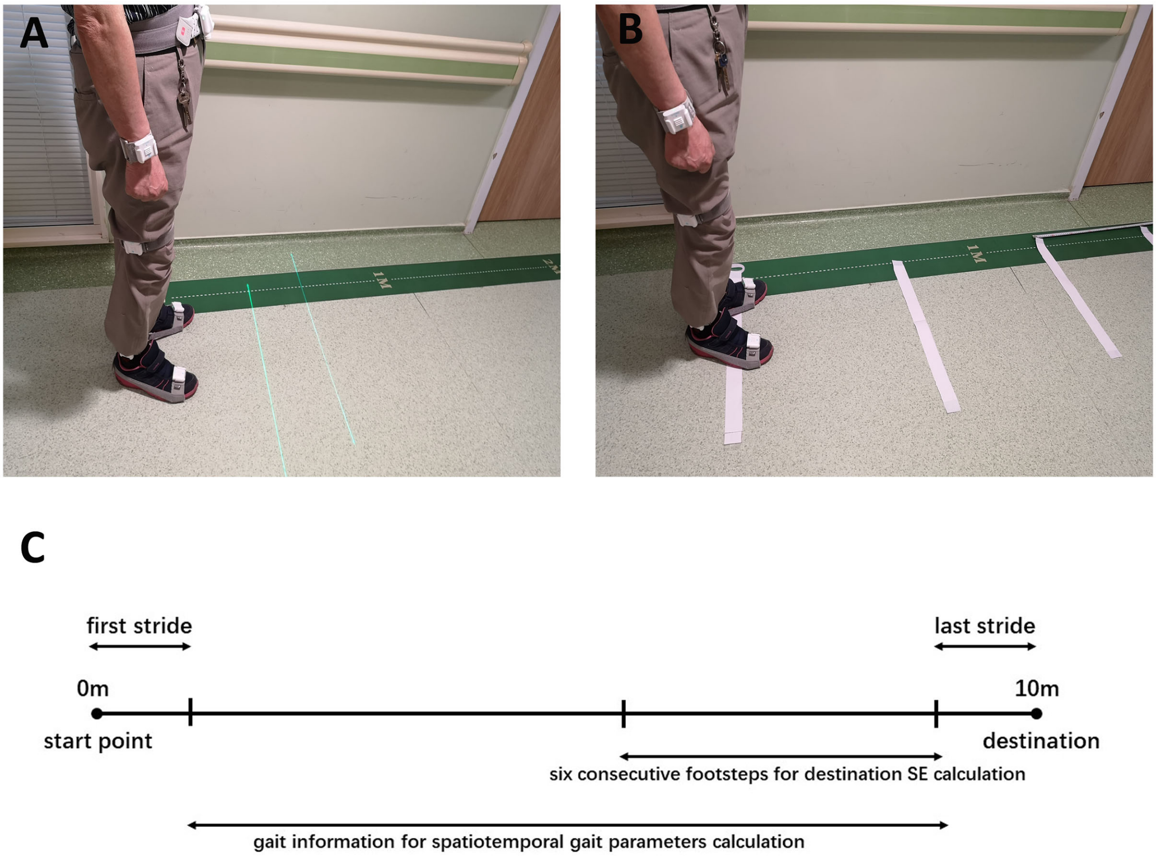

FIGURE 1 | (A) The wearable laser lights used as visual cues. **(B)** The transverse strips used as visual cues. **(C)** Ten-meter walking trial and data used for calculating destination SE and gait parameters.

space to avoid environmental factors that might contribute to FOG.

All participants received gait assessment at least 3 h after the last dopaminergic medication intake (in an end-of-dose state) (21, 22). After the investigator confirmed that each sensor was placed correctly, the participant stood still at the start point of a 10-m straight pathway and prepared. When the investigator issued the instruction, they began to walk straight, and then stopped at the end point of the 10-m distance. Each participant was guided to walk at comfortable pace. Ten-meter walking trials were tested in three conditions: no cue, laser lights and transverse strips on the floor. In the laser lights condition (**Figure 1A**), a laser device fixed on waist belt was used to provide two parallel transverse laser lines in front of the participant. Participants were guided to step over the laser line while walking at a comfortable pace. In the last condition (**Figure 1B**), transverse white strips, measuring 60 cm long and 48 mm wide, were placed on the floor with a distance in between the strips of 40% of the patient's height rounded to the nearest 5 cm, based on previous studies (21, 23). For patients whose step length was unable to be normalized, the strip intervals were set referring to their daily steps. Participants were guided to step on each strip in sequence while walking at a comfortable pace. In order to analyze the spatiotemporal parameters in a continuous gait process, the participants were required to complete each 10-m walking trial continuously without pause. If there was a freezing episode or pause during the walking, we would ask the participant to stop the experiment and have a rest. The experiment was repeated as the participant was in a better state. Three valid and analyzable trials were conducted for each walking condition, with a short break between each walking trial. If occasionally the patient was unable to complete all walking trials, each condition was only repeated twice. Walking trials in the no cue condition were always conducted first to avoid any influence from other conditions with visual cues. The remaining two conditions with different visual cues were tested in random order among the participants, thus counterbalancing the order effect.

Gait Outcome Variables

Sequence Effect

The SE was measured as a regression slope, and the step to step data of each trial was extracted for further determining the slope of SE.

When calculating the regression slopes for the section of walking trials toward a destination, step length data for the six consecutive footsteps ahead of the last stride was used to avoid the influence of sharp deceleration (**Figure 1C**). After being numbered in sequence, the step length was plotted against step number in each walking trial, according to previous studies (11, 14, 24). The regression slopes (β), representing the sequence effect toward a destination for each individual walk, were averaged to formulate group mean average slopes, which were compiled for each condition (no cue, laser lights and transverse strips).

Gait Parameters

To identify spatiotemporal gait parameters in steady state for each trial, the first and last strides were excluded, avoiding acceleration and deceleration during walking (**Figure 1C**). For each trial, step length, step length variability, step length asymmetry, step time, step time variability, step time asymmetry, cadence, velocity, and double limb support were calculated. Left and right footstep recordings were pooled together to include more data points. Variability characteristics (e.g., step length variability and step time variability) was calculated using the coefficient of variation (CV) as $CV = (SD/mean) \times 100$, for each trial. Asymmetry characteristics (e.g., step length asymmetry and step time asymmetry) were determined as the percentage of the average absolute difference between left and right steps for each walking trial.

These gait parameter values were averaged across three or two trials and their means combined to provide group mean data in each condition.

Statistical Analysis

Statistical analysis was performed using SPSS 23. The differences in the study variables between the PD+FOG group and PD−FOG group, including demographic and clinical characteristics and spatiotemporal gait parameters, were assessed with Student's t-test and Mann–Whitney test as appropriate; $p < 0.05$ was considered significant. Satterthwaite's approximation was used for t-test with unequal variance. When comparing the differences in destination SE between the PD+FOG group and PD−FOG group, multiple linear regression was applied to control the baseline differences between two groups. One-way repeated-measures ANOVA was calculated to examine the differences between the three walking conditions. The *post hoc* analysis was corrected using Bonferroni correction, and $p < 0.0167$ was considered significant.

RESULTS

Clinical Features

Demographic and clinical characteristics for each group can be found in **Table 1**. The PD+FOG group and the PD−FOG group were well-matched for age and height ($p = 0.057$ and $p = 0.434$, respectively). The UPDRS-III score ($p = 0.007$) and Hoehn and Yahr scale ($p < 0.001$) were significantly higher in the PD+FOG group than in the PD−FOG group, which may be related to the significantly longer disease duration of the PD+FOG group ($p = 0.014$). There were no significant differences in MMSE ($p > 0.05$) between the two groups, while the MoCA-B and GDS score of the PD+FOG group was significantly higher than that of the PD−FOG group ($p = 0.011$ and $p = 0.001$, respectively). As expected, the PDQ-39 score for evaluating quality of life was significantly higher in the PD+FOG group than in the PD−FOG group ($p = 0.004$).

Group Differences in the No-cue Condition

Sequence Effect

The destination SE was measured by the regression slopes (β). A negative or positive value of slope (β) represents a successive decrease or increase of the step length before reaching the destination, respectively.

The PD+FOG group had greater absolute β values than the PD−FOG group (**Table 2**). In the no-cue condition, both groups had negative β values. Using clinical features (disease duration, UPDRS-III, H&Y) and gait parameters (step length and step length variability) as covariates in the analysis, the PD+FOG group demonstrated a significantly higher absolute β-value compared to the PD−FOG group (PD+FOG, -1.29 ± 0.54; PD−FOG, -0.33 ± 0.32; $p < 0.001$) (**Figure 2**).

Gait Dynamics

Spatiotemporal gait characteristics in the no-cue condition for each group are shown in **Table 3**. Without visual cues, the PD+FOG group had significantly shorter step length (PD+FOG, 48.04 ± 15.08 cm; PD−FOG, 60.87 ± 5.35 cm; $p = 0.006$), slower velocity (PD+FOG, 0.84 ± 0.28 m/s; PD−FOG, 1.06 ± 0.11 m/s; $p = 0.009$), greater step length variability (PD+FOG, $6.73 \pm 4.35\%$; PD−FOG, $2.88 \pm 0.60\%$; $p = 0.004$) and asymmetry (PD+FOG, $1.30 \pm 1.36\%$; PD−FOG, $0.48 \pm 0.20\%$; $p = 0.037$) compared with the PD−FOG group. No significant differences were found in other gait parameters between the two groups in the no-cue condition.

TABLE 1 | Demographic and clinical characteristics for each group.

Group characteristics	PD+FOG ($n = 15$), mean (SD)	PD−FOG ($n = 20$), mean (SD)	p
Age (years)	71.47 (6.51)	67.55 (5.25)	0.057[a]
Height (m)	1.66 (0.09)	1.68 (0.06)	0.434[a]
Disease duration (years)	8.07 (2.94)	5.50 (2.86)	**0.014**[a]
H&Y scale	2.53 (0.30)	1.58 (0.54)	**<0.001**[b]
UPDRS-III	38.27 (15.12)	26.60 (8.58)	**0.007**[a]
NFOG-Q	18.73 (5.75)	–	–
MMSE	27.60 (2.20)	28.25 (1.45)	0.587[b]
MoCA-B	24.80 (1.90)	26.65 (1.93)	**0.011**[b]
GDS	12.20 (6.57)	5.85 (3.82)	**0.001**[a]
PDQ-39	51.40 (35.82)	19.55 (9.84)	**0.004**[#]

H&Y, Hoehn and Yahr scale; UPDRS, unified Parkinson's disease rating score; NFOGQ, New Freezing of Gait Questionnaire; MMSE, Mini-Mental State Examination; MoCA-B, Montreal Cognitive Assessment-Basic; GDS, Geriatric Depression Scale; and PDQ-39, 39-item Parkinson's Disease Questionnaire.
Dashes indicate where variables are not available.
[a]*Student's t-test independent.* [#]*Satterthwaite's approximation is used.*
[b]*Mann–Whitney test. Significant P-values ($p < 0.05$) are marked in bold.*

TABLE 2 | Summary of average slope (β) values for the two groups across conditions for each group.

Group	Condition		
	No-cue, mean (SD)	**Strip, mean (SD)**	**Laser, mean (SD)**
PD+FOG (N = 15)	−1.29 (0.54)	0.22 (0.39)*	−0.83 (0.65)
PD–FOG (N = 20)	−0.33 (0.32)	0.20 (0.24)*	−0.32 (0.38)

Significant difference from all other conditions (p < 0.0167).

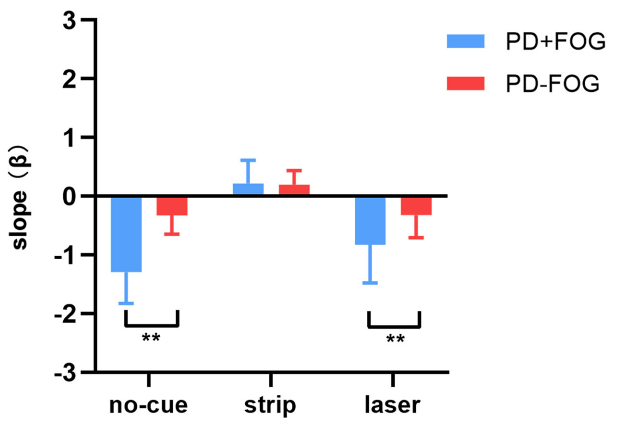

FIGURE 2 | Differences in destination sequence effect (represented by β values) between the PD+FOG group and the PD–FOG group across three conditions (** p < 0.01).

TABLE 3 | Spatiotemporal characteristics of gait in the no-cue condition for each group.

Spatiotemporal variables	PD+FOG (n = 15), mean (SD)	PD–FOG (n = 20), mean (SD)	p
Step length (cm)	48.04 (15.08)	60.87 (5.35)	**0.006#**
Step length variability (%)	6.73 (4.35)	2.88 (0.60)	**0.004#**
Step length asymmetry (%)	1.30 (1.36)	0.48 (0.20)	**0.037#**
Step time (s)	0.56 (0.08)	0.55 (0.04)	0.708
Step time variability (%)	7.40 (7.32)	5.06 (2.12)	0.182
Step time asymmetry (%)	9.55 (8.70)	6.82 (4.00)	0.224
Cadence (steps/min)	111.35 (13.62)	110.28 (8.45)	0.777
Velocity (m/s)	0.84 (0.28)	1.06 (0.11)	**0.009#**
Double limb support (%)	22.93 (6.78)	19.72 (3.15)	0.106#

p-values are determined by t-test. #Satterthwaite's approximation is used. Significant p values (p < 0.05) are marked in bold.

Effects of Different Visual Cues

Sequence Effect

After using transverse strips on the floor, the absolute β values in the two groups both decreased; there were no significant differences of the positive β values between the two groups (PD+FOG, 0.22 ± 0.39; PD–FOG, 0.20 ± 0.24; p = 0.844) (**Figure 2**). In contrast, using wearable laser lights failed to decrease the β values in the two groups, and the absolute β value in the PD+FOG group remained significantly greater than that in the PD-FOG group (PD+FOG, −0.83 ± 0.65; PD–FOG, −0.32 ± 0.38; p = 0.007) (**Figure 2**). These comparisons had already taken into account the between-group differences in clinical features (disease duration, UPDRS-III, H&Y) and gait parameters (step length and step length variability).

When comparing within each group (**Table 2**), the β values were significantly different across three walking conditions in both PD+FOG group [$F_{(2,28)}$ = 56.884, p < 0.001] and PD–FOG group [$F_{(2,38)}$ = 21.511, p < 0.001]. Within each group, *post hoc* tests revealed that the β values of the strip condition were significantly reduced compared to the other two conditions, while there were no significant differences between the no-cue and the laser conditions.

For a single age-matched individual, the PD+FOG participant (**Figure 3A**) had negative and steeper slopes in both no-cue (β = −1.54) and laser (β = −1.78) conditions, indicating that the marked SE occurred before reaching the destination. In contrast, the PD–FOG participant had negative but relatively flat slopes in both no-cue (β = −0.39) and laser (β = −0.11) conditions (**Figure 3B**), indicating the presence of the mild SE toward the destination. For each participant, destination SE was improved only in the strip condition (PD+FOG, β = −0.04; PD–FOG, β = 0.13), while step length was increased in both strip and laser conditions.

Gait Dynamics

Both visual cues improved gait parameters. There were significant differences in step length across conditions for both the PD+FOG group [$F_{(2,28)}$ = 14.877, p < 0.001] and the PD–FOG group [$F_{(2,38)}$ = 18.329, p < 0.001] (**Figure 4A**). *Post hoc* tests determined the differences in step length between the no-cue condition and the other visual cue conditions. Step length was increased significantly with either of the visual cues (both p < 0.01). In addition, the step length variability also differed significantly across conditions for both the PD+FOG group [$F_{(2,28)}$ = 13.861, p < 0.001] and the PD–FOG group [$F_{(2,38)}$ = 15.861, p < 0.001] (**Figure 4B**). *Post hoc* tests confirmed that the step length variability in the strip condition was significantly smaller than that in the no-cue and laser conditions (both p < 0.01).

DISCUSSION

This study determined that PD patients who experienced FOG displayed much greater SE before approaching a destination. Both visual cues could improve gait parameters. However, only the transverse strips on the floor could alleviate destination SE in PD patients.

Our study found that the destination SE was more severe in the PD+FOG group than in the PD–FOG group, which indicates that PD patients with FOG could exhibit more progressive decrease in step length toward their destination. Step length reduction and occurrence of SE have been proposed to be dual requirements for inducing FOG (11, 13). Therefore, motor blocks will not occur in the absence of SE. In fact, motor blocks can be induced with even larger step length, because the effect of SE

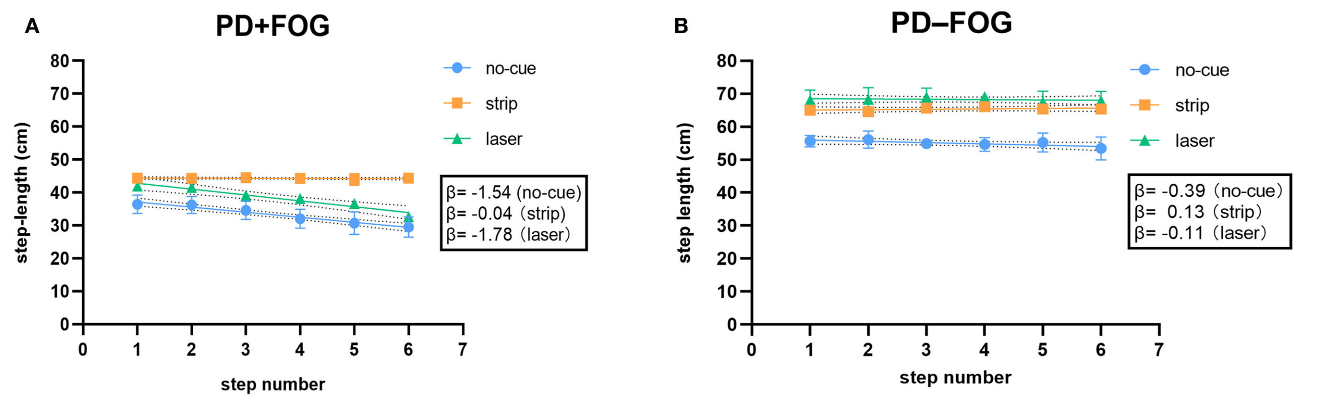

FIGURE 3 | (A) Relationship between step length and step number for a single PD+FOG participant toward a destination in the no-cue, strip and laser conditions. **(B)** Relationship between step length and step number for a single PD–FOG participant toward a destination in the no-cue, strip and laser conditions. (Dotted area behind the linear regression line represents 95% confidence bands).

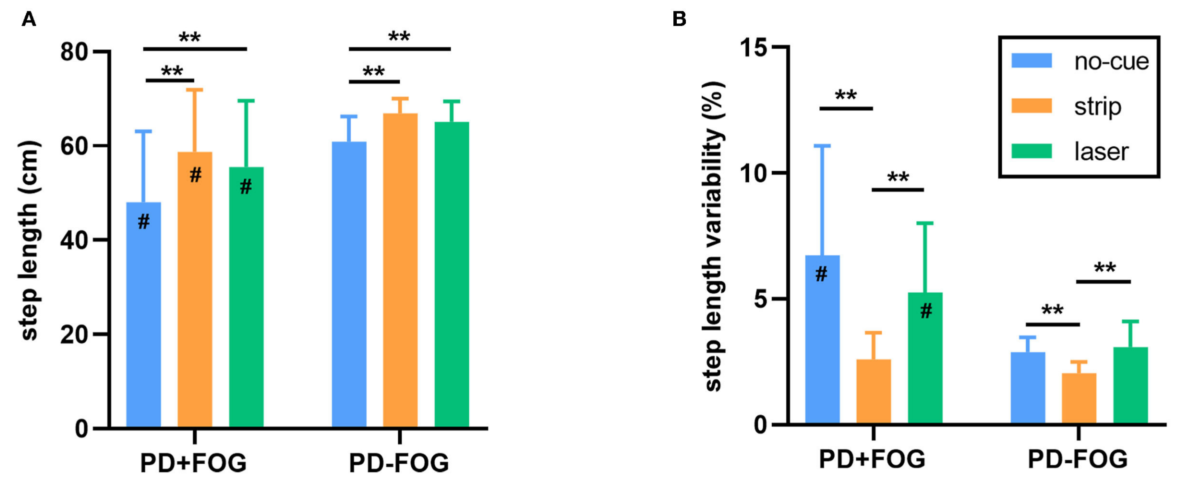

FIGURE 4 | (A) The step length of each walking condition in the PD+FOG group and the PD–FOG group. **(B)** The step length variability of each walking condition in the PD+FOG group and the PD–FOG group. [**$p < 0.01$, #significantly different than the PD–FOG group ($p < 0.05$)].

can be much greater in some circumstances than in others. In other words, if the SE is great enough and able to get command of stepping, the steps will become smaller and smaller until a motor block occurs. In addition to the significant destination SE, the step length of the PD+FOG group was also smaller in this study. Therefore, our findings could make proper interpretation of why FOG patients are likely to freeze when approaching their destination.

The mechanism of destination SE in PD patients could be explained by the concept of BG function defects in running automatic movement (11, 13). In conjunction with the supplementary motor area (SMA), the BG runs automatic movement by maintaining motor set and providing timing cue. In PD patients, the timing cues are disrupted, thus leading to the SE (13). The differences in destination SE between the two groups might be related to the differences in degree of BG function injury, and the PD+FOG group may be more severely injured. Similarly, there was a successive decrease in step length (SE) prior to turning or when passing a doorway in PD patients, and a significantly greater decline in step length was observed in the FOG patients (15, 16). Due to impaired automation, gait control is often dependent on attention, especially in PD patients with FOG. Overall, destination, turning and doorway are well-known environmental factors that can trigger FOG in PD patients (3). These variable environments could be distracting, and then the stepping might switch from attention to uncompensated automatic control. Therefore, FOG could be induced by the presence of SE and reduced step length.

Wearable laser lights and transverse strips on the floor had disparate effects on the destination SE. Both visual cues could increase step length. However, only the transverse strips on the floor could alleviate destination SE. As noted earlier, FOG during walking will not occur unless the SE is present (13). Increasing background step length would make the SE less significant, thereby reducing the likelihood of freezing (11, 14). Transverse lines on floor are well-known strategies to reduce FOG (25–27). In recent years, wearable laser lights have been designed to deal with FOG in PD patients. However, wearable laser lights failed to rescue FOG in some previous studies (28–30). Our results might explain this variability properly. Laser lights could increase step length but fail to alleviate the SE. Therefore, if the SE is significant enough and exceeds the compensation, FOG will be induced (13). In contrast, transverse strips on the floor could not only increase step length, but also alleviate the SE, thus greatly reducing the risk of FOG. Our findings are similar to those of Iansek et al. who observed that medication, attentional strategies and visual cues all improved hypokinesia, whereas only visual cues, in the form of transverse white strips on the floor, were able to eliminate the SE (11). Strategies that can eliminate SE are likely to be the only rescue plan for on-state freezing. Compared to wearable laser lights, the strips on the floor are not portable. Strips on the floor may be more suitable for indoor FOG rehabilitation, while wearable laser lights offer the potential for alleviating freezing in daily activities. A recent research showed that pavement patterns designed in the form of large transversal visual cues could help improve gait in PD patients (27), and this may be a feasible strategy.

The slope of destination SE could be visualized in a scatterplot. Since linear regression of all subjects in one graph might complicate the results, the scatterplot for a single age-matched individual in each group was presented (**Figure 3**). This could make the main findings on destination SE easier to understand. In the no-cue condition, the slope of the PD+FOG participant (**Figure 3A**) was steeper than that of the PD–FOG participant (**Figure 3B**), which is consistent with the group findings that PD patients with FOG displayed much greater SE before approaching a destination. For each participant, destination SE was improved only in the strip condition, while step length was increased in both strip and laser conditions. These were also consistent with the group findings.

In this study, the PD+FOG group had greater step length variability and asymmetry during baseline walking, which is a hallmark feature of gait instability. The results are consistent with other researches on gait analysis of PD patients (31, 32). The presence of SE is often accompanied by greater step length variability (11, 14). We also observed a similar phenomenon that the PD+FOG group exhibited both greater destination SE and step length variability. Gait variability measures have received great attention in PD and disease progression (33, 34). In our results, step time variability, step time asymmetry and double limb support were higher in the PD+FOG group but did not reach statistical significance. Despite this, double limb support was reported significantly higher in PD patients than in the age-matched healthy control group (31, 35). When the PD+FOG group walked with a shorter step length and longer step time in the no-cue condition, they would naturally walk at a significantly slower speed.

In line with previous studies (14), the PD+FOG group had significantly higher UPDRS motor scores, H&Y scales and NFOG-Q scores, along with longer disease duration. It is reported that in early stages of PD, between 21 and 27% of patients experience freezing, while this number rises up to 80% in the advanced stages (36). As anticipated, advanced PD patients could have more severe motor performance and higher H&Y scales. Depression is considered to be related to FOG in PD patients (37). Our results consistently showed that the PD+FOG group had mild depression on average, while the PD–FOG group had a relatively normal GDS scores. The FOG patients suffered from disturbing symptoms, and as a result, their quality of life was severely impaired.

There are some limitations in current study. First, while the two groups were matched for age and height, there was a considerable difference in the reported clinical features (disease duration, UPDRS-III and H&Y scores) and gait parameters (step length and step length variability) in the no-cue condition. However, multiple regression analysis suggests the slopes are independent of these variables which supports the conclusion that FOG patients had significantly greater destination SE than PD patients without FOG. Second, to ensure the safety of the participants, our study was investigated in end-of-dose state instead of off-state. FOG patients might present greater SE but easily fall in the off-state. Third, due to this relatively small sample size, actual freezing episodes were not involved in the analysis.

CONCLUSION

In summary, this study demonstrated that PD patients with FOG presented significantly greater destination SE compared to PD patients without FOG. These findings might explain why FOG patients tend to freeze when they reach their destination. Both the transverse strips on the floor and the wearable laser lights are able to increase step length. However, only the transverse strips can alleviate destination SE. Therefore, visual cues using transverse strips on the floor might be a more effective strategy for FOG rehabilitation.

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 Tongren Hospital, Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-SC contributed to the conception of the study, data acquisition, and writing of the first draft. X-PW contributed to the design and organization of the work, manuscript review, and critique. X-ZY, S-HW, and RT contributed to the data acquisition, manuscript review, and critique. All authors read and approved the final manuscript.

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Using Transcranial Direct Current Stimulation to Augment the Effect of Motor Imagery-Assisted Brain-Computer Interface Training in Chronic Stroke Patients—Cortical Reorganization Considerations

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Introduction: Transcranial direct current stimulation (tDCS) has been shown to modulate cortical plasticity, enhance motor learning and post-stroke upper extremity motor recovery. It has also been demonstrated to facilitate activation of brain-computer interface (BCI) in stroke patients. We had previously demonstrated that BCI-assisted motor imagery (MI-BCI) can improve upper extremity impairment in chronic stroke participants. This study was carried out to investigate the effects of priming with tDCS prior to MI-BCI training in chronic stroke patients with moderate to severe upper extremity paresis and to investigate the cortical activity changes associated with training.

Methods: This is a double-blinded randomized clinical trial. Participants were randomized to receive 10 sessions of 20-min 1 mA tDCS or sham-tDCS before MI-BCI, with the anode applied to the ipsilesional, and the cathode to the contralesional primary motor cortex (M1). Upper extremity sub-scale of the Fugl-Meyer Assessment (UE-FM) and corticospinal excitability measured by transcranial magnetic stimulation (TMS) were assessed before, after and 4 weeks after intervention.

Results: Ten participants received real tDCS and nine received sham tDCS. UE-FM improved significantly in both groups after intervention. Of those with unrecordable motor evoked potential (MEP-) to the ipsilesional M1, significant improvement in UE-FM was found in the real-tDCS group, but not in the sham group. Resting motor threshold (RMT) of ipsilesional M1 decreased significantly after intervention in the real-tDCS group. Short intra-cortical inhibition (SICI) in the contralesional M1 was reduced significantly following intervention in the sham group. Correlation was found between baseline UE-FM score and changes in the contralesional SICI for all, as well as between changes in UE-FM and changes in contralesional RMT in the MEP- group.

Conclusion: MI-BCI improved the motor function of the stroke-affected arm in chronic stroke patients with moderate to severe impairment. tDCS did not confer overall additional benefit although there was a trend toward greater benefit. Cortical activity changes in the contralesional M1 associated with functional improvement suggests a possible role for the contralesional M1 in stroke recovery in more severely affected patients. This has important implications in designing neuromodulatory interventions for future studies and tailoring treatment.

Clinical Trial Registration: The study was registered at https://clinicaltrials.gov (NCT01897025).

Keywords: stroke, motor recovery, transcranial direct current stimulation, brain-computer interface, motor imagery

INTRODUCTION

Post-stroke recovery of upper extremity (UE) function remains a challenge. Less than 15% of stroke survivors with severe impairment experience complete motor recovery (1, 2). Intensive and repetitive practice is effective for motor recovery (3), but is labor-intensive and costly. More effective rehabilitation strategies that will deliver better functional outcomes without increasing cost of care are needed.

Motor imagery (MI), or mental practice is a mental rehearsal process of a specific movement without physical performance to enhance post-stroke upper extremity motor recovery (4–10). It has been demonstrated to be a safe, self-paced method to improve motor performance in athletes (6) and is effective in augmenting the effects of motor practice in stroke patients (7–9).

MI shares similar neural substrates with motor execution (11, 12). Functional neural changes induced by MI is similar to that of short-term motor learning (5) with corresponding changes in corticospinal excitability and reorganization of motor representation have been demonstrated with MI (4, 13).

Robot-assisted training is typically applied to deliver intensive, task-specific training in rehabilitation of motor function, but has also been used to provide appropriate sensorimotor integration through guidance of movement along a trajectory (14–18). The coupling of MI and robot-assisted arm movement through brain computer interface (MI-BCI) has been postulated to enhance sensorimotor integration by bridging the motor intent and providing appropriate somatosensory feedback through passive manipulation of the paretic arm, thereby guiding activity-dependent cortical plasticity through feedback on brain activity (19). Our previous studies of MI-BCI in chronic stroke demonstrated better improvement in motor function with fewer repetitions in the same time of training (20, 21). Others have found similar benefit using BCI-driven orthoses for rehabilitation of severe UE paresis (22).

Transcranial direct current stimulation (tDCS) is a non-invasive method of modulating corticospinal excitability by changing the firing threshold of neuronal membrane and modifying spontaneous activity according to the direction of current, such that cathodal tDCS decreases cortical excitability while anodal tDCS increases it (23–25). Good functional recovery has frequently been associated with a rebalancing of interhemispheric inhibition (17, 26). Based on this, cathodal tDCS is applied to the contralesional primary motor cortex (M1) and anodal tDCS to the ipsilesional M1 to enhance corticospinal excitability. This is the paradigm most frequently studied to enhance motor recovery after stroke (27–31), and has thus far yielded mixed results (32).

Additionally, tDCS has also been explored as a priming tool to improve the accuracy of BCI, both in healthy subjects (33, 34) and in stroke patients with mixed results (35, 36). We had previously reported the preliminary results of the first ever study to investigate the effect of a course of training with BCI-assisted motor imagery (MI-BCI) with tDCS priming (simultaneous anodal stimulation to the ipsilesional M1 and cathodal stimulation to the contralesional M1) prior to each session, compared to MI-BCI with sham tDCS, on recovery of chronic stroke patients with moderate to severe impairment (37). This population was chosen as they have the most difficulty engaging in active motor task training. The stimulation protocol was selected based on the intent to rebalance transcallosal inhibition, as suggested by previous studies (28, 30, 38). Clinical improvement was observed post-training, with online BCI accuracies being significantly better in the tDCS group, compared to the sham group.

The neurobiological principles that govern post-stroke recovery of motor function are incompletely understood. While task-specific training, and MI as an extension, is applied based on principles of activity-dependent cortical plasticity, and non-invasive brain stimulation is applied based on rebalancing of interhemispheric inhibitions, a more detailed understanding of the cortical reorganization associated with the combination of therapeutic modalities, and indeed of the recovery process itself,

Abbreviations: APB, abductor pollicus brevis; BCI, brain-computer interface; EEG, electroencephalogram; ISI, inter-stimulus interval; MEP, motor evoked potential; MI, motor imagery; MI-BCI, motor imagery-assisted brain-computer interface; POST1, within 1 week after the intervention; POST2, 4 weeks post-intervention; PRE, 1 week prior to commencement of the intervention; RMT, Resting motor threshold; SICF, intracortical facilitation; SICI, Short intra-cortical inhibition; tDCS, Transcranial direct current stimulation; TMS, transcranial magnetic stimulation; UE, upper extremity; UE-FM, upper extremity component of the Fugl-Meyer Assessment.

is required in order to tailor therapeutic approaches. TMS may be used to probe these changes in cortical excitability. Here we report the changes in cortical activity associated with this training protocol, which will inform the design of future studies.

PARTICIPANTS AND METHODS

Participants

A total of 42 participants were screened for eligibility for the study. All screening and study procedures were performed at the National University Hospital, Singapore. All partcipants provided voluntary, written informed consent in accordance with the Declaration of Helsinki. The study was approved by the National Healthcare Group Domain-Specific Review Board and was registered at https://clinicaltrials.gov (NCT01897025).

Patients 21–80 years old with a history of unilateral, single, hemorrhagic, or ischemic supratentorial stroke more than 9 months prior to enrolment, with upper extremity component of the Fugl-Meyer Assessment (UE-FM) (39) between 11 and 45 (moderate to severe motor impairment of arm) were eligible for inclusion. Participants were excluded based on the following: (1) inability to operate the MI-BCI system; (2) contraindications to TMS/tDCS including previous cranial surgeries, ferromagnetic implants, and seizures; (3) other factors affecting UE movement: severe pain in the affected UE that may be exacerbated by the use of the robotic device, major depression; (4) other neurological disorders.

Sample Size Calculation

Sample size calculation was based on the minimal clinically important difference (MCID) score of the UE-FMA score, which is estimated to be 10 in a population of stroke patients with severe UE paresis (standard deviation of 10.73) (40). Based on a two-sided level of significance of 5% and a statistical power of 80%, the number of participants required is estimated to be 40 for a two-armed parallel-design study.

Study Design and Randomization

This was a prospective, double-blinded, randomized controlled trial. Participants were randomized into real- or sham-tDCS intervention groups using a computer-generated stratified randomization approach. The randomization number generated was kept in a sealed envelope and was issued to the study coordinator before the start of intervention for each participant. Both the participants and assessors were blinded to the intervention that participants received.

Intervention

Participants were initially screened for eligibility and ability to effectively activate the BCI system. Those who passed screening were randomly allocated to either real-tDCS or sham-tDCS group. Each received 10 sessions of real- or sham-tDCS, followed immediately by MI-BCI assisted robotic arm training. The intervention was conducted daily over 2 consecutive weeks.

Transcranial Direct Current Stimulation (tDCS)

Direct current was delivered by a stimulator (NeuroConn, Germany) through rubber electrodes embedded in saline-soaked 50×70 mm^2 sponge bags at an intensity of 1 mA. The anodal electrode was placed over the ipsilesional M1 and the cathodal electrode was placed over the contralesional M1. Stimulation intensity was ramped up to 1 mA over 30 s and maintained for 20 min, before ramping down. Sham-tDCS was delivered by similarly ramping up to 1 mA but maintained for only 20 s to give participants the same scalp sensation, before ramping down (29). tDCS intervention lasted for 20 min for both groups so that participants were blinded to their group allocation.

Motor Imagery—Assisted Brain-Computer Interface (MI-BCI) Coupled With Robotic Arm Training

The MI-BCI protocol has been detailed in previous publication (37). In short, 27-channel electroencephalogram (EEG) signals were recorded by NuAmp EEG amplifier (Compumedic, Germany). The Inmotion[2] MIT-Manus robot (Interactive Motion Technologies, MA, USA) was used to provide unrestricted unilateral passive and active shoulder and elbow movements in the horizontal plane (41). Visual feedback from the screen indicated the success or failure of MI detection for each MI task. Once motor intention was successfully detected, the robot-assisted motion would be triggered according to the clock exercise therapy of the MIT-Manus robot (42).

Outcome Measures

All outcome measures were performed within 1 week prior to commencement of the intervention (PRE), within 1 week after the intervention was completed (POST1), and again at 4 weeks post-intervention (POST2).

Upper Extremity Motor Function Assessment

The UE-FM (39) was the primary outcome measure in this study. UE-FM assessment was performed by a single senior occupational therapist who was blinded to the group allocation.

Corticospinal Excitability Measurement by TMS

TMS measurement of corticospinal excitability was performed by a single research assistant. Resting motor threshold (RMT), short intra-cortical inhibition (SICI) and short intra-cortical facilitation (SICF) were measured using transcranial magnetic stimulation of the primary motor cortex, with participant sitting upright in a chair with back supported, looking forward, with both forearms resting comfortably on pillows and elbows supported at 90°. Motor-evoked potentials (MEPs) were recorded from the abductor pollicus brevis (APB) via surface electrodes in a belly-tendon arrangement, by Medelec Synergy Electromyography (EMG) system (VIASYS Healthcare, UK). Single- and paired-pulse TMS were delivered through a 70 mm figure-of-eight coil using Bistim 200[2]

(Magstim Co., UK). The coil was placed on the scalp with the handle pointing posteriorly at a 45° between the coronal and sagittal planes. The optimal scalp position for activating APB was determined from initial exploration over a 1-cm grid marked on a swimming cap worn over the head.

RMT was defined by the lowest intensity eliciting peak-to-peak MEP amplitude of 50 μV, in at least five out of 10 trials from single-pulse TMS stimulation (43). SICI and SICF were measured using paired-pulse stimulation with a conditioning stimulus of 80% of RMT followed by a test stimulus of 120% of RMT. MEPs were recorded with different inter-stimulus intervals (ISIs). ISI of 2 ms typically induces SICI while ISIs of 10 and 15 ms reflect SICF (44, 45).

Adverse effects were monitored using a questionnaire documenting pain and discomfort at the stimulation site. The Beck Depression Inventory, the Fatigue Severity Scale, and the forward and backward digit span tests were administered for possible psychological and cognitive changes which may be potential confounders.

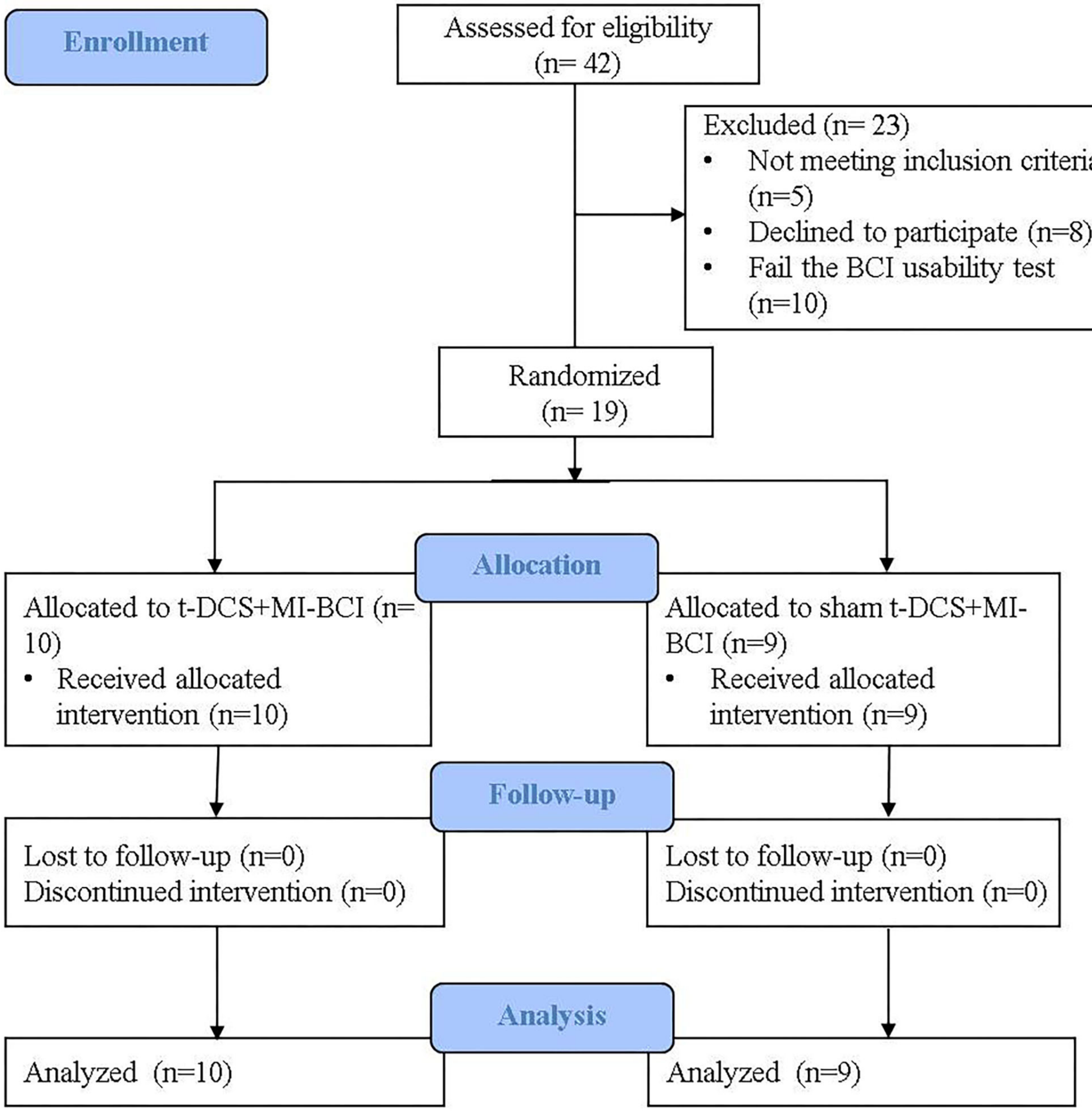

FIGURE 1 | CONSORT flow diagram. Forty-two participants were screened. Nineteen participants completed the intervention and follow-up evaluation and were included in the final analysis—10 in the real-tDCS group, nine in the sham-tDCS group.

Statistical Analysis

All statistical analysis was carried out using the IBM SPSS version 23 software. Linear mixed model with an unstructured covariance matrix and Bonferroni adjustment was used to compare differences between the two intervention groups (real-tDCS vs. sham tDCS) and among three time points (PRE, POST1, and POST2). Differences in the baseline UE-FM between two groups were analyzed by the student *t*-test. Chi-Square test was used to compare differences between categorical data. Correlation of non-parametric data was analyzed using Spearman Correlation. $P < 0.05$ was set as the level for statistical significance.

TABLE 1 | Clinical-demographics characteristics.

Group	Gender	Age (year)	Stroke duration (months)	Affected hemisphere	Affected region	Ischaemic/ Haemorrhagic	Comorbidities	UE-FM	MEP
Real tDCS	M	29	11	R	Parietal	I	hypertension, hyperlipidaemia	51	+
	M	54	28	L	CR, IC	I	hypertension, hyperlipidaemia, DM	29	+
	F	38	29	R	BG	H	DM, Turner's syndrome	38	-
	F	60	51	R	BG H. extending to temporal and CR	H	hypertension	26	+
	F	48	49	L	BG H. extending to frontal and CR	H	hypertension	39	-
	M	59	13	L	MCA territory subcortical	I	DM, hypertension, hyperlipidaemia, IHD	31	+
	M	65	27	L	CR	I	DM, hypertension, hyperlipidaemia	41	-
	F	57	10	L	BG, CR	H	none	40	-
	M	47	9	R	MCA territory subcortical	I	Atrial fibrillation	30	-
	M	65	86	R	CR, IC, BG	I	DM, hypertension, hyperlipidaemia	28	-
Mean ± SD	6M/4F	52.2 ± 11.8	31.3 ± 24.5	5L/5R	-	6I/4H	-	35.3 ± 7.8	4+/6-
Sham tDCS	M	51	44	R	MCA territory subcortical	I	IHD, hyperlipidaemia,	33	+
	M	39	25	L	Subcortical (intracranial large vessel disease)	I	Acute myeloid leukemia	36	-
	M	59	52	R	BG	H	Hypertension hyperlipidaemia	41	+
	F	70	19	R	MCA territory subcortical	I	Hyperlipidaemia, rheumatic heart disease	23	-
	M	59	44	R	MCA territory subcortical	I	DM, hypertension, hyperlipidaemia	29	-
	M	58	29	L	MCA territory subcortical	I	Hypertension, hyperlipidaemia	28	-
	M	58	25	R	BG	H	Hypertension, hyperlipidaemia	20	+
	M	47	10	L	Thalamus	I	Hypertension, hyperlipidaemia	40	-
	M	67	52	R	CR	I	-	43	+
Mean ± SD	8M/1F	56.4 ± 9.6	33.3 ± 15.1	3L/6R	-	7I/ 2H	-	32.6 ± 8.1	4+/5-
Statistics	$\chi_{(1)} = 2.04$, $p = 0.15$	$t = 0.86$, $p = 0.40$	$t = 0.21$, $p = 0.83$	$\chi_{(1)} = 0.69$, $p = 0.40$	-	$\chi_{(1)} = 0.54$, $p = 0.46$	-	$t = 0.75$, $p = 0.46$	$\chi_{(1)} = 0.84$, $p = 1.00$

No statistical differences in demographic data were found between the real-tDCS and the sham-tDCS group, including the initial UE function. Data was analyzed by the independent student t-test or Pearson's Chi-Square test. Data shows Mean ± SD or number of cases.

M, male; F, female; L, left; R, right; CR, corona radiata; IC, internal capsule; BG, basal ganglia; MCA, middle cerebral artery; I, ischemic stroke; H, haemorrhagic stroke; DM, Diabetes Mellitus; IHD, Ischemic Heart Disease; UE-FM, Upper extremity sub-scale of the Fugl-Meyer Assessment; +, MEP is recordable from the ipsilesional M1; -, MEP is not recordable from the ipsilesional M1.

We further analyzed the data from participants whose MEP of the ipsilesional M1 were unrecordable even at maximal TMS stimulator output (MEP-). Absence of MEP is associated with poorer functional outcomes in stroke patients (46).

RESULTS

We were not be able to reach the planned recruitment target. Of 42 chronic stroke patients who underwent screening, 19 were recruited, 10 to the real-tDCS group and nine to the sham-tDCS group. All completed the intervention and the follow-up evaluations (**Figure 1**). Six patients in the real-tDCS group and five patients in the sham-tDCS group were MEP- at the baseline. There was no statistical difference between groups in baseline demographic and stroke characteristics (**Table 1**), as has been reported previously (37).

Upper Extremity Motor Function Measurement

Both the real- and sham-tDCS groups improved significantly in the UE-FM after intervention [from 35.3 ± 7.8 (PRE) to 36.2 ± 8.8 (POST1) and 40.3 ± 7.8 (POST2), $F = 7.64$; $p = 0.01$ for real-tDCS group; from 32.6 ± 8.1 (PRE) to 35.3 ± 9.6 (POST1) and 37.8 ± 11.4 (POST2), $F = 4.85$; $p = 0.04$ for sham group], with no statistically significant difference between groups ($F = 0.23$, $p = 0.64$). The analysis on ΔUE-FM (UE-FM compared to pre-intervention) was previously reported (37). ΔUE-FM was significantly higher at POST2, compared to POST1 in real-tDCS group [from 0.9 ± 3.0 (POST1) to 5.0 ± 4.4 (POST2), $F = 13.64$; $p = 0.005$], but not in the sham group [from 2.8 ± 4.0 (POST1) to 6.1 ± 5.7 (POST2), $F = 4.45$; $p = 0.07$] (**Figure 2**).

When MEP- participants were considered alone, significant improvement in UE-FM was found only in the real-tDCS group [from 36.0 ± 5.5 (PRE) to 38.0 ± 6.4 (POST1) and 41.3 ± 7.1 (POST2), $F = 9.71$, $p = 0.02$], but not in the sham-tDCS group [from 31.2 ± 6.8 (PRE) to 32.6 ± 8.3 (POST1) and 32.5 ± 6.5 (POST2), $F = 0.88$, $p = 0.50$] (**Figure 3**).

Neurophysiological Outcome Measures—RMT

There was significant difference in RMT of the ipsilesional M1 over time in real-tDCS group [from 0.80 ± 0.04 (PRE) to 0.72 ± 0.07 (POST1) and 0.67 ± 0.06 (POST2), $F = 12.67$; $p = 0.00$], but not in the sham-tDCS group [from 0.83 ± 0.17 (PRE) to 0.87 ± 0.08 (POST1) and 0.82 ± 0.12 (POST2), $F = 3.00$; $p = 0.19$]. *Post-hoc* Bonferroni test showed that RMT of the real-tDCS group was significantly lower at POST1 and POST2, compared to PRE ($p = 0.0001$ and 0.01, respectively). The overall difference between real and sham groups was statistically significant ($F = 15.12$; $p = 0.01$). No significant within- and between-group differences in the RMT were found in the contralesional M1 (**Figure 4**).

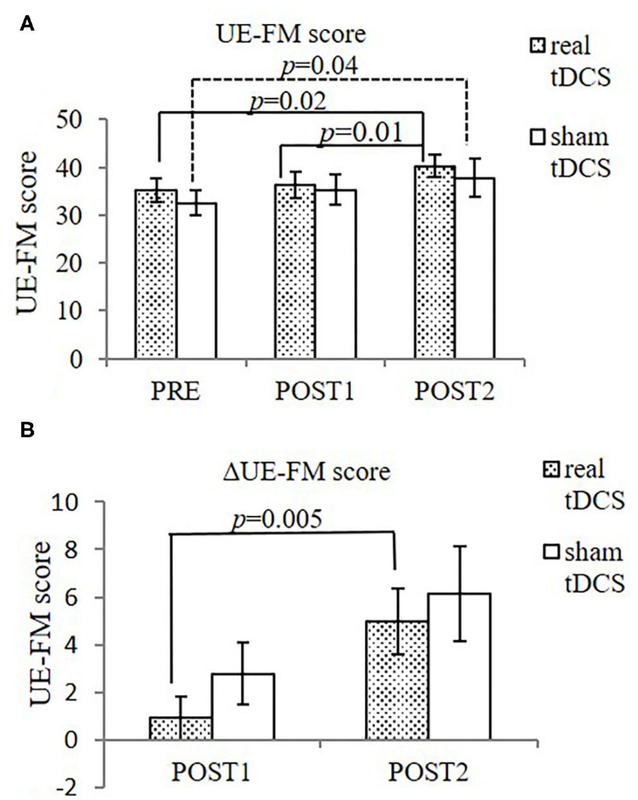

FIGURE 2 | UE-FM score **(A)** and ΔUE-FM **(B)** in both groups. **(A)** Both groups improved significantly in UE-FM at POST2 after intervention ($n = 10$ for real-tDCS group, $n = 9$ for sham-tDCS group). Between group difference was not statistically significant. **(B)** ΔUE-FM (changes in UE-FM score compared to PRE) was significantly higher at POST2, compared to POST1 in the real-tDCS group, not in the sham group. Data shows mean ± SEM.

Neurophysiological Outcome Measures—SICI and SICF in the Contralesional M1

The interventions reduced SICI in the contralesional M1 significantly, as measured at ISI of 2 ms ($SICI_{2ms}$), in the contralesional M1 ($F = 9.34$, $p = 0.00$), when both groups were combined. The sham-tDCS group had significantly reduced $SICI_{2ms}$ following intervention [from −52.2 ± 11.6 (PRE) to −36.3 ± 8.3 (POST1) and −35.9 ± 8.7 (POST2), $F = 27.15$, $p = 0.00$]. The difference in the real-tDCS group was not significant, as was the difference between groups (**Figure 5**). There was no significant difference in SICF between groups, or over time.

Relationship Between UE-FM and Contralesional Corticospinal Excitability

Spearman's correlation was used to investigate the relationships between clinical outcome measures (UE-FM) and contralesional corticospinal excitability. Correlation was found between the UE-FM score and the contralesional RMT such that a higher UE-FM score was associated with lower contralesional RMT ($r = -0.315$, $p = 0.019$). A lower UE-FM score was also associated

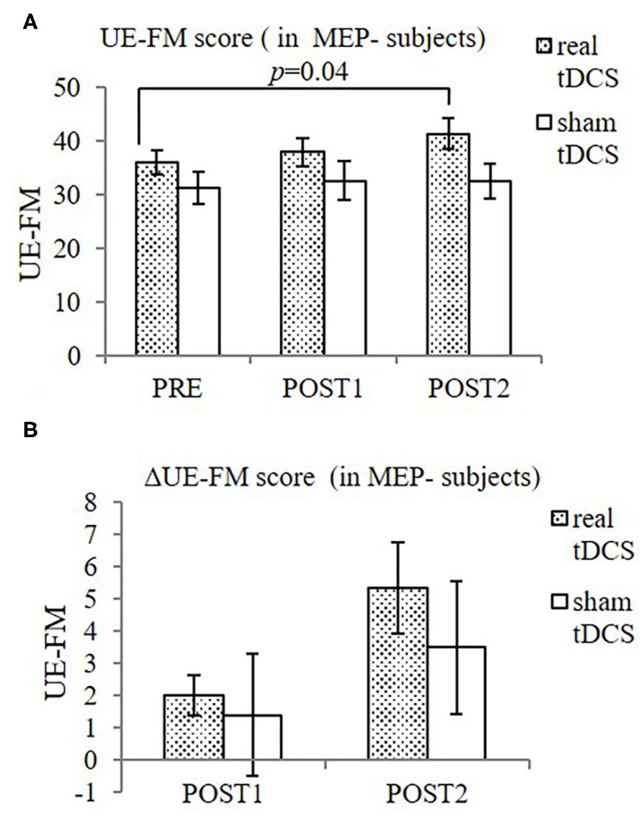

FIGURE 3 | UE-FM **(A)** and ΔUE-FM **(B)** in both groups in MEP- participants. **(A)** Significant improvement in UE-FM in the real-tDCS group ($n = 6$), but not the sham-tDCS group ($n = 5$). **(B)** No significant difference in ΔUE-FM was shown between groups, or over time. Data shows mean ± SEM.

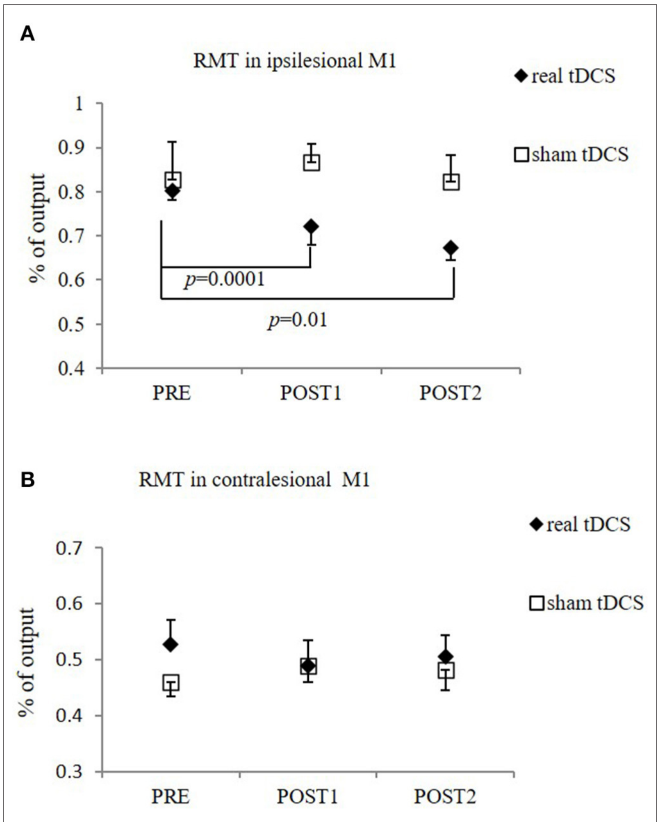

FIGURE 4 | RMT in the ipsilesional M1 **(A)** and contralesional M1 **(B)**. **(A)** Significant reduction in RMT in ipsilesional M1 in real-tDCS ($n = 6$) group at POST1 and POST2, compared to PRE, but not in sham-tDCS group ($n = 5$). The overall difference between groups was statistically significant. **(B)** No significant difference in RMT in contralesional side between two groups ($n = 10$ for real-tDCS group, $n = 9$ for sham-tDCS group), or over time. Data shows mean ± SEM.

with greater changes in contralesional $SICI_{2ms}$ ($\Delta SICI_{2ms}$) ($r = -0.420$, $p = 0.012$) (**Table 2**). When MEP- participants were considered alone, a greater reduction in contralesional RMT (ΔRMT, difference from PRE) was associated with greater improvement in UE-FM score (ΔUE-FM, difference from PRE) ($r = -0.463$; $p = 0.034$) (**Table 2**).

Side Effects of Intervention

No complications of tDCS or MI-BCI were reported by participants during and after intervention. There was no within- and between-group difference in the forward and backward digit-span, the Beck Depression Inventory and the Fatigue Severity Scale.

DISCUSSION

In this preliminary study, both the real- and sham-tDCS groups improved significantly in UE function with MI-BCI training. The intervention of MI-BCI with tDCS prior to it was safe and well-tolerated by our patients. MI-BCI training was again demonstrated to improve motor function despite initial moderate to severe motor impairment, with gains continuing up to 4 weeks post-intervention, which were greater in extent in the real-tDCS group.

Previous evidence suggests that modulation of cortical excitability with tDCS prior to task training may result in greater improvements in motor outcomes (27, 29–31, 47). A recent systematic review suggested that response to contralesional inhibitory neuromodulation may be affected by timing—while smaller studies demonstrated a definite effect in UE stroke recovery in the post-acute stage, one large study in the chronic stage did not demonstrate improved UE function (48). Whether this was because of the heterogeneity of the participants or the decreased response to modulation in the chronic phase is debatable. The lack of clear, additional clinical benefit in adding tDCS to MI-BCI training in our study may be attributed to the small sample size which had not reach our planned recruitment target, and the relatively short training period in the context of chronic stroke. Indeed, there was a trend toward significant difference between the tDCS and sham groups, in favor of the tDCS group. With the inclusion of more patients and a longer training duration, we may see a significant effect between groups.

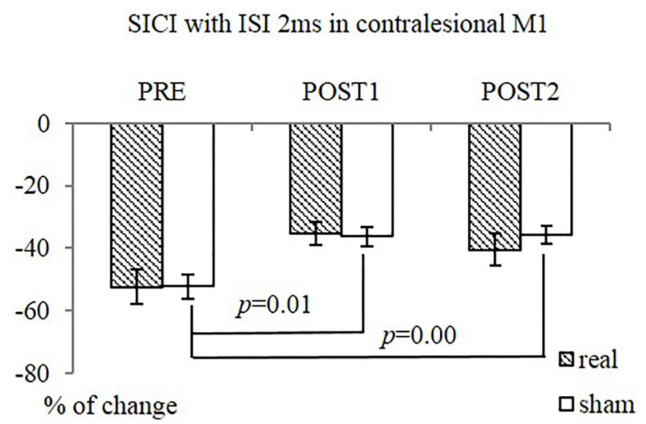

FIGURE 5 | SICI (ISI 2ms) in contralesional M1 in both groups. The sham-tDCS group ($n = 9$) had significantly reduced $SICI_{2ms}$ at POST1 and POST2, compared PRE. No difference over time was observed in real-tDCS group ($n = 10$). Between-group difference was not significant.

TABLE 2 | Correlation between UE-FM and corticospinal excitability in the contralesional M1.

	All participants			
	UE-FM		ΔUE-FM	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Contralesional RMT	−0.315*	0.019	−0.174	0.309
ΔRMT	−0.325	0.053	−0.14	0.414
$SICI_{2ms}$	0.127	0.36	0.022	0.902
$\Delta SICI_{2ms}$	−0.420*	0.012	−0.057	0.744
	MEP − participants			
Contralesional RMT	−0.204	0.263	−0.201	0.382
ΔRMT	−0.369	0.099	−0.463*	0.034
$SICI_{2ms}$	0.180	0.332	−0.220	0.352
$\Delta SICI_{2ms}$	−0.415	0.069	−0.110	0.645

*UE-FM score is negatively correlated with RMT and $\Delta SICI_{2ms}$ (changes in $SICI_{2ms}$ compared to PRE). When MEP- participants were considered alone, moderate correlation was found between a decrease in RMT (ΔRMT, changes in RMT compared to PRE) in the contralesional M1, and an improvement in UE-FM score (ΔUE-FM). *$p < 0.05$.*

Patient selection and the stimulation protocol selected, may have also contributed to the lack of observable difference. Recent literature suggests that recovery of motor function post-stroke follows a relatively predictable "proportional recovery rule" (49–51), which describes the potential for recovery ∼70% of the maximum possible. Integrity of the corticospinal tract is an important factor determining adherence to this rule ("fitters") (49, 51). Those without intact corticospinal tracts tend to be "non-fitters" to the rule, have more severe impairments and show poorer recovery.

Our population of patients were mostly those with undetectable MEPs at the time of recruitment. It has been suggested that such "non-fitters" may adopt different neural mechanisms to achieve recovery compared to those with greater integrity of the corticospinal tracts. Di Pino et al. proposed a bimodal balance-recovery model in which those with high structural reserves would achieve best recovery through rebalancing of interhemispheric inhibition, while those with low structural reserves (i.e., Larger area of damage and more severe impairment) may achieve better outcomes through promotion of vicarious activity in the unaffected hemisphere (52). We based our choice of tDCS protocol on the intent to rebalance interhemispheric inhibition, based on previous literature, without considering the integrity of the corticospinal tract. This may have contributed to the lack of observed efficacy. Indeed, more recent studies have applied a stratified approach using clinical and functional imaging cut-offs to facilitate selection of a tailored stimulation protocol (facilitation vs. inhibition of the contralesional hemisphere) (53).

Notwithstanding, we were able to observe a clinical improvement in both groups. We found a correlation between the degree of impairment in the stroke-affected arm and the degree of change in intracortical inhibition on the non-lesioned hemisphere. Furthermore, in the MEP- group, improvement in function was associated with increased corticospinal excitability on the contralesional motor cortex. These findings suggest a role of the contralesional hemisphere in the recovery of motor function post-stroke.

Cortical reorganization, with an increase of excitability of the contralesional hemisphere has been observed repeatedly following stroke (54–56). But the significance of this in motor recovery remains uncertain (57). Inhibition of the contralesional hemisphere has been shown to lead to worsening of function in the stroke-affected limb in both animals and humans (58, 59). Whether bilateral activation during task performance reflects poorer outcomes is debated. Some have found that bilateral activation portends poor outcome (60), while others have found it persists in well-recovered stroke patients (61, 62). Of note, the extent of contralesional activation relates to the degree of motor skill challenge (63) and would be an important consideration in relation to the extent of motor impairment. In terms of exploring alternative approaches to non-invasive brain stimulation, the contralesional premotor cortex has been identified as a promising target in preliminary studies to augment recovery for the more severely affected stroke patients, while little effect has been demonstrated with facilitation or perturbation of the contralesional M1 (53, 59).

The mechanism by which the contralesional motor cortex may facilitates motor recovery is a matter of active investigation. Indeed, the interhemispheric inhibition in stroke recovery has been questioned in recent studies. Premovement interhemispheric inhibition in a group of mild to moderately impaired stroke patients was found to be preserved early post-stroke and only became abnormal in the chronic phase, with no cross-sectional correlation with functional recovery (64). Studies using TMS have demonstrated that the increased contralesional M1 excitability is not causally related to the decreased transcallosal inhibition from the ipsilesional M1 (56). But rather, a decrease in intracortical inhibition as measured by SICI, which reflects the activity of $GABA_A$ergic interneurons (65), may mediate the contralesional M1 reorganization. The relatively suppressed inhibitory effect of the conditioning stimulus at higher intensity suggests a shift in the balance of excitatory and inhibitory activity toward an increase in contralesional excitatory activity (55). Such a reduction in SICI in the subacute period post-stroke is associated with significant functional improvement and may reflect the unmasking of latent networks critical for cortical reorganization (55, 66). Our finding that clinical improvement correlated with a reduction in contralesional SICI suggests that such a decrease in $GABA_A$-mediated inhibition may also play a role in contralesional reorganization associated with functional improvement, even in the chronic phase of stroke. Further investigation is required to ascertain this.

Finally, with regard to how tDCS may augment MI-BCI training, we had previously demonstrated an increase in MI detection accuracy with real-tDCS compared to sham-tDCS (21). A higher accuracy for classifying MI was observed in stroke participants following bi-hemispheric tDCS (67). Others have demonstrated a modulation of event-related desynchrony during MI with tDCS, which may enhance BCI accuracy and contribute to more effective training (35, 68, 69).

Anodal tDCS may also exert influence on training efficacy through enhancing implicit motor learning (24), or by improving attention (70). The greater delayed improvement demonstrated by the tDCS group may also reflect NMDA-dependent long-term changes in synaptic efficacy, an important mechanism underlying learning, and memory processes (23, 71).

In conclusion, MI-BCI resulted in significant UE improvement in chronic stroke patients with moderate to severe impairment. A trend toward better outcomes in the real-tDCS group was observed with significant benefit seen in the MEP- group. Future studies with more participants should focus on elucidating the specific neural mechanisms underlying motor recovery and the interaction of individual and stroke factors, tailoring neuromodulatory interventions using a stratified approach, and determining the optimal approach to combining MI-BCI with non-invasive brain stimulation to enhance motor recovery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Healthcare Group Domain-Specific Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EC, YN, and CG designed and directed the study. CG and KA developed the MI-BCI EEG analysis system. KP and LZ carried out the clinical trial procedures including MI-BCI training and trial coordination. EC, W-PT, and NT contributed to the data analysis and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Corrigendum: Using Transcranial Direct Current Stimulation to Augment the Effect of Motor Imagery-Assisted Brain-Computer Interface Training in Chronic Stroke Patients—Cortical Reorganization Considerations

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Keywords: stroke, motor recovery, transcranial direct current stimulation, brain-computer interface, motor imagery

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The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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PERSPECTIVE
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Virtual Reality Meets Non-invasive Brain Stimulation: Integrating Two Methods for Cognitive Rehabilitation of Mild Cognitive Impairment

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Mild cognitive impairment (MCI) refers to a subtle, general cognitive decline with a detrimental impact on elderlies' independent living and quality of life. Without a timely diagnosis, this condition can evolve into dementia over time, hence the crucial need for early detection, prevention, and rehabilitation. For this purpose, current neuropsychological interventions have been integrated with (i) virtual reality, which immerses the user in a controlled, ecological, and safe environment (so far, both virtual reality-based cognitive and motor rehabilitation have revealed promising positive outcomes); and (ii) non-invasive brain stimulation, i.e., transcranial magnetic or electric brain stimulation, which has emerged as a promising cognitive treatment for MCI and Alzheimer's dementia. To date, these two methods have been employed separately; only a few studies (limited to motor rehabilitation) have suggested their integration. The present paper suggests to extend this integration to cognitive rehabilitation as well as to provide a multimodal stimulation that could enhance cognitive training, resulting in a more efficient rehabilitation.

Keywords: virtual reality, transcranial magnetic stimulation, mild cognitive impairment, cognitive rehabilitation, cave, dorsolateral prefrontal cortex, non-invasive brain stimulation, executive functions

INTRODUCTION

To a certain degree, cognitive decline is a physiological change occurring during the aging process that occasionally evolves into a subtle condition known as mild cognitive impairment (MCI) (1). Despite being undiagnosable as proper dementia, at least following a categorical approach, this condition can have a detrimental impact on elderlies' cognitive functioning and worsen their conditions over time, even up to a point where an elderly presents with a frank dementia. However, MCI is also likely to either revert back to normal cognition or stabilize over time (2).

Both MCI patients and their caregivers frequently report concerns about worsening cognition in areas such as everyday memory, language, visuospatial skills, planning, organization, and divided attention (3). The decline in cognitive functioning negatively affects elderlies' independent living and their ability to safely and autonomously carry out instrumental activities of daily life (IADLs), an assessment instrument that measures an individual's ability to perform daily activities (4) such as grocery shopping, managing medications and/or money, and housework. In fact, MCI individuals are less able to perform IADLs than their healthy counterparts (5), with detrimental effects on their wellbeing (3, 6) and an increased risk of developing dementia (7). Since activity restriction underlies the expression of cognitive impairment in daily life, IADLs might enable the detection of early deficits experienced during daily activities beyond those captured by neuropsychological tests (8).

MCI is most commonly referred to as a degenerative etiology (i.e., Alzheimer's disease [AD], frontotemporal dementia, dementia with Lewy bodies), but vascular (i.e., vascular cognitive impairment), psychiatric (e.g., depression), genetic (APOE and TOMM40 genes) and other medical conditions (e.g., uncompensated heart failure, poorly controlled diabetes mellitus, or chronic obstructive pulmonary disease) can also contribute to the determination of cognitive impairment (9, 10). Clinicians classify MCI into broadly differentiated subtypes—amnestic (aMCI) and non-amnestic (naMCI)—based on whether the condition impairs one or multiple cognitive domains (1). aMCI refers to patients who exhibit episodic memory impairments as confirmed by neuropsychological tests and is associated with higher risk of further conversion to AD (11, 12). naMCI refers to patients with neuropsychological deficits in non-memory cognitive domains (12).

Neurobiological studies have revealed that cognitive impairment affecting memory (e.g., episodic memory) and other domains (e.g., executive control, language, or visuospatial abilities) is associated with altered neural activity in prodromal AD (i.e., aMCI): the entorhinal cortex and hippocampus are first affected by histopathological changes, followed by the parahippocampal gyrus, the temporal pole, and the inferior and middle temporal gyri (9, 12–16). While primary cortices seem to be less vulnerable to deterioration, associative areas are the most compromised: among them, the prefrontal cortex (PFC) shows a higher decline (17). Discriminating between normal and pathological neural changes is crucial in order to formulate an accurate diagnosis and a prompt treatment plan (18).

The conversion to dementia usually occurs within 3 years after the diagnosis of MCI, and this rate critically drops in the following years (19). Therefore, a delayed intervention could be ineffective when the cognitive decline is close to the dementia stage (20). Furthermore, the timing of the intervention also affects cost-effectiveness: therefore intervening 2 years prior to standard diagnosis would allow the maximum net benefit of the disease-modifying intervention (19).

Thus, this long "intermediate" phase provides a critical opportunity for therapeutic intervention. Cognitive interventions for MCI usually encompass a variety of approaches, heterogeneous in terms of methods and contents. Among them, cognitive training could be considered as a secondary prevention method, particularly for "at risk" groups. It generally consists of theoretically driven skills and strategies which guide and encourage patients to perform tasks engaging several cognitive domains (21). Previous studies have showed that, on one hand, MCI patients show impairments in everyday memory, language, visuospatial skills, planning, organization, and divided attention affecting daily activities, as also confirmed by worse scores in IADL (7, 12); on the other hand, MCI patients could exhibit different neural impairments, as previously mentioned (12).

Considering that MCI is characterized by both cognitive-behavioral and neural impairments, a successful rehabilitation process should address both of them and could benefit from the integration of technological advancements. A plausible candidate could be virtual reality (VR) due to its psychological and technological features: VR scenarios simulate daily life situations in which the user can feel immersed and interact with an environment updated in real-time, while also receiving dynamic multisensory feedback (21–25). A recent systematic meta-analysis showed that specific VR environments built on principles of neurorehabilitation that potentially enhance learning and recovery seem more efficacious than non-specific VR-based treatments or conventional therapies (26). Non-invasive brain stimulation (NIBS) including transcranial magnetic stimulation (TMS) has been showed to be efficacious for cognitive rehabilitation as well (27).

The widespread of neurodegenerative diseases have increased the demand for the development of new techniques to support the rehabilitation. Since the recovery is complex, there is a growing interest in the development of new technologies for improving outcomes of conventional clinical intervention strategies. The aim of the present paper is two-fold: first, to provide a brief review of current evidence regarding the benefits of non-invasive technologies (VR and TMS) on MCI cognitive rehabilitation. Second, to propose an integrated intervention approach consisting of VR-based cognitive training and neural stimulation by means of TMS. The integration of existing technologies does not replace MCI's standard rehabilitative methods, but rather upgrades them in order to create a novel approach that guarantees an ecological setting and takes action on different aspects of this clinical entity, thereby fostering cognitive improvements. Therefore, the present paper aims to propose a new integrated, multimethod approach acting on both a neural-cognitive and behavioral-cognitive level for MCI by means of VR and TMS.

A NEW INTEGRATED APPROACH

This section will be structured as follows: (i) the features of two existing interventions for MCI (i.e., VR and TMS) will be summarized, as well as (ii) the recent literature about their integration in motor rehabilitation of MCI and other clinical applications; (iii) finally, a discussion of a novel approach integrating these methods for MCI cognitive rehabilitation.

Virtual Reality in Rehabilitation

Available methods for MCI rehabilitation consist of cognitive stimulation or cognitive training, usually in the paper-and-pencil format and conducted in an isolated and non-ecological setting (28), consisting, for example, of exercises of categorization, semantic association, classification and mental imagery according to specific goals (memory for proper names, object location, etc.) (28). Recently, new technologies have been increasingly implemented in clinical settings: VR is an immersive technology using 3D computer generated environments. When a user is immersed in virtual reality, he/she experiences the sense of "being there" inside the virtual environment while knowing for sure that he/she is not (29, 30); this allows to recreate lifelike contexts in an ecological, safe and controlled setting (31–34). The sense of presence can be considered as a neuropsychological phenomenon resulting from our biological inheritance and our experience as active agents in our surrounding environment. Fully immersive VR scenarios create a strong sense of Place Illusion and Plausibility Illusion for the user, and result in realistic emotional reactions to the situations encountered in VR, perceptual accuracy, and a strong sense of agency and control over the virtual environment (34–36). These crucial features have fostered the widespread employment of VR in clinical rehabilitation (22, 25, 37, 38). Depending on the degree of immersiveness, VR devices can fall into three categories: non-immersive (e.g., user interacts with the environment with a keyboard and mouse); semi-immersive (e.g., user usually stands in front of a large screen, and gesture and location can be tracked); and fully-immersive [e.g., user wears a head-mounted display (HMD) that involves the entire vision or is immersed in the cave automatic virtual environment (CAVE), a four-walled virtual environment that provides a stronger sense of presence). VR also allows users to interact with virtual objects and to receive multisensory feedback (e.g., visual, auditory, kinesthetic) corresponding to that received in real life through the sensory system (39, 40). Synchronization of the different stimuli corresponding to different sensory streams allows the user to experience the virtual environment as realistic and results in realistic behaviors of users experiencing place illusion (41). Indeed, place illusion is defined as "the illusion of being in a place in spite of the sure knowledge that you are not there" and it differs from the plausibility illusion which is defined as "the illusion that what is apparently happening is really happening, in spite of the sure knowledge that it is not" (42, 43). The behavioral correlate of these illusions is that the user behaves in the virtual environments as he would do in the real world (44). This important feature of VR is what distinguishes it from all other types of media. Moreover, VR allows personalized therapies in a controlled way by modulating difficulty level, environments (e.g., adding or removing cues) and modality of interaction tailored to the patient's needs. The possibility of creating safe, ecological, and standardized settings has supported the employment of VR in neurorehabilitation because it allows cognitive trainings that are relevant for real contexts (22, 45, 46), supported by its potential to promote neuroplasticity (47–50). With respect to MCI, various studies have showed VR's potential to enhance cognitive functions [for reviews, see (36, 38)]. For instance, Optale and colleagues (51) showed that 36 sessions of VR-based memory training in a fully immersive environment (provided by an HMD and enriched by visual and auditory stimuli) improved patients' post-treatment Mini Mental State Examination (MMSE) scores compared to the control group—receiving musical therapy intervention—whose MMSE scores decreased instead. Moreover, memory showed improvements as well, as assessed by digit span forward and verbal story recall (51). Similar promising results were observed in an MCI sample after non-immersive VR sessions consisting of performing tasks and navigating a virtual home and supermarket (52). Patients exhibited significant improvements on the Montreal Cognitive Assessment (MoCA) and IADL after a 3-week VR-based cognitive and physical training: interestingly, after the VR intervention, functional near-infrared spectroscopy (NIRS) revealed decreased brain activation of the prefrontal areas as a result of increased neural efficiency during the training (53). Overall, several studies have highlighted the potential of VR in memory (54–57) and executive functions rehabilitation (58–61). In particular, it has been shown that the multisensory stimulation has a positive impact on both the sense of presence and memory functioning (62). At the same time, by creating complex and ecological environments, VR provides the possibility to train different executive functions (e.g., visual attention, planning, problem solving) along with motor demands, enhancing cognitive functions in daily living (59).

In fact, according to the compensatory model, demented brains show broader activation as a compensatory strategy to preserve intact cognitive functions (63, 64). Therefore, this study expands previous literature about VR efficacy to improve neural efficiency in prefrontal areas (53). Besides cognitive enhancement, VR treatments have beneficial psychological effects: participants reported feeling more enthusiastic, relaxed, energetic and, most importantly, less worried, stressed, and anxious (65). Despite these promising results, however, the heterogeneity of the studies, in terms of VR devices' different degrees of immersivity and the variety of protocols, makes it difficult to clarify the mechanisms underlying VR's effectiveness. A recent meta-analysis (66) suggests three plausible mechanisms. (i) Enjoyment: VR provides fun and engaging experiences with different tasks (e.g., exploration, challenges) that motivate patients to complete them. Conversely, patients perceive conventional rehabilitation methods, consisting of repeated behaviors without immediate feedback, as repetitive and boring. (ii) Physical fidelity: VR offers realistic scenarios that allow users to perform and practice behaviors resembling daily activities, whereas traditional rehabilitation programs focus on non-familiar behaviors. (iii) Cognitive fidelity: VR environments can be built according to specific cognitive tasks and the cognitive load required by the transfer environment. On the contrary, conventional rehabilitation is set in a relatively stimulus-free environment with limited cognitive fidelity.

Transcranial Magnetic Stimulation (TMS) in Rehabilitation

TMS is a form of non-invasive brain stimulation that induces an electrical field through a coil placed on the surface of the scalp over a targeted stimulation site (67). Depending on selected parameters (i.e., frequency, intensity, number of pulses delivered, type of coil, and location of the stimulation), TMS pulses can either excite or inhibit cortical activity and induce long- or short-term neural and behavioral changes (68). Depending on the number of pulses delivered, TMS can be single-pulse (i.e., when only one stimulus at a time is employed), paired-pulse (i.e., when pairs of stimuli separated by an interval are delivered) or repetitive (rTMS) in case of trains of stimuli (69).

TMS has increasingly been applied in several research and clinical fields (70), including in cognitive rehabilitation of MCI and dementia (27, 71–73). One study (27) reviewed the potential of TMS in modulating cognitive functions both in MCI and AD: the majority of the studies employed multiple sessions of high-frequency (>5 Hz) rTMS over the dorsolateral prefrontal cortex (DLPFC). Overall, TMS appeared effective at significantly improving memory and executive functions. Another study (72) reported long-term memory and executive functioning improvements after 10 high-frequency rTMS sessions over the left DLPFC. One study (74) considered the effectiveness of rTMS over the DLPCF at reducing apathy, a symptom frequently reported in MCI patients: a significant improvement in apathy scores resulted following 10 sessions of active TMS compared to sham. Interestingly, authors observed positive outcomes in executive functions as well, as assessed by the Trail Making Test (75). Cognitive benefits resulting from TMS interventions can be explained by the reorganization of the brain networks following the induced changes in cortical excitability. In other words, high-frequency rTMS sessions may determine an improvement in terms of synaptic plasticity, with implications for reorganization of cognitive domains (76, 77).

However, the mechanisms underlying TMS effects are still unclear. One hypothesis is that high-frequency TMS induces intracortical inhibition. In other words, discharging an electrical field causes gamma-aminobutyric acid (GABA) levels to increase, suppressing the activity (78). This temporary neuro-disruption, called a "virtual lesion," causes a disruption of perceptual, motor, and cognitive processes in the human brain (79). Another hypothesis is that TMS might determine a random neural noise by amplifying the background activity (80). Other authors suggested that TMS could disrupt the temporal relation between neurons implicated in a more extended circuit activated by the task (81). Overall, the effects of TMS are heterogeneous and seemingly dose- and context-dependent. On one hand, the effectiveness of TMS depends on the frequency and duration of the stimulation: its effects are more pronounced as long as both TMS trains and frequency increase. On the other hand, the effects depend on the level of cortical excitability at the moment of the stimulation: the pulse recruits as many neurons are close to the firing threshold (76). Overall, the effectiveness of TMS remains hindered by a number of methodological challenges, including a lack of clear consensus about the optimal stimulation parameters, with variability in the type, frequency, intensity, location, and duration of stimulation.

Virtual Reality and Non-invasive Brain Stimulation

The joint application of NIBS and VR has been previously investigated in different clinical settings to improve the clinical outcomes of conventional therapies. VR provides a controlled, ecological, and appealing setting that could be personalized according to the patient needs, whereas NIBS might alter the neurophysiology underpinning cognitive functions. For this purpose, different studies have suggested that the combination of these technologies could be more synergic than stand-alone treatments. For instance, it has been employed to induce embodiment for an artificial hand (82), to treat spider phobia (83) and in interventions in different populations, such as children with cerebral palsy, post-stroke patients, and healthy people (84). In rehabilitation settings, different studies have investigated the potential of joining VR and transcranial direct current stimulation (tDCS)/TMS for the rehabilitation of the upper limb, one of the most common deficits following a stroke (84–89). Kim and colleagues (90) found that VR wrist exercise after tDCS had greater immediate and sustained corticospinal facilitation effects than exercise without tDCS and tDCS without exercise. Furthermore, this corticospinal facilitation lasted for 20 min after the exercise in the VR+tDCS condition compared to the control groups. Recently, a meta-analysis (88) proved the effectiveness and suitability of NIBS-VR integration for motor rehabilitation of the upper limb. While different studies have proved the efficacy of the joint application of NIBS and VR for motor rehabilitation, to our best knowledge, no studies have investigated the same approach for cognitive rehabilitation.

Virtual Reality and Transcranial Magnetic Stimulation for Cognitive Rehabilitation

This section discusses an integrated intervention approach that encompasses both TMS and a training VR for cognitive rehabilitation of MCI.

VR interventions showed positive outcomes in cognitive and motor functioning in patients with MCI or dementia, as reported by a recent meta-analysis (46). Despite the mechanisms underlying the application of TMS for cognitive rehabilitation being uncertain, heterogeneous, and ambivalent, studies targeting cognitive rehabilitation suggested that aMCI and AD patients benefited from its employment (27). Therefore, a plausible hypothesis is that high-frequency rTMS over the left DLPFC might recruit more neural resources from the prefrontal cortex by inducing an electrophysiologically excitatory effect. This stimulation could also enhance the efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing. In other words, rTMS could induce a greater activation and efficacy of the prefrontal cortex (91), an area that is involved in accomplishing the VR tasks. In fact, an eclectic approach to cognitive rehabilitation achieves greater improvements based on the assumption that cognitive deficits are also determined and influenced by physical (e.g., illness, blood pressure, pain, sleep), emotional (e.g., anxiety, annoyances, arousal, mood), social (e.g., relationships, status, social pressure) and motivational (e.g., distractibility, goals, incentives) aspects (92). Specifically, a plausible integrated intervention could include 10 training sessions of 40 min, composed of rTMS (active or sham) and the virtual-based training. Before the first session and at the end of the tenth, aMCI patients will receive a neuropsychological assessment. First, high-frequency rTMS will be delivered over the left DLPCF, a region known to be involved in executive functions and in long-term memory due to its interaction with the medial-temporal network, including the hippocampus (93–95). After each session of rTMS, patients

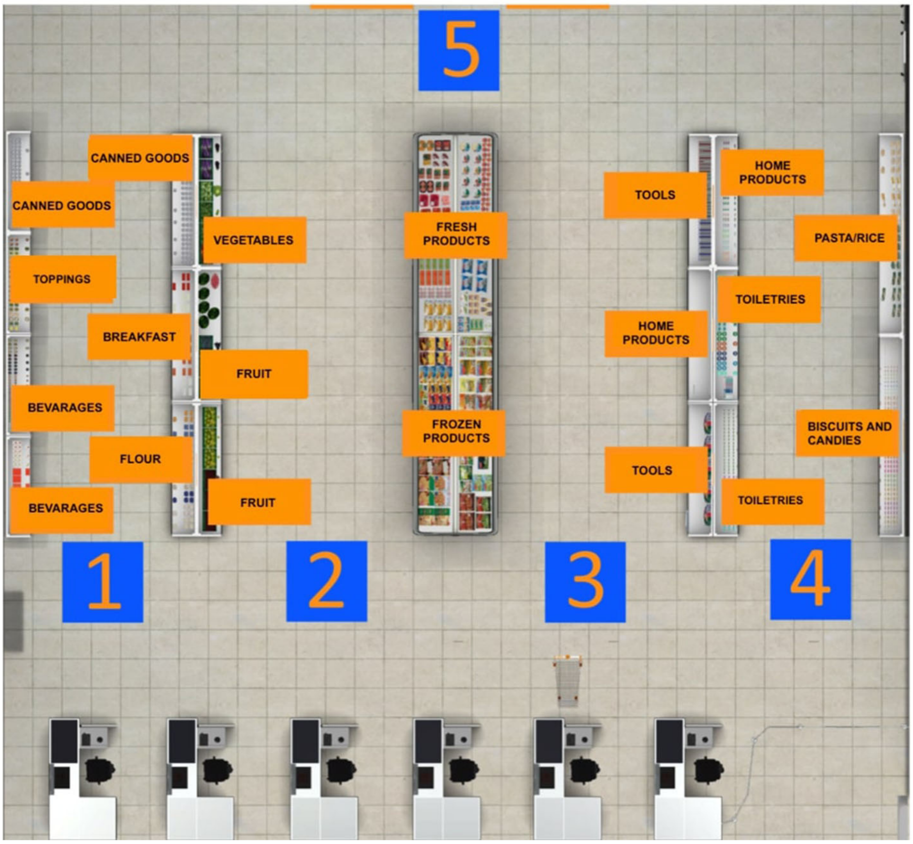

FIGURE 1 | Virtual supermarket task map. Before starting the navigation into the virtual supermarket, this map is projected on one of the four walls of the CAVE. The patient has to memorize the position of every category of products he/she has to buy.

wearing 3-D glasses will be immersed inside a CAVE[1], a virtual room-sized cube, at I.R.C.C.S. Istituto Auxologico Italiano (Milan, Italy), in which they will be exposed to two different environments (96). Patients will be first immersed in a virtual supermarket (**Figure 1**) in which they would be able to move around thanks to an Xbox controller. Tasks will consist of selecting different products on shelves according to precise rules, with increasing difficulty. Every task, according to rules and goals, will require both executive (e.g., planning, problem solving, and divided attention) and memory functioning (e.g., remembering rules). Patients will be then immersed in a virtual city (**Figure 2**) in which they will be required to perform two tasks. At the beginning, they will be placed in the center of a square and asked to move around in the virtual city, looking for a target object previously identified with the therapist. Then, they will be placed in a random location in the city and asked to retrieve the position of that object. This city task will aim to enhance spatial memory, navigation, and planning strategies.

The neuropsychological assessment will target general cognitive functioning through Addenbrooke's Cognitive Examination (ACE-R) (97) and MoCA (98). Executive functioning (planning, initiating, and monitoring) will be assessed with the Trail Making Test (TMT version A and B) (75) and the Stroop test (99). Memory abilities will be evaluated by Digit Span (100) and Babcock (101). Visuo-spatial abilities will be evaluated by Tower of London (ToL) (102). Mood will be assessed by the State-Trait Anxiety Inventory (STAI) (103) and Geriatric Depression Scale (GDS) (104). Lastly, activities of daily living (ADL) (105) and IADL (4) will be collected.

During the entire intervention, physiological measures (e.g., heart rate variability, skin conductance) will be collected.

[1]The CAVE is a virtual room-sized cube in which the 3-D visualization of the virtual environments occurs thanks to the combination of four stereoscopic projectors and four screens. Two graphics workstations, mounting Nvidia Quadro K6000 GPU with dedicated Quadro Sync cards, are responsible for the projection surfaces, user tracking and functional logic. A Vicon motion tracking system with four infrared cameras allows the tracking of specific reflective markers positioned on target objects and a correct reading of the simulated spaces and distances with a 1:1 scale ratio, thus enhancing the feeling of being immersed in the virtual scene.

DISCUSSION AND CONCLUSION

MCI is a transitional subclinical entity creating a fine line between normal and pathological aging. Thus, early interventions are essential to preserving cognitive functioning and, as far as possible, to decelerating its evolution toward

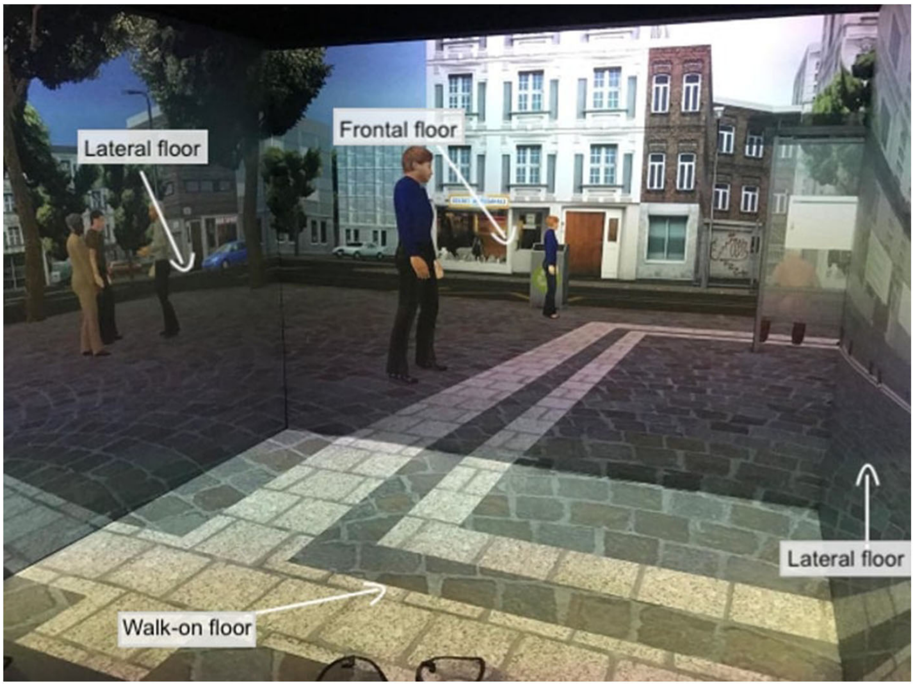

FIGURE 2 | Virtual city task. This figure shows the patient's point of view when immersed in the 3-D CAVE. The projections on the four floors move synchronously with the user's navigation through the controller.

dementia. MCI may benefit from an efficacious intervention deeming that the brain might still be able to compensate for its deficiencies and to support the acquisition and retention of the impaired cognitive functions. With the progression of pathological conditions and the spreading of lesions instead, the brain might no longer be able to compensate (106, 107). Thus, a prompt rehabilitation might be helpful in delaying the progression to dementia. Considering that both VR-based training and neuromodulation capitalize on neuroplasticity, they can enhance the therapeutic mechanisms in a complementary way. On one hand, rTMS aims to increase excitability within the lesioned hemisphere and to suppress stimulation to the contralesional hemisphere, namely, reducing inter-hemispheric inhibition from the contralesional side (108–111). Specifically in aMCI patients, the DLPFC is characterized by abnormal functional connectivity, determining several cognitive and emotional impairments (112). Stimulation of the prefrontal cortex is expected to enhance activation and efficiency in this area responsible for both executive functions (e.g., working memory and flexibility) and long-term memory due to its connection with the medial-temporal network (e.g., the hippocampus) (93–95). On the other hand, VR-based intervention will provide patients with lifelike functional tasks (like doing groceries and walking around the city) that involve cognitive domains, physical activity, and emotional–behavioral aspects. Given the potential of VR to provide an ecological and immersive setting, along with immediate feedback, the repetitive practice of these functional tasks would facilitate a complex cognitive processing strengthened by enjoyment and attractiveness, which might facilitate motivation and engagement. Patients would be required to tap into their attentional, mnemonic, planning, flexibility, and navigation abilities to accomplish the virtual tasks. It is plausible to expect that this multi-session, multi-modal intervention would facilitate the transfer of these abilities to real-life daily activities as well. Furthermore, elderlies' enjoyment could promote their engagement and treatment adherence.

The integration of VR and TMS may allow a more sensitive rehabilitation of cognitive symptoms while simultaneously modulating the impaired neural circuits to provide a stronger beneficial effect. It is plausible that the implementation of neural modulation within an ecological virtual environment may allow elderlies to benefit even more than stand-alone intervention. Besides, available interventions for MCI are frequently conducted in isolated and artificial situations, thus allowing evaluation biases.

The sense of presence, i.e., the subjective sense of being there in a virtual environment rather than in the actual physical environment, is central in a VR experience. As the other subjective feeling states, presence depends on a set of predictions about the interoceptive state of the body (113). In this regard, predictive coding theory can be used to describe the relationship between top-down prediction/expectation signals and bottom-up prediction error signals. In immersive environments, the experience of being there is based on the synchronization between expected and actual sensorimotor signals, leveraging a prediction-based model of behavior (114). In this way, immersive environments could allow to foster cognitive modeling/change, by providing realistic life-like multisensory experiences. According to it, we expect that neural and cognitive manipulation through rTMS and VR, respectively, might yield more beneficial outcomes than standard intervention both in paper-and-pencil and computer methods. Similarly to previous results, we expect that this integrated approach would determine improvements in general cognitive, memory, visuospatial, and particularly executive functioning, as well as in IADL and ADL scores for elderlies affected by MCI. In fact, both memory and executive impairments are associated with greater ADL/IADL worsening (115). VR intervention might possibly enhance complex cognitive processing as patients repetitively practiced IADL-based functional tasks. This hypothesis is in accordance with recent literature supporting the advantages of VR in improving global cognition and IADL (53).

Moreover, by collecting physiological indexes, it would be possible to record implicit measures of internal states during the whole experience, evaluating the impact of specific experiences without interfering with them (116). Indeed, biosensors are considered a reliable method for quantitative and objective measurement of the psychophysiological signals the and behavior of participants. The potential of these measures is that they provide additional information that could deepen the understanding of peculiar patterns (116).

Nevertheless, a study based on this approach is not exempt from limitations: for instance, the different stages of aMCI patients' functional levels could provide heterogeneous results. Also, some patients might not be able to complete the intervention due to dizziness or cybersickness [i.e., motion sickness including eye fatigue, nausea, headaches, and sweating (91, 92)] when immersed in virtual environments, although studies have revealed that VR is generally well-tolerated by the elderly (101). TMS could provoke discomfort and headache as well (69). Furthermore, the heterogeneity of neural impairments of MCI and the unclear beneficial effects of TMS might influence the effectiveness of this integrated approach. However, previous studies have showed promising results in the integration of neuromodulation and VR technologies for motor rehabilitation in stroke patients (85, 90). On one hand, TMS enabled shifts in cortical activity from contralesional to ipsilesional motor areas; on the other hand, VR provided repetitive, intensive, and motivating movement tasks with real-time multimodal feedback, applying motor learning principles for stroke neurorehabilitation (49, 117).

Consistent with both empirical evidence and scientific background, we thus expect that the combination of two approaches (TMS + VR) tapping into the same mechanisms will yield deeper and longer clinical outcomes in MCI patients.

AUTHOR CONTRIBUTIONS

VM and CS-B conceived, defined, and wrote the first draft of the perspective. GR supervised the study. All authors revised the final version of the manuscript.

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CLINICAL TRIAL
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Effects of Upper-Extremity Rehabilitation Using Smart Glove in Patients With Subacute Stroke: Results of a Prematurely Terminated Multicenter Randomized Controlled Trial

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Background: Although there have been many trials and interventions for reducing upper-extremity impairment in stroke survivors, it remains a challenge. A novel intervention is needed to provide high-repetition task-specific training early after stroke.

Objective: This study aimed to investigate the effect of smart glove training (SGT) for upper-extremity rehabilitation in patients with subacute stroke.

Methods: A prospective, multicenter, randomized, controlled study was conducted in patients with upper-extremity hemiparesis with Brunnstrom stage for arm 2–5 in the subacute phase after stroke. Eligible participants were randomly allocated to the SGT group or the control group. The SGT group underwent 30 min of standard occupational therapy plus 30 min of upper-extremity training with smart glove. The control group underwent standard occupational therapy for 30 min plus upper-extremity self-training (homework tasks at bedside) for 30 min. All participants underwent each intervention 5 days/week for 2 consecutive weeks. They were evaluated before, immediately after, and 4 weeks after the intervention. The primary outcome measure was the change in the score of the Fugl-Meyer assessment of the upper extremity (FMA-UE).

Results: Twenty-three patients were enrolled. Repeated-measures analysis of covariance after controlling for age and disease duration showed significant time × group interaction effects in the FMA-UE, FMA-distal, and FMA-coordination/speed ($p = 0.018$, $p = 0.002$, $p = 0.006$). Repeated-measures analysis of variance showed significant time × group interaction effects in the FMA-UE, FMA-distal, and Box and Block Test ($p = 0.034$, $p = 0.010$, $p = 0.046$). Mann-Whitney *U*-test showed a statistically higher

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increase in the FMA-UE and FMA-distal in the SGT group than in the control group ($p = 0.023$, $p = 0.032$).

Conclusion: Upper-extremity rehabilitation with a smart glove may reduce upper-extremity impairment in patients with subacute stroke.

Clinical Trial Registration: ClinicalTrials.gov (NCT02592759).

Keywords: rehabilitation, stroke, occupational therapy, upper extremity, subacute care

INTRODUCTION

Stroke is one of the leading causes of death and disabilities worldwide (1). Upper-extremity dysfunction is a common complication after stroke (2, 3). The incidence of upper-extremity dysfunction has been reported to be up to 80% in stroke survivors (4). This leads to disability and reduced quality of life because upper-extremity function is crucial for activities of daily living (ADLs) (5). Therefore, restoring upper-extremity function is an important goal of stroke rehabilitation.

Conventional occupational therapy has been a primary treatment to improve upper-limb function in stroke survivors. However, the method and quality of treatment differ depending on the therapist or clinic, and the treatment is also labor-intensive (6). As the prevalence of stroke increases, occupational therapists are increasingly burdened with the growing demand for occupational therapy for stroke survivors (7). Moreover, it is difficult to provide sufficient repetition or intensity of conventional occupational therapy to produce functional improvement (8). Therefore, there is an increasing need for a novel intervention that is effective and standardized but is less labor-intensive.

A variety of interventions for upper-extremity rehabilitation have been introduced to overcome the limitations of conventional occupational therapy for promoting the recovery of arm and hand function after stroke (9). In particular, constraint-induced movement therapy and task-specific training programs have shown evidence for enhancing upper-limb motor recovery. Consequently, highly repetitive task-specific training is required to minimize impairment (10, 11). However, it is not easy to provide sufficient high-repetition task-specific training for all patients. In addition, despite various rehabilitation efforts, about one-half of stroke survivors show no recovery of upper-limb function at 6 months after stroke (12).

Robot-assisted training using robotic devices enables highly repetitive, intensive, and task-specific training with less labor-intensive (13, 14). Hand exoskeletons have been introduced in response to the expectations for improving dexterity and ADLs. Traditional hand exoskeletons have mechanisms of rigid linkage-based or wire driven (15, 16). Rigid components and rigid linkages are used in those mechanisms. Due to the rigidity and heavyweight, the devices impede natural hand movement and ADLs. In addition, the large size interfered with visual feedback and prevented them from comfortable wearing.

The smart glove used in the present study is a soft glove with bending sensors for monitoring individual finger movements and built-in inertial measurement unit sensors for capturing wrist and hand motions. It can provide intensive and repetitive training through the patients' own efforts without the assistance of therapists (8, 17). Additionally, it can measure the range of motion, thus enabling the quantitative evaluation of motor recovery. Besides, it allows active training with visual feedback while the patients are playing the game content. Adaptive level control by an artificial intelligence component in the software provides appropriate training tailored to the patient's condition. As a result, patients are provided individualized repetitive task-specific training that has been known to enhance neuroplasticity while they are enjoying the game.

In this study, we aimed to investigate the effect of smart glove training (SGT) for upper-extremity rehabilitation in patients with subacute stroke by comparing this training method with homework tasks.

MATERIALS AND METHODS

This study was a prospective, multicenter, single-blind, randomized controlled trial conducted between October 2015 and June 2018 at 2 university hospitals in Korea. The study protocol was registered at ClinicalTrials.gov (NCT02592759) and approved by the institutional review board of each hospital (approval nos. J-1507-002-684 and 16-2015-74/071) in accordance with good clinical practices and the Helsinki Declaration. Written informed consent was obtained from every participant or legal representative.

Participants

Patients who were hospitalized for stroke from October 2015 to June 2018 were recruited from the two centers. The inclusion criteria were (1) age $\geq$19 years, (2) unilateral hemiparesis caused by a first-ever stroke (ischemic, hemorrhagic) that was confirmed on computed tomography or magnetic resonance imaging, (3) in the subacute phase after 72 h and within 3 months from stroke onset, (4) upper-extremity hemiparesis with Brunnstrom stage for arm 2–5, and (5) can tolerate sitting for at least 1 h to receive treatment. The exclusion criteria were (1) inability to perform tasks during occupational therapy because of severe hemineglect or hemianopia, (2) upper-extremity contracture due to severe limitation of motion, (3) spasticity in the wrist and fingers with Modified Ashworth Scale score $>$ 2, (4) Fugl-Meyer assessment (FMA)-wrist and hand score $\geq$ 21, (5) moderate to severe cognitive dysfunction with Mini-mental State

Examination score < 18, (6) severe aphasia, and (7) a diagnosis of a malignant tumor.

Randomization

Eligible participants were randomly allocated to either the SGT group or control group with a block randomization size of 4. Permuted block randomization is useful to ensure the balance of the number of patients assigned to each group (18). By selecting a block size of 4, every 2 participants in one block would be assigned to the intervention and control groups in random order. In this manner, the desired allocation to each group is guaranteed. An independent researcher who was not in contact with any patient performed the randomized allocation. The ratio between the SGT and control groups was 1:1 at each hospital. The principal investigator, outcome assessors, and data analysts were blinded to the group allocations of the participants until statistical analysis.

Intervention

The participants in the SGT group underwent 30 min of conventional occupational therapy plus 30 min of upper-extremity training with the smart glove, whereas those in the control group underwent 30 min of conventional occupational therapy plus 30 min of upper-extremity rehabilitation homework (self-training after receiving instructions from an occupational therapist). Each intervention was conducted for 5 days/week for 2 consecutive weeks. Conventional occupational therapy such as stacking cone, graded range of motion arc, or pegboard activities was provided by occupational therapists according to the ability of the participant.

The smart glove (RAPAEL^{TM}; Neofect, Seongnam, Rep. of Korea) was used in the experimental intervention group. It monitors the movements of the fingers, hand, and wrist. The glove has flexible bending sensors in the finger parts, which are variable resistors that change with bending and computes the amount of individual finger movements. The wrist part of the smart glove has inertial measurement unit sensors that detect 9-axis movement and the position of the hand and wrist. Data from the sensors of the smart glove are transferred *via* Bluetooth to the application installed in a tablet personal computer. Thereafter, motion analysis is conducted including measurement of active and passive range of motion. With these bio-mechanical evaluations, the application provides visual feedback by showing hand and wrist movements of a patient in real time on a monitor while the patient is conducting various motion tasks related to ADLs (**Figure 1**). The representative motion tasks include forearm supination and pronation, wrist flexion and extension, wrist radial and ulnar deviation, and finger flexion and extension.

The participants in the control group conducted rehabilitation homework tasks using the affected hand. The homework tasks consisted of following 10 items: (1) grasping and releasing a grip ball, (2) wiping a table using a soft towel, (3) pushing a rubber clay, (4) putting large beads into a cup, (5) imitating spooning up, (6) imitating drinking water from a cup, (7) putting pins in diamond-shaped holes of a pegboard, (8) making small dumplings with rubber clay, (9) flipping and matching cards, and (10) turning a notebook 1 sheet at a time. An occupational therapist chose three items according to the ability of the participant. The clinical research coordinator confirmed that self-training was implemented appropriately.

Outcome Measures

The primary outcome measure was the change in the score of the Fugl-Meyer assessment of the upper extremity (FMA-UE). The FMA-UE is the most frequently used assessment tool for motor impairment after hemiplegic stroke (19, 20). It has shown excellent inter-rater reliability and validity in patients with stroke (21, 22). Thirty-three items are rated on a 3-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully). The FMA-UE (score, 0–66) was subdivided into FMA-proximal (shoulder, elbow, and forearm; score, 0–36), FMA-distal (wrist

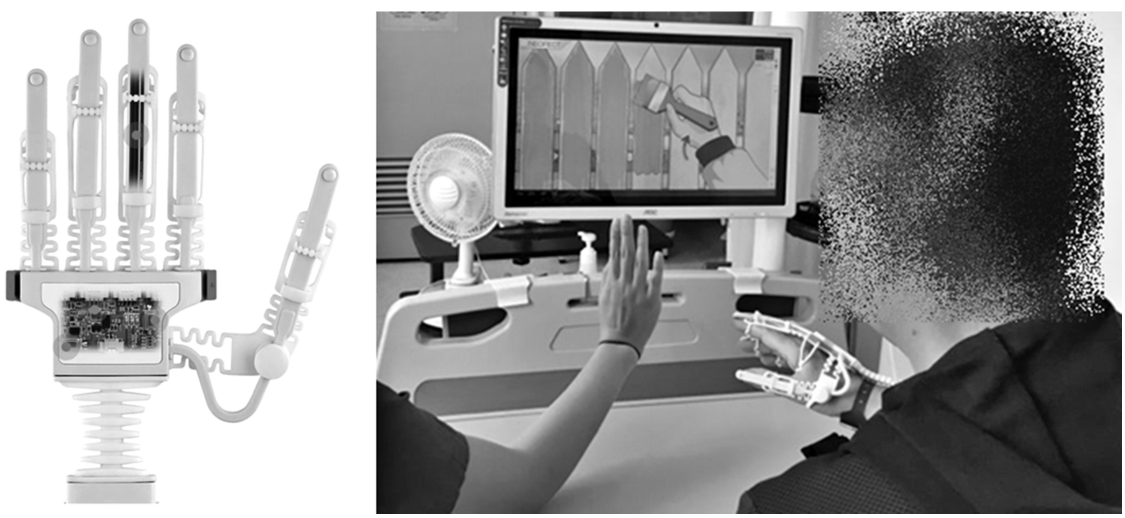

FIGURE 1 | The RAPAEL smart glove and a patient in smart glove training.

and hand; score, 0–24), and FMA-coordination/speed (score, 0–6). Higher scores indicate better motor function.

The secondary outcome measures included the changes in the scores of the FMA-proximal, FMA-distal, FMA-coordination/speed, Jebsen-Taylor Hand Function Test, Box and Block Test, grip strength, Modified Barthel Index-upper extremity (MBI-UE), and Carer Burden Scale. The FMA-proximal, distal, and coordination/speed subscales were analyzed as secondary measures to determine which subdomains were changed. The Jebsen-Taylor Hand Function Test provided a measure of hand function required for ADLs (23). It is a reliable and valid tool in patients with hemiparesis after stroke (24). The time taken to perform seven tasks was measured. A scoring system that ranges from 0 to 105 (each subset score, 0–5) was used in this trial (25). The Box and Block Test was used to measure gross manual dexterity. It has been shown to be reliable and valid in patients with stroke (26). The number of 1-inch blocks transported from 1 box to the adjacent box within 60 s was measured (27). Grip strength was used to evaluate arm function after stroke (28). Maximum grip strength is reliable in

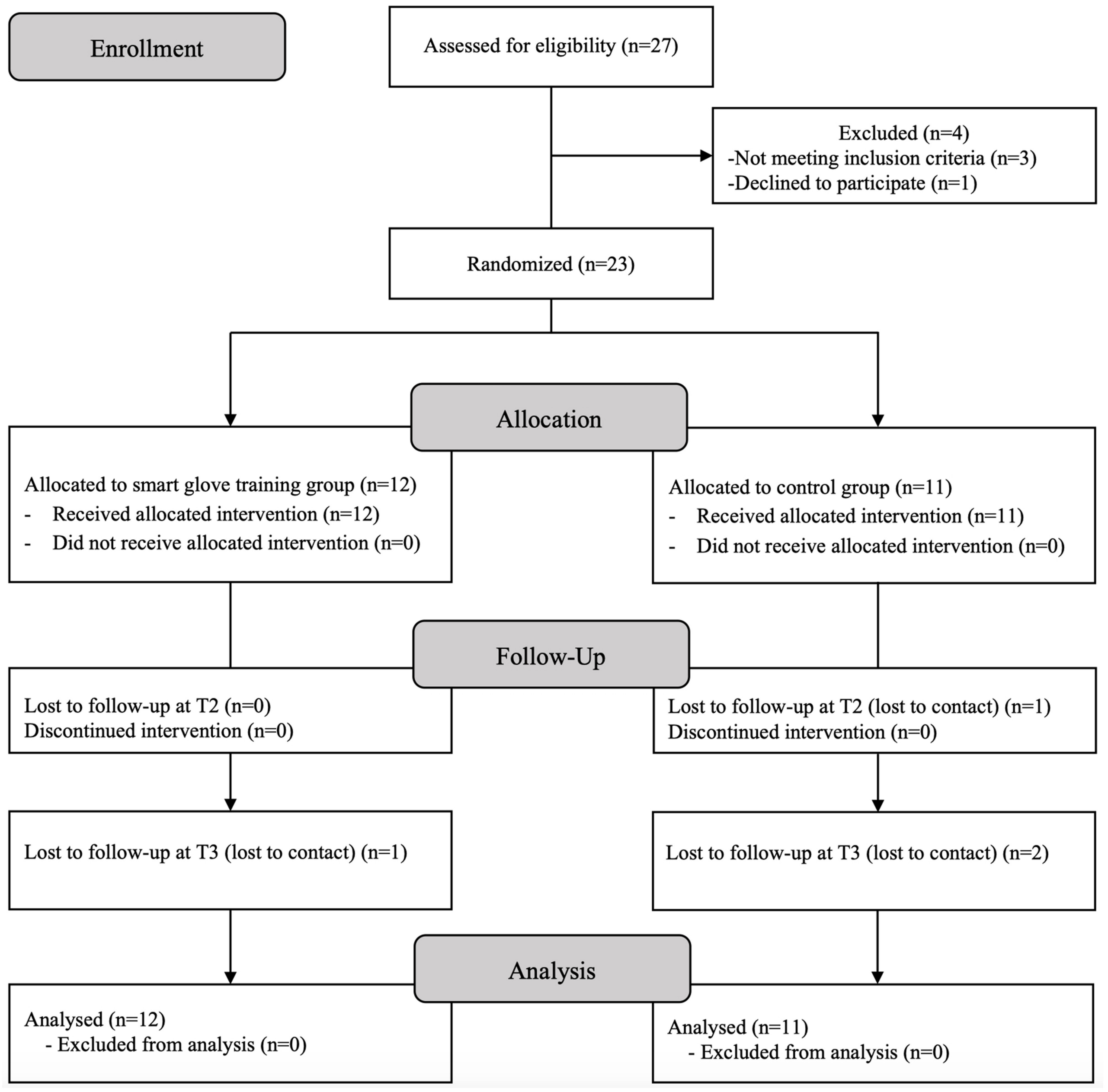

FIGURE 2 | CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

hemiparetic patients with stroke (29). The strength (lb) of the affected hand was measured using a dynamometer. The MBI provided a measure of the ability to perform ADLs (30). It has shown excellent inter-rater reliability and concurrent validity in subjects after stroke (31, 32). The maximum total score of MBI-UE ranged from 0 to 30, and the maximum subscale score was 5 (personal hygiene and bathing) or 10 (dressing and feeding). The Carer Burden Scale was used to measure the burden of care among the caregivers (33). It consisted of 4 items (cleaning the palm, cutting fingernails, dressing, and cleaning under the armpit), and each item was graded from 0 (no care burden) to 4 (maximum care burden). The total score of Carer Burden Scale ranges from 0 to 16, and higher scores indicate a higher feeling of burden.

All outcome measures were evaluated before (T1), immediately after (T2), and 4 weeks after (T3) the intervention.

Sample-Size Calculation

A previous study reported that additional upper-extremity rehabilitation with an ergonomic glove resulted in an additional increase of 6.7 points in the FMA (8). We conducted a sample-size estimation to achieve 80% power with a 2-tailed α of 0.05, by using the result of an ergonomic glove that was similar to the smart glove used in the present study. Considering a 20% dropout rate, the sample size was estimated to be 24 participants in each group, for a total of 48 participants.

Statistical Analysis

Baseline characteristics were compared between the SGT and control groups by using Pearson's chi-square test for categorical variables and the Mann-Whitney U-test for continuous and ordinal variables. The changes in outcome measures among time points were compared using repeated-measures analysis of variance (RM-ANOVA) and repeated-measures analysis of covariance (RM-ANCOVA) in the intention-to-treat populations. The last observation carried forward method was used to impute missing values. Statistical significance was accepted at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (IBM Corp, Armonk, NY, USA).

RESULTS

The trial was prematurely terminated owing to slow recruitment. A total of 23 participants were finally included in the study, and all participants completed the entire training sessions. One participant was lost to follow-up at T2, and three participants were lost at T3. Statistical analysis was performed for the 23 participants according to intention-to-treat analysis (**Figure 2**).

Table 1 shows the baseline characteristics of the participants in each group. Despite random allocation, differences were observed in age and disease duration. Participants in the SGT group were significantly younger than those in the control group (50.92 ± 16.68 vs. 64.64 ± 13.83 years; $p = 0.044$), whereas the disease duration of the SGT group was longer than that of the control group (30.75 ± 20.01 vs. 19.00 ± 9.85 days; $p = 0.059$). To offset the possible selection bias, RM-ANCOVA with age and disease duration as confounding variables was performed in the final analysis.

TABLE 1 | Baseline characteristics of the participants ($N = 23$).

Characteristics	SGT group ($n = 12$)	Control group ($n = 11$)	p-Value
Age (years)	50.92 ± 16.68	64.64 ± 13.83	0.044*
Sex			0.537
Male	7 (58.3%)	5 (45.5%)	
Female	5 (41.7%)	6 (54.5%)	
Hemiplegic side			0.469
Right	5 (41.7%)	3 (27.3%)	
Left	7 (58.3%)	8 (72.7%)	
Stroke type			0.827
Hemorrhagic	6 (50.0%)	5 (45.5%)	
Infarct	6 (50.0%)	6 (54.5%)	
Disease duration (days)	30.75 ± 20.01	19.00 ± 9.85	0.059
MMSE	24.83 ± 3.33	26.27 ± 3.17	0.260

Variables are presented as number (%) or mean ± standard deviation.
SGT, smart glove training; MMSE, Mini-mental State Examination.
$^*p < 0.05$.

Table 2 shows the outcome measures at each time point and the results of the Mann-Whitney U-test, RM-ANOVA, and RM-ANCOVA. In RM-ANCOVA after controlling for age and disease duration, the FMA-UE, which was the primary outcome measure, showed a significant time × group interaction effect ($F = 4.479$, $p = 0.018$). RM-ANOVA also showed a significant interaction effect of group and time in FMA-UE ($F = 3.653$, $p = 0.034$). The Mann-Whitney U-test showed a statistically higher increase of the FMA-UE score in the SGT group than in the control group at T3 ($p = 0.023$) but not at T2 ($p = 0.316$). **Figure 3** shows the estimated marginal means of the FMA-UE after controlling for age and disease duration over time.

In RM-ANCOVA after controlling for age and disease duration, the FMA-distal and FMA-coordination/speed showed significant time × group interaction effects ($F = 7.169$, $p = 0.002$; $F = 5.780$, $p = 0.006$). RM-ANOVA showed a significant time × group interaction effect in the FMA-distal ($F = 5.182$, $p = 0.010$) but not in the FMA-coordination/speed ($F = 2.973$, $p = 0.062$). The Mann-Whitney U-test showed a statistically higher increase of the FMA-distal score in the SGT group at T3 ($p = 0.032$) but not at T2 ($p = 0.211$). The FMA-distal showed similar statistical results with the FMA-UE, but the FMA-proximal and FMA-coordination/speed did not. RM-ANCOVA showed no significant interaction effects in the other secondary outcome measures including the FMA-proximal ($F = 0.703$, $p = 0.465$), Jebsen Hand Function Test ($F = 1.641$, $p = 0.213$), Box and Block Test ($F = 2.917$, $p = 0.072$), grip strength ($F = 0.803$, $p = 0.455$), MBI-UE ($F = 1.546$, $p = 0.229$), and Carer Burden Scale ($F = 0.813$, $p = 0.451$). Adverse events or serious adverse events did not occur in all participants during the trial.

DISCUSSION

The results of this study showed that SGT produced greater improvements of upper-extremity impairment, according to

TABLE 2 | Changes in outcome measures across time points in the SGT and control groups.

Time	SGT group (n = 12)	Control group (n = 11)	Contrasts[a]	P	Unadjusted F[b]	P	Adjusted F[c]	P
FMA-UE					3.653	0.034*	4.479	0.018*
T1	33.83 ± 13.99	35.55 ± 15.06						
T2	47.83 ± 14.26	45.09 ± 15.40	T1 to T2	0.316				
T3	55.42 ± 11.20	46.91 ± 14.98	T1 to T3	0.023*				
FMA-proximal					0.441	0.580	0.703	0.465
T1	23.58 ± 8.01	21.73 ± 7.50						
T2	29.25 ± 7.34	27.64 ± 7.30	T1 to T2	0.928				
T3	31.00 ± 6.54	27.73 ± 6.68	T1 to T3	0.608				
FMA-distal					5.182	0.010*	7.169	0.002*
T1	8.50 ± 6.60	11.09 ± 7.50						
T2	15.33 ± 7.06	15.73 ± 6.99	T1 to T2	0.211				
T3	19.17 ± 6.25	16.09 ± 7.40	T1 to T3	0.032*				
FMA-coordination/speed					2.973	0.062	5.780	0.006*
T1	1.75 ± 2.01	2.73 ± 2.05						
T2	3.25 ± 2.22	3.64 ± 1.86	T1 to T2	0.347				
T3	3.92 ± 1.68	3.09 ± 2.34	T1 to T3	0.079				
Jebsen Hand Function Test					1.329	0.271	1.641	0.213
T1	7.00 ± 11.70	9.09 ± 17.48						
T2	25.92 ± 26.95	26.91 ± 27.97	T1 to T2	0.928				
T3	40.08 ± 30.02	29.64 ± 33.10	T1 to T3	0.288				
Box and Block Test					3.560	0.046*	2.917	0.072
T1	10.75 ± 12.93	9.91 ± 15.20						
T2	19.08 ± 17.14	22.91 ± 19.43	T1 to T2	0.235				
T3	31.33 ± 19.19	23.82 ± 15.87	T1 to T3	0.260				
Grip strength					0.645	0.530	0.803	0.455
T1	12.33 ± 10.49	14.71 ± 18.04						
T2	19.75 ± 13.62	23.80 ± 25.35	T1 to T2	0.695				
T3	24.67 ± 14.54	24.03 ± 20.88	T1 to T3	0.608				
MBI-UE					2.165	0.138	1.546	0.229
T1	16.83 ± 6.24	11.55 ± 5.66						
T2	20.75 ± 5.59	20.00 ± 6.07	T1 to T2	0.051				
T3	25.17 ± 5.95	21.64 ± 4.84	T1 to T3	0.786				
Carer Burden Scale					0.537	0.588	0.813	0.451
T1	10.50 ± 3.87	12.82 ± 4.33						
T2	7.25 ± 3.60	9.91 ± 4.32	T1 to T2	0.695				
T3	6.17 ± 2.95	9.36 ± 4.72	T1 to T3	0.566				

Variables are presented as mean ± standard deviation.
SGT, smart glove training; FMA-UE, Fugl-Meyer assessment-upper extremity; MBI-UE, Modified Barthel Index-upper extremity.
[a]*Comparisons of the changes between groups with the Mann-Whitney U-test.*
[b]*Time × group interaction in repeated-measures analysis of variance.*
[c]*Time × group interaction adjusted for age and disease duration in repeated-measures analysis of covariance.*
*p < 0.05.

the FMA-UE, FMA-distal, and FMA-coordination/speed, than control tasks in patients with subacute stroke within 3 months from onset. The improvements in the FMA-UE and FMA-distal were significantly greater in the SGT group than in the control group at 4 weeks after the intervention. However, greater improvements were not observed immediately after the intervention. Our hypothesis for this result is that better but not statistically greater improvements in motor impairment immediately after SGT might have encouraged the participants to consistently use their paretic arm and hand, which gradually widened the gap of recovery between the SGT and control groups. On the other hand, the number of participants might be insufficient to prove the significance of the difference at immediately after the intervention because of the early termination of the study.

A previous trial showed that SGT was superior to conventional occupational therapy in improving upper-extremity function and quality of life in patients with chronic stroke (17). Although upper-extremity function measured using the Box and Block Test showed a marginally significant difference between the 2 groups,

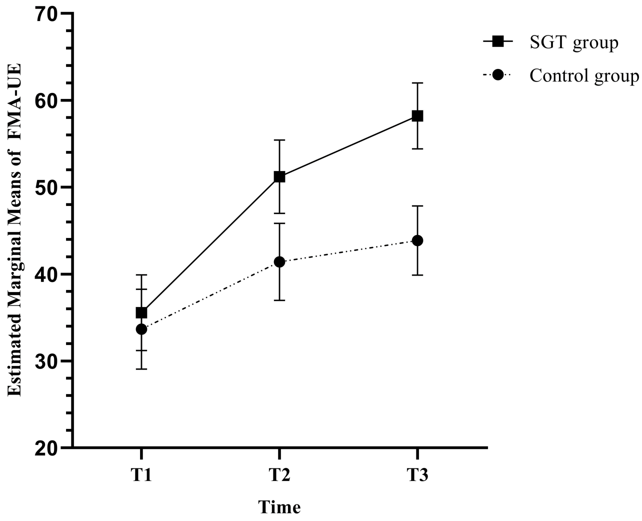

FIGURE 3 | Estimated marginal means and standard errors of the Fugl-Meyer assessment of the upper extremity (FMA-UE) in repeated-measures analysis of covariance (RM-ANCOVA) with correction for age and disease duration.

the analysis did not reveal greater improvement of ADLs. The findings of the present study are in concordance with those of a previous study in which ADLs did not show statistically greater improvements after SGT than after control tasks. To guarantee better recovery of ADLs, greater improvement of proximal-arm function might be needed, which was not a primary goal of SGT. In addition, further ADL training may be necessary to translate the improvement of upper-extremity impairment to improvement of ADLs.

The timing and dose of rehabilitation are important factors in gaining functional recovery after stroke. Starting rehabilitation early after stroke is important for functional recovery (34). Earlier rehabilitation is correlated with better-preserved cortical maps, and the training effect of rehabilitation decreases over time (35). The dose and intensity of arm training is also a critical factor to optimize rehabilitation efficacy (36). Animal studies suggested that a critical threshold of rehabilitation intensity was required for poststroke recovery and a high dose of arm training leads to effective recovery of arm function and neuroplastic changes (37–39). It is recommended that patients on an inpatient stroke rehabilitation meet the standard of 1 h of occupational therapy per day but generally they receive less than the required time (40). A review article reported that stroke survivors participate in upper-extremity training during occupational therapy <11 min in the acute phase and 12 min in the subacute phase (41). Besides, there is a substantial amount of inactive time outside of occupational therapy time. In this study, one of the explanations for the effect of SGT may be that the smart glove training had compensated for the lack of required dose and intensity of rehabilitation.

The possible mechanism of greater improvement in SGT may be based on motor learning principles. Feedback and practice are known to be important for motor learning in occupational therapy (42, 43). Intrinsic feedback includes visual information and sensory information from muscles, joints, and tendons. During SGT, intrinsic feedback is scarcely disturbed owing to the small size, lightweight, and elasticity of the device. Extrinsic feedback enhances the intrinsic feedback through external sources such as directions from therapists or biofeedback from devices. Visual feedback via the display screen during SGT helps in correcting the movements as an extrinsic feedback (44). Skill is known to improve in relation to the amount of practice (45) and repetitive massed practice is required to enhance brain reorganization (38, 46). In this trial, SGT enabled intensive massed practice through correcting the motions from intrinsic and extrinsic feedback, and this effect might be extended to promote improvement of motor impairments.

This study has several limitations. First, the sample size was not sufficient to validate the effect of SGT. It was difficult to recruit eligible participants because of the narrow inclusion/exclusion criteria. In addition, most stroke patients with mild to moderate impairment were discharged from the tertiary university hospitals before study enrollment. Therefore, the trial was prematurely terminated before reaching the initially estimated sample size of 48 patients. Although the results of this study showed the significant effect of SGT on the primary outcome measure, the lack of significance in the secondary outcome measures might have resulted from insufficient statistical power. Second, the baseline patient age was statistically different between the SGT and control groups. Age and disease duration are critical for recovery, especially in the subacute period after stroke. Therefore, RM-ANCOVA was performed to rule out the effect of age and disease duration. Third, the interventions in both groups included conventional occupational therapy, which precluded direct comparison between SGT and homework tasks. In the strict sense, this study compared the additional effect of SGT or homework tasks on conventional occupational therapy. This was ethically unavoidable because there is no evidence of the effect of SGT alone for improving upper-extremity function. Fourth, SGT trains only the distal part of the upper extremity. Combining proximal function training may be more efficient in improving upper-extremity function and ADLs in subacute stroke patients. A further study combining SGT and proximal arm training is expected to optimize upper-extremity rehabilitation.

CONCLUSION

This study suggests that SGT may be a safe and effective intervention for upper-extremity rehabilitation, especially for the improvement of distal motor impairment in patients with subacute stroke. Recovery of distal arm and hand function rather than proximal arm function may be the therapeutic target. Larger clinical trials are needed to confirm the effect of SGT based on this study.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by (1) The institutional review board of Seoul National University Hospital (2) The institutional review board of Seoul National University Boramae Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-GK analyzed data and drafted the manuscript. SY recruited patients and collected data. SL and B-MO designed the study protocol and supervised execution of the study. HL recruited patients and collected data. HS supervised execution of the study, interpreted data, and revised the manuscript. S-UL supervise design of the study and interpreted data. All authors read and approved the manuscript.

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Robotic Rehabilitation: An Opportunity to Improve Cognitive Functions in Subjects With Stroke. An Explorative Study

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Background: After a stroke, up to three-quarters of acute and subacute stroke survivors exhibit cognitive impairment, with a significant impact on functional recovery, quality of life, and social engagement. Robotic therapy has shown its effectiveness on motor recovery, but its effectiveness on cognitive recovery has not fully investigated.

Objective: This study aims to assess the impact of a technological rehabilitation intervention on cognitive functions in patients with stroke, using a set of three robots and one sensor-based device for upper limb rehabilitation.

Methods: This is a pilot study in which 51 patients were enrolled. An upper limb rehabilitation program was performed using three robots and one sensor-based device. The intervention comprised motor/cognitive exercises, especially selected among the available ones to train also cognitive functions. Patients underwent 30 rehabilitation sessions, each session lasting 45 minutes, 5 days a week. Patients were assessed before and after the treatment with several cognitive tests (Oxford Cognitive Scale, Symbol Digit Modalities Test, Digit Span, Rey–Osterrieth Complex Figure, Tower of London, and Stroop test). In addition, motor (Fugl–Meyer Assessment and Motricity Index) and disability (modified Barthel Index) scales were used.

Results: According to the Oxford Cognitive Scale domains, a significant percentage of patients exhibited cognitive deficits. Excluding *perception* (with only one patient impaired), the domain with the lowest percentage of patients showing a pathological score was *praxis* (about 25%), while the highest percentage of impaired patients was found in *calculation* (about 70%). After the treatment, patients improved in all the investigated cognitive domains, as measured by the selected cognitive assessment scales. Moreover, motor and disability scales confirmed the efficacy of robotics on upper limb rehabilitation in patients with stroke.

Conclusions: This explorative study suggests that robotic technology can be used to combine motor and cognitive exercises in a unique treatment session.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT04164381.

Keywords: rehabilitation, robotics, stroke, executive function, attention, memory

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INTRODUCTION

Cognitive dysfunctions are common consequences of stroke (1, 2). The reported percentages of patients with cognitive impairment after stroke are variable (3) and depend on several aspects, such as the inclusion of recurrent strokes, time of evaluation after stroke, dementia criteria, and exclusion of aphasic patients (4). It is estimated that up to three-quarters of acute and subacute stroke survivors exhibit cognitive impairment (5, 6). Cognitive impairment can significantly compromise functional recovery, quality of life, and social engagement after stroke (6–8). Indeed, some authors showed that the impairment of the cognitive functions can negatively influence rehabilitation strategies (9) and be a negative predictor of functional and motor outcomes after upper limb robotic therapy in patients with stroke (10).

Robotic therapy has been proposed as a viable approach for the rehabilitation of the upper limb, as a way to increase the amount and the intensity of the therapy, and to standardize the treatment (11). The most recent meta-analysis suggests that robotics can improve upper limb motor function and muscle strength after stroke (12), and, when compared to a similar amount of conventional therapy, no significant differences in terms of motor recovery are detected (13, 14).

On the contrary, to the best of our knowledge, the efficacy of robotics in restoring cognitive deficits was never explored. Robotic and technological devices can present a variety of solutions with different levels of technology, in terms of mechanical structure, level of assistance, and complexity of exercises. Even though the first devices were pretty basic in terms of rehabilitation scenario and required tasks, nowadays the implementation of new graphical interfaces and more ecological scenarios, as well as more cognitively demanding tasks, can allow an active physical and cognitive engagement of patients during robotic therapy. This can be promoted through adaptive assistance (15), to promote patient's engagement (16), as well as through cognitive challenge (17), automated task difficulty adaptation (18, 19), and motivating visual and auditory feedback (20). Feedback about movement performance not only enhances motivation but also facilitates plasticity in the motor cortex if it arrives synchronously with the

FIGURE 1 | The robotic set: Pablo (upper left), Amadeo (lower left), and Diego (lower right) from Tyromotion and Motore (upper right) from Humanware.

motor output (21), promoting the mechanisms of connectivity remodulation (22).

Therefore, we hypothesized that a robotic treatment, based on the execution of exercises, specifically selected, based on concurrent motor/cognitive tasks can improve cognitive deficits beyond motor function in patients with stroke. The current study is an explorative study aimed to evaluate the effects of upper limb robotic rehabilitation training on the cognitive functions of subacute stroke patients.

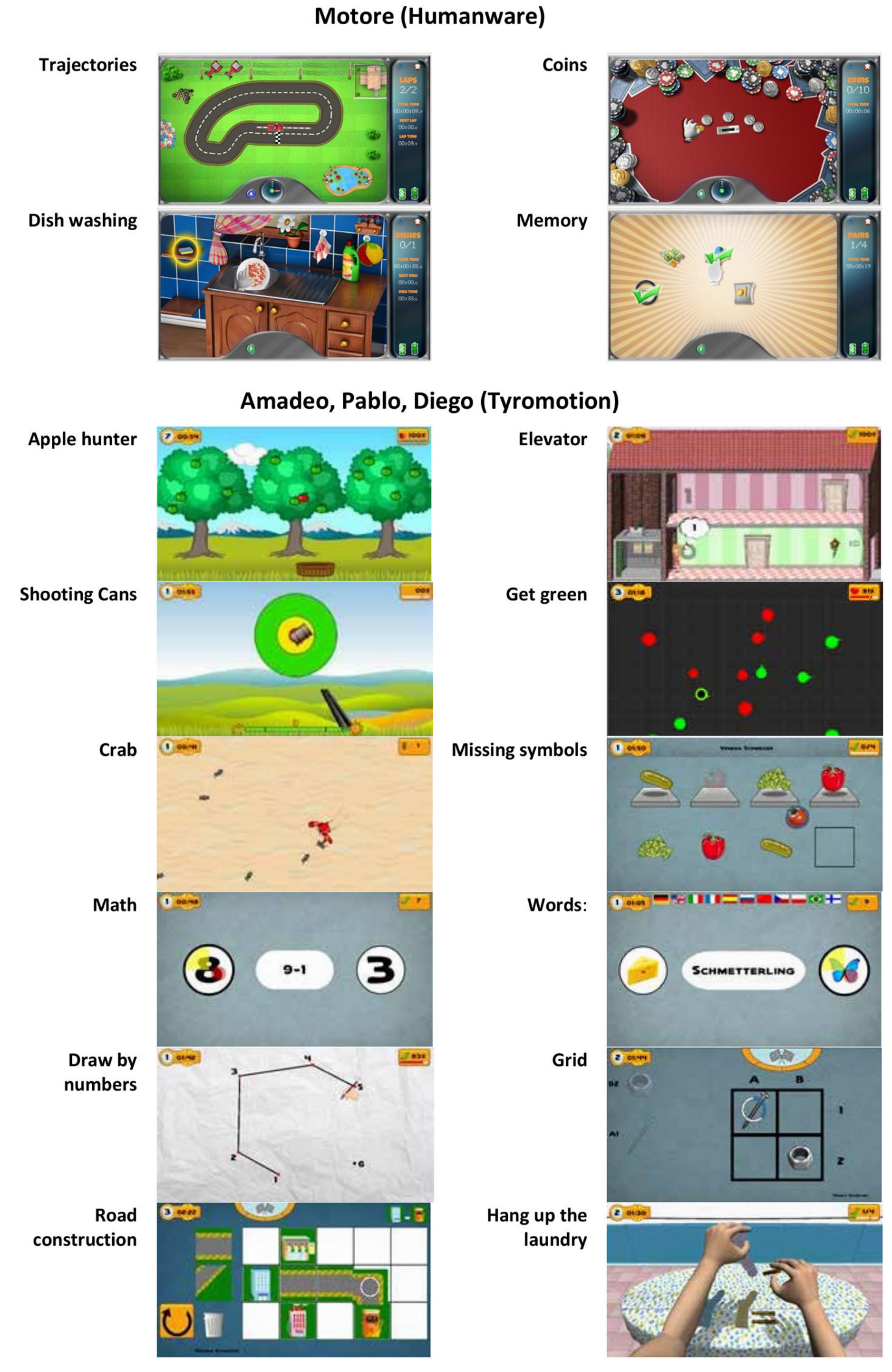

FIGURE 2 | List of motor/cognitive exercises performed with the devices.

MATERIALS AND METHODS

Study Design and Participants

In this pilot study we recruited a sample of consecutive subjects with (a) a single ischemic or hemorrhagic stroke (verified by MRI or CT), (b) age between 35 and 85 years, (c) a time since stroke within 6 months, (d) cognitive abilities adequate to understand the experiments and follow instructions (Token test corrected by age and school level $\geq$26.5), and (e) upper limb impairment (Fugl–Meyer Assessment score $\leq$58). We excluded patients with (a) a history of recurrent stroke, (b) behavioral and cognitive disorders and/or reduced compliance, (c) fixed contraction in the affected limb (ankylosis, Modified Ashworth Scale equal to 4), and (d) severe deficits in visual acuity. The study was conducted following the International Conference on Harmonization Good Clinical practice guidelines and the Declaration of Helsinki. All participants gave written informed consent before study participation. The institutional Ethics and Experimental Research Committee approved the study protocol on March 13, 2019 (FDG_13.3.2019) that was registered on Clinicaltrial.gov (ClinicalTrials.gov Identifier: NCT04164381).

Assessment

Demographic, anamnestic, and clinical data were recorded before the treatment (T0). Cognitive functions, upper limb performance, and dependence in activities of daily living were assessed at T0 and after the robotic rehabilitation intervention (T1).

Cognitive Assessment

As a cognitive screening tool, we used the Italian version of the *Oxford Cognitive Screen* (OCS), recently developed with the specific aim to describe the cognitive deficits after stroke (23, 24). The scale consists of 10 tasks encompassing five cognitive domains: attention and executive function, language, memory, number processing, and praxis. Furthermore, it includes a brief evaluation of visual field defects.

The effects of robotic rehabilitation on cognitive functions were explored using specific tools, in addition to the OCS. The cognitive assessment lasted about 90 minutes; sometimes, two sessions were requested to conclude the tests. Specifically, the tests listed below were used.

Symbol Digit Modalities Test (Attention and Processing Speed)

It is an easily administered test for overall neurocognitive and executive functioning including attention, planning, and organizing in addition to visual scanning, and motor speed. The subject is presented with a page where, in the first row, nine symbols are one-to-one associated with nine digits, from 1 to 9. Then, the rows below contain only symbols, and subjects are required to orally report the digit associates with each symbol. The number of correct responses in 90 seconds is measured. A higher score indicates higher cognitive functions (25, 26).

Digit Span Task (Memory)

We used the Digit span forward task originally proposed by Hebb (27). The examiner pronounces a list of digits, at a rate of approximately one digit per second, and the subjects are required to immediately repeat the list in the same order. If they succeed, a list one digit longer is presented. If they fail, a second list of the same length is presented. If subjects are successful on the second list, a list one digit longer is given, as before. However, if subjects also fail on the second list, the test is ended. The length of the digit sequences gradually increases, starting with a sequence of three numbers (e.g., 5, 8, 2) to a sequence of a maximum of nine items (e.g., 7, 1, 3, 9, 4, 2, 5, 6, 8). The span is established as the length of the longest list correctly recalled (28).

Rey–Osterrieth Complex Figure (Visuospatial Abilities and Visual Memory)

The task, originally designed by Rey (29) and later standardized by Osterrieth (30), requires the subject to copy a complex geometrical figure (immediate copy condition) (29, 31). For the test, performance accuracy was calculated by applying the standard scoring criteria, in which the geometrical figure is divided into 18 units and scored on a 2-point scale for both accuracy and placement (32).

Tower of London (Executive Functions)

It is a useful neuropsychological instrument to measure planning and problem-solving abilities (33–36). Briefly, it consists of a

TABLE 1 | List of motor/cognitive exercises performed with the set of devices, grouped according to the trained cognitive domain, and the availability for patients with different degree of severity, according to the Fugl–Meyer Assessment for Upper Extremity (FMA-UE): severe (FMA-UE 0–28), moderate (FMA-UE 29–42), and mild (FMA-UE 43–66) (43).

	Severe	Moderate	Mild
Attention Processing speed	Trajectories Coins Applehunter Elevator	Trajectories Coins Applehunter Elevator Get green Crab Missing symbols Draw by numbers Grid	Trajectories Coins Applehunter Elevator Get green Crab Missing symbols Draw by numbers Grid Shooting cans Math
Visuospatial ability	Trajectories Coins Applehunter Elevator	Trajectories Coins Applehunter Elevator Get green Crab Draw by numbers	Trajectories Coins Applehunter Elevator Get green Crab Draw by numbers Shooting cans Road construction
Memory	Washing dishes Memory	Washing dishes Memory Words Grid	Washing dishes Memory Words Grid
Executive Functions Planning	Washing dishes Elevator	Washing dishes Elevator Missing symbols	Washing dishes Missing symbols Math Road construction Hang up the laundry

board with three vertical pegs of different increasing length in which three different wooden balls of different colors are placed. The shortest peg only accommodates one ball, the second two, and the third three. Subjects are presented with a given configuration of balls inside the pegs and a picture of the final configuration. Subjects are then required to move the balls to reach the final configuration, without breaking some rules (each peg can accommodate a different number of balls, just one ball might be moved at a time, the balls cannot be placed outside the pegs, and a maximum number of moves is allowed). In this study, three scores were computed: *points*, *time* (measured as the sum of the planning and the execution time), and *errors* (36).

Stroop Color and Word Test (Executive Functions)

It is a neuropsychological tool widely used in clinical practice to assess selective attention, cognitive flexibility, and sensitivity to interference, abilities that have been linked to the frontal lobes. We used the short version (37) in which three tasks are proposed: (1) *word* (word reading)—3 lists of 10 words ("red," "blue," "green") are provided in random order to the patients, each written with black ink; they must read the written words; (2) *color* (color designation)—3 lists of 10 colored (red, blue, green) circles are provided in random order to the patients; they must name the color of the circles; and (3) *color–word* (interference test)—3 lists of 10 words ("red," "blue," "green"), each written with colored ink (red, blue, or green) different from the name of the color indicated by the word, in all possible combinations, are proposed to the patients in random order, and they are asked to name the color of the ink used to write the word, not the word itself. For each test, the execution time (T1, T2, and T3) and any errors made are recorded. Two interference effects are then calculated and used as outcomes: *time* (difference between the time spent in the third test and the average time spent in the two previous tasks) and *error* (difference between the number of

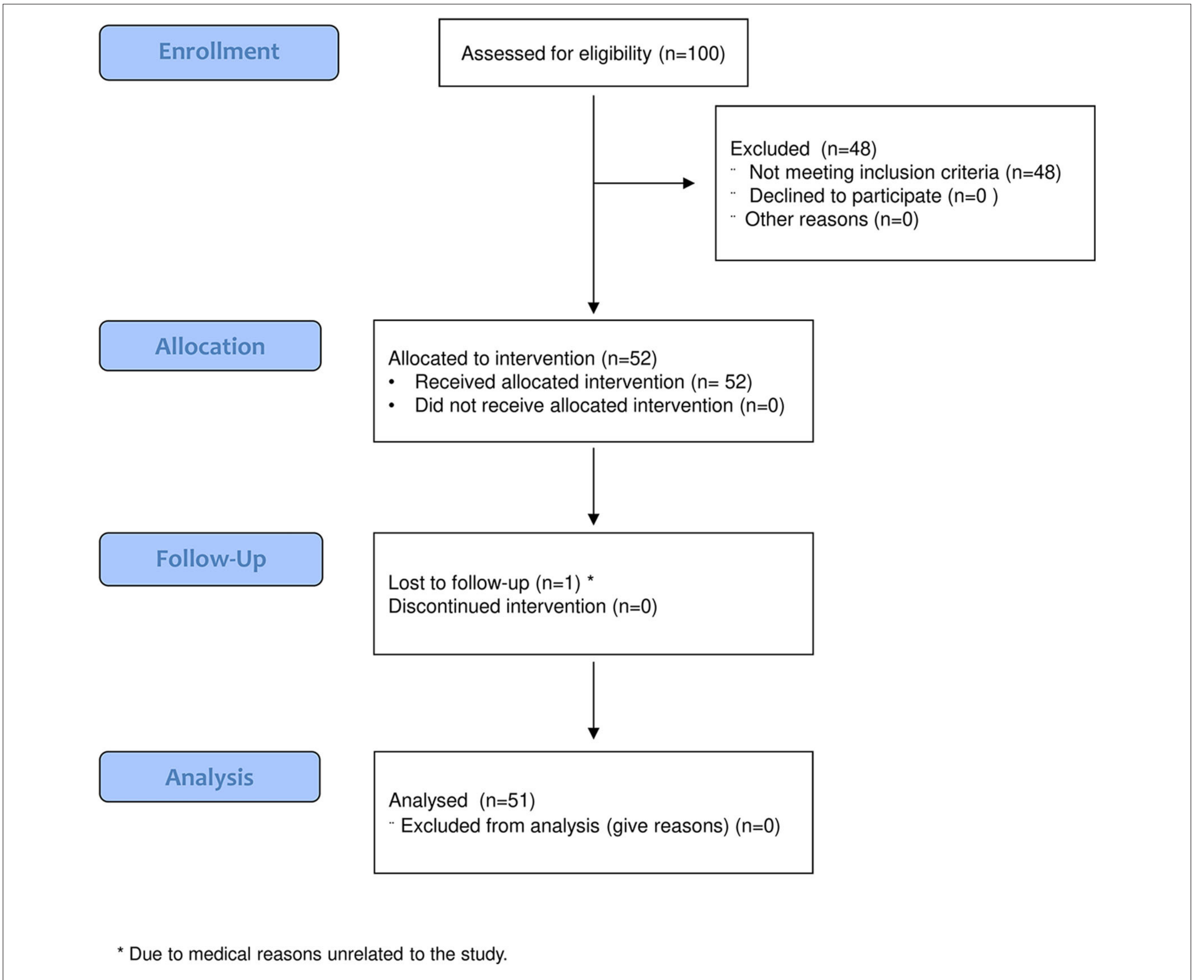

FIGURE 3 | Flow chart of the study.

errors made in the third test and the average time spent in the two previous tasks).

Upper Limb Motor Performance and Activities of Daily Living Dependence

The effects of the rehabilitation were evaluated using also the following outcome measures: the Fugl–Meyer Assessment for Upper Extremity (FMA-UE) (38), to evaluate motor function; the upper-extremity subscale of the Motricity Index (39), to evaluate upper limb muscle strength; and the Modified Barthel Index (40), to evaluate activities of daily living and mobility.

Treatment

Patients were treated with a set of three robots (i.e., with motors: Motore, Amadeo, and Diego) and one sensor-based device (i.e., without motors: Pablo) shown in **Figure 1** (41, 42). The treatment was performed daily for 45 minutes, 5 days a week, for 30 sessions.

Motore (Humanware) is a robotic device that allows passive, active, and active-assistive planar movements of the shoulder and elbow joints. Amadeo (Tyromotion) is a robotic device that allows passive, active, and active-assistive finger flexion and extension movements. Pablo (Tyromotion) is a device based on a handle equipped with two sensors (a dynamometer and an inertial measurement unit), able to record the movement of the hand in the space and the forces applied to it but not to provide motorized assistance. The tasks require to perform unimanual or bimanual three-dimensional movements of the shoulder, elbow, and wrist or to apply forces to the handle; bimanual movement are performed through two additional tools, namely, the multiboard and the multiball (14). Diego (Tyromotion) is a robotic system that allows three-dimensional, unimanual, and bimanual movements of the shoulder joint, with arm weight support.

During the treatment, patients performed both motor and cognitive tasks, and the devices provided visual and auditory feedback to help them. In particular, a set of motor/cognitive exercises was selected among those available in the robotic devices to train attention, memory, executive function, speed of processing, and visuospatial abilities (**Figure 2**). The rehabilitation program was focused on interactive games, performed through the support of the assistive forces provided by the robotic devices. In patients with mild impairment, it was also possible to reduce or remove this support, including in the intervention also motor/cognitive tasks performed without external help through the sensor-based device.

Specifically, using the robot Motore, the following exercises were executed:

- *Trajectories*—the patient is asked to drive his car along a track (training for visual scanning, attention, visuospatial ability);
- *Coins*—the patient is asked to identify and collect some golden coins arranged along an arc (while the others remain silver) and bring them back to the center of the worktop (training for visual scanning and attention);
- *Dishwashing*—this exercise simulates a daily life activity: the patient is asked to wash the dishes according to a pre-established sequence of actions, such as bring the plate into the sink, open the tap, reach the sponge, etc. (training for procedural memory, semantic memory, planning abilities, and attention);
- *Memory*—groups of icons are presented to the patient who is asked to identify and associate the icons (one by one) by meaning (training for memory).

Using Pablo, Diego, and Amadeo, the following exercises were executed (these devices shared the same software):

- *Applehunter*—falling apples (changing color from green—on the tree—to yellow—immediately before falling—to red) must be caught with a basket moved by the patient (training for coordination, selective attentiveness, processing speed, visual scanning);
- *Elevator*—the patient is asked to move an elevator in a building, with the aim of picking up people and taking them to the correct floor (training for concentration and attention, visuospatial ability, coordination, understanding numbers);
- *Shooting cans*—the patient is asked to pull a trigger to shoot the cans moving past a fixed reticule on the screen (training for concentration and attention, processing speed, visuospatial ability);
- *Get green*—the patient controls a dot and must guide it into the green circles while avoiding the red circles (training for responsiveness and processing speed, selective attentiveness);

TABLE 2 | Demographic and clinical characteristics of the analyzed sample ($N = 51$).

Entry Characteristics	
Age (years), mean (SD)	68.4 (12.4)
Sex, *n* (%)	
Men	29 (56.9%)
Women	22 (43.1%)
Education years, *n* (%)	
5	11 (21.6%)
8	15 (29.4%)
13	22 (43.1%)
18	3 (5.9%)
Index stroke type, *n* (%)	
Ischemic	36 (70.6%)
Hemorrhagic	15 (29.4%)
Dominant side, *n* (%)	
Right	47 (92.2%)
Left	4 (7.8%)
Affected side, *n* (%)	
Right	23 (45.1%)
Left	28 (54.9%)
Language impairment, *n* (%)	11 (21.6%)
Neglect syndrome, *n* (%)	10 (19.6%)
Days from index stroke to enrollment, mean (SD)	74.6 (41.3)

- *Crab*—the patient controls the direction and the speed of a crab, running around on a beach; the goal is to catch as many of the ants, which try to run away from the crab (training for visuospatial ability and spatial orientation, processing speed, attention);
- *Missing symbols*—the patient has to move the device to select and place in the correct location the missing symbol (training for selective attentiveness and planning);
- *Math Mental*—solving of simple arithmetic problems and selecting the correct solution (training for calculus ability);
- *Words*—reading of simple words and assigning them to the respective symbols (training for reading and understanding ability).
- *Draw by numbers*—the patient controls the pen and must connect the dots in the correct order (training for visuospatial ability, number count ability, attention, visual scanning);
- *Grid*—place the symbols in the designated grid positions (training for attention, visuospatial ability, memory, visual scanning);
- *Road construction*—build a street between the buildings displayed on the upper right of the screen (training for visuo-spatial and constructive ability, planning);
- *Hang up the laundry*—laundry items and clothespins must be taken from the table and attached to the clothesline (training for planning).

For each device, the exercises were selected to target, during the 30-session rehabilitation intervention, all the investigated cognitive functions. Moreover, being differently demanding from a motor point of view, the exercises were also selected for each patient according to her/his severity, based on the FMA-UE score (43), as reported in **Table 1**. In addition, the level of difficulty for each exercise varied according to the patient's ability and improvement.

During the treatment, a group of three subjects was supervised by one physiotherapist. During each session, the physiotherapist used one device for each patient to minimize the time required to move the subject from one system to another, but throughout the 30-session rehabilitation intervention, all the devices were used; with respect to the sensor-based device, patients with moderate or severe impairment performed bimanual task only, i.e., with the support of the unimpaired arm.

Further, patients underwent a comprehensive rehabilitation program including individual conventional physiotherapy (six times/week), lasting 45 minutes, focused on lower limbs, sitting and standing training, balance, and walking. Patients with language disorders performed speech training.

Statistical Analysis

Visual inspection and Shapiro–Wilk test showed that data did not meet the criteria for parametric analysis, and therefore, non-parametric tests were used. Specifically, to assess the effects of the

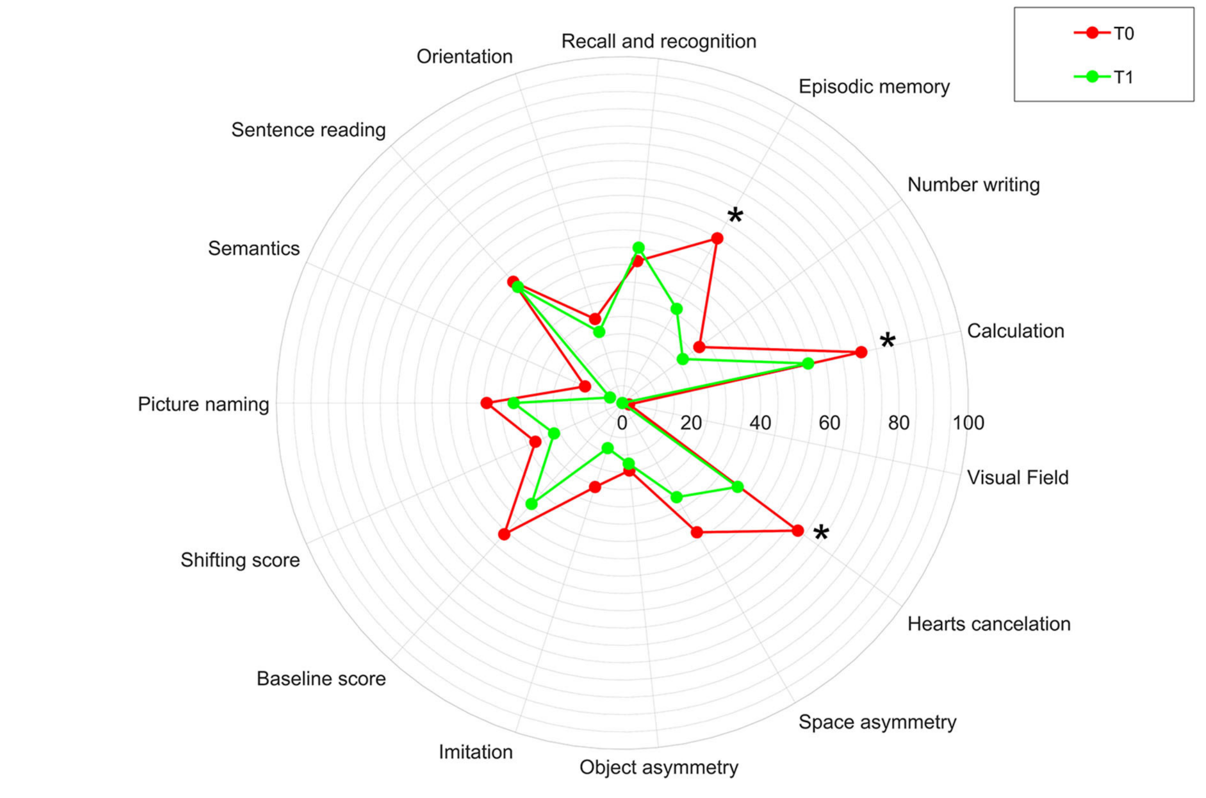

FIGURE 4 | Percentage of patients obtaining a pathological score in the Oxford Cognitive Screen (OCS) in our sample before (T0) and after (T1) the rehabilitation treatment. The asterisk indicates a statistically significant difference between T0 and T1 in our sample.

rehabilitation intervention on motor and cognitive domains, data obtained at T0 and T1 were compared by means of Wilcoxon signed-rank tests for numeric and ordinal data and the McNemar test for proportions. For all the statistical analyses, a p value of 0.05 was deemed significant. Statistical analysis was performed with SPSS (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY).

RESULTS

One hundred patients were assessed for eligibility, 48 of whom were excluded because of the inclusion criteria. Fifty-two patients were evaluated at T0 and received the allocated intervention. Of those, one patient did not undergo the follow-up evaluation, and therefore, 51 patients were evaluated at T1 and considered for the

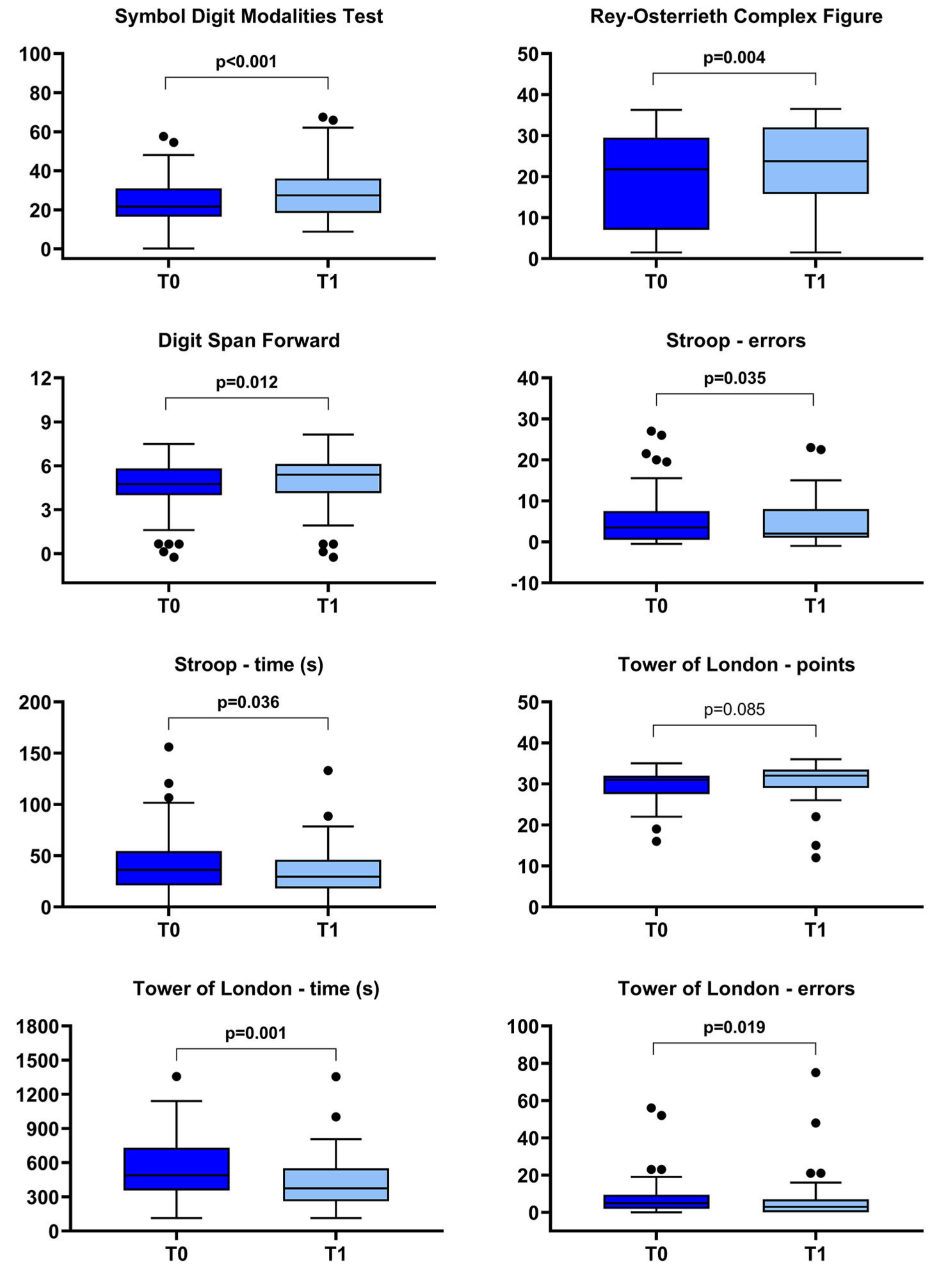

FIGURE 5 | Box-plot diagrams showing the scores obtained before (T0) and after (T1) the robotic treatment in the cognitive tests assessing attention and processing speed (*Symbol Digit Modalities Test*), visuospatial abilities and visual memory (*Rey–Osterrieth Complex Figure*), memory (*Digit Span*), and executive functions (Stroop and Tower of London tests). The boxes show the interquartile range (IQR, from the 25th to the 75th percentile). The horizontal line within each box indicates the median. The vertical bars (whiskers) indicate the range of observations excluding outliers. Dots represent outliers, i.e., observations higher than the 75th percentile plus 1.5 times IQR or lower than the 25th percentile minus 1.5 times IQR. *P* values refer to the Wilcoxon signed-rank test and are marked in bold when a statistically significant difference at $p < 0.05$ level between T0 and T1 was detected.

analysis (**Figure 3**). The demographic and clinical features of the analyzed sample are given in **Table 2**.

Figure 4 shows the percentages of patients obtaining a pathological score in the Oxford Cognitive Screen before and after the treatment. In particular, pathological scores have been found in *language and memory* domains in about half of the cases, *number domains* and in particular calculation function in 70.6% of the cases and number writing in the 27.5% of the cases, *perception* (visual field) in only one case, *spatial attention* in about 60% of the cases, *praxis* in about 25% of the cases, and e*xecutive function* in about 50% of the cases. After treatment, the percentage of patients obtaining a pathological score in the OCS subscore significantly reduced in the episodic memory ($p = 0.008$), calculation ($p = 0.021$), and visual attention (heart cancelation task, $p = 0.001$) fields.

In **Figure 5**, the changes in cognitive functions, as measured by the selected outcome measures, are reported. A statistically significant improvement was found in all the investigated domain: attention and processing speed (Symbol Digit Modalities Test), memory (Digit Span score), visuospatial abilities and visual memory (Rey–Osterrieth complex figure), and executive functions (Stroop errors and time, Tower of London error and time). Only the subscore "points" of the Tower of London Test did not significantly change.

Regarding the dependence on activities of daily living, the sample showed a T0 a severe disability, as measured using the modified Barthel Index, associated with a moderate to severe impairment in upper limb motor functions and strength (as measured by the Fugl–Meyer Assessment and the Motricity Index, respectively). **Table 3** shows the effects of the robotic treatment on the upper limb motor performance and daily living activities. In particular, after the treatment, a significant improvement was observed in upper limb impairment, measured using the Fugl–Meyer Assessment (mean change, 11.9 ± 10.1; $p < 0.001$); upper limb muscle strength, as measured by the Motricity Index (mean change, 16.2 ± 12.9; $p < 0.001$); and ability in activities daily living, as shown by the modified Barthel Index (mean change, 22.6 ± 15.5; $p < 0.001$).

DISCUSSION

The improvement in cognitive functions is among the top 10 research priorities relating to life after stroke, according to a consensus from stroke survivors, caregivers, and health professionals (2). Moreover, cognitive impairment was considered as a priority in the rehabilitation path of patients after stroke (44) because it influences the recovery of the motor function and ability in life daily activities. In the last Cochrane Review on cognitive rehabilitation for attention deficits following stroke (45), the authors highlight that improving attention, also in the short term, is very important during motor and functional rehabilitation program because high attention may enable people to engage better the exercises proposed with a high ability to cope with proposed tasks.

Several digital applications have been developed to train cognitive deficits. Some authors reported that an interactive virtual training is a useful treatment capable of stimulating cognitive abilities (amnesic-attentive functions and visuospatial cognition), executive processes, and behavioral abilities in patients with neurological disorders (46). In general, the advantage of incorporating virtual reality into rehabilitative programs is to create a positive learning experience that can also be fun and motivating for the patient (47). These virtual reality programs, developed to increase the patient's engagement, can contain cognitive exercises, and, sometimes, they can be integrated into robotic devices designed for motor rehabilitation. Therefore, rehabilitation robotics in the last years has included virtual reality programs and exercises stimulating cognitive functions, which can be proposed and performed during motor exercises. Nevertheless, usually, the aim of the robotic treatment is the improvement in motor performance and activities of daily living, while the cognitive deficits are often ignored or treated independently from motor impairment (48).

A cognitive treatment is crucial for the subjects in which cognitive and motor impairments are often present at the same time, as stroke patients (49). Indeed, the limited transfer of upper limb motor improvement in upper limb motor ability to different domains, as the activities of daily living, observed in several studies (50), could be due to the lack of attention toward the coexistent cognitive impairment. Few studies explored the cognitive effects of a robotic rehabilitation program (51, 52), and they did not use tools to investigate specific cognitive functions.

This is the first pilot study in which cognitive training and upper limb motor rehabilitation are combined thanks to the use of robotic and sensor-based devices on a sample of subacute stroke patients, using a cognitive screening tool and a set of cognitive outcome measures investigating attention and processing speed, memory, visuospatial abilities, visual memory,

TABLE 3 | Motor and cognitive assessment scores before (T0) and after the robotic treatment (T1), together with the p values of the Wilcoxon signed-rank test (with values in bold indicating a statistically significant difference between T0 and T1).

Investigated domain	Measure	T0		T1		Change from baseline		p
		Mean	SD	Mean	SD	Mean	SD	
Ability	Barthel Index ($N = 51$)	40.3	18.3	62.8	24.0	22.6	15.5	**<0.001**
Muscle strength	Motricity Index ($N = 51$)	37.3	27.9	53.5	29.0	16.2	12.9	**<0.001**
Impairment	Fugl–Meyer ($N = 51$)	21.5	18.1	33.4	21.0	11.9	10.1	**<0.001**

and executive functions. As a cognitive screening tool, we choose to use the Oxford Cognitive Screening because our group was part of the Italian OCS Group and participated in the study detecting cognitive impairment in Stroke patients using OCS, so an adequate training to the administration of OCS was performed to our researchers. The OCS, even if this is a simple cognitive screening tool, showed that, after robotic treatment, our patients significantly improved in spatial attention, episodic memory, and calculation.

Interesting results emerged when a battery of specific cognitive tools was used to test specific cognitive domains. After upper limb robotic treatment, all the explored cognitive domains significantly improved, in particular attention and processing speed, visuospatial abilities visual memory, executive functions, and memory. Then, this explorative study shows preliminary but encouraging data on the opportunity offered by robotic technology to combine motor and cognitive exercises in a unique treatment session. Note that we have selected the cognitive domain to be investigated and, therefore, the cognitive measures based on the exercises available in our set of robots and sensor-based devices. Physicians and physiotherapists need to identify specific cognitive exercises that are feasible using the robots and the technologies that are available in their rehabilitation ward. In this sense, it is also important to adopt the correct cognitive assessment tools able to intercept the possible change in the targeted cognitive fields. In our work, the use of a cognitive screening tool, together with a pool of specific cognitive tools, could seem redundant, but our aims were (a) to characterized our sample in term of general cognitive decline and then (b) to evaluate the improvement in some specific cognitive functions, which are the target of our robotic rehabilitation.

The proposed approach can be a resource to a more efficient rehabilitation treatment because it permits to treat at the same time two aspects often impaired in stroke patients; however, it is important to consider that this approach is feasible only if some requirements are satisfied: (a) the devices must include motor exercises specifically designed to stimulate cognitive functions (as visual memory, processing speed, etc.) and (b) the presence of a multidisciplinary team, made of neuropsychologists, physiatrists, physiotherapists, and speech therapists, with expertise in robotic rehabilitation, working synergistically on a new vision for the robotic rehabilitation.

The main limitation of this study is the lack of a control group, and therefore, the results of this pilot study have to be considered as a starting point that certainly encourages us to better use the potentiality of robotics and technologies. In the light of the above-mentioned limit, it is not possible to exclude that the cognitive functions here explored have improved spontaneously or because of the conventional rehabilitation that our patients performed in addition to the upper limb robotic rehabilitation. However, in a previous study in which the responsiveness and predictive validity of the Tablet-Based Symbol Digit Modalities Test was tested in a sample of 50 stroke patients undergoing a rehabilitation treatment (53), the authors found an increment of 3.3 points on the Symbol Digit Modalities Test, lower than the improvement that we observed in our sample (5.6 points). Indeed, this result suggests a beneficial effect of the proposed robotic intervention. Unfortunately, we did not find similar studies using the other cognitive tools proposed in our study (as the Rey–Osterrieth Complex Figure, the Digit Span, the Stroop, or the Tower of London tests) to compare our results with. Moreover, this study has investigated the combined effect of robotic and sensor-based devices on cognitive rehabilitation, so the specificity of the result in relation to each type of intervention (i.e., robotic vs. sensor-based vs. traditional treatment) is hard to establish. To better investigate the efficacy of the cognitive exercises administered using robotic or sensor-based devices (within motor rehabilitation program) compared to cognitive exercises administered using conventional methods, further studies, and randomized clinical trials, should be designed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico della Sezione IRCCS Fondazione Don Carlo Gnocchi del Comitato Etico IRCCS Regione Lombardia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization was carried out by IA, SG, and MG. IA, SG, and MG implemented the methodology. MG analyzed the data. GG, VC, DP, AM, LC, SM, and AR performed the investigation. IA and MG wrote and prepared the original draft. All authors reviewed and edited the manuscript.

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Healthcare Professionals' Acceptance of Digital Cognitive Rehabilitation

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With technological possibilities in healthcare steadily increasing, more tools for digital cognitive rehabilitation become available. Acceptance of such technological advances is crucial for successful implementation. Therefore, we examined technology acceptance specifically for this form of rehabilitation in a sample of healthcare providers involved in cognitive rehabilitation. An adjusted version of the Technology Acceptance Model (TAM) questionnaire was used, including the subscales for perceived usefulness, perceived ease of use, subjective norm (toward use), and intention to use, which all contribute to actual use of a specific technology. Results indicate a generally favorable attitude toward the use of digital cognitive rehabilitation and positive responses toward the TAM constructs. Only for subjective norm, a neutral mean response was found, indicating that this could pose a potential obstacle toward implementation. Potential differences between subgroups of different age, gender, and professional background were assessed. Age and gender did not affect the attitude toward digital cognitive rehabilitation. Occupational therapists showed lower scores than healthcare psychologists and physiatrists with regard to perceived usefulness, possibly linked to a difference in operational and managerial tasks. The findings of his study stimulate further implementation of digital cognitive rehabilitation, where the role of subjective norms should be specifically considered.

Keywords: digital cognitive rehabilitation, technology acceptance, implementation, eHealth, neuropsychology

INTRODUCTION

A clear increase in the use of technology in rehabilitation is observable over the last decades. Many of the newly developed methods focus on the rehabilitation of motor skills. For instance, robotics, virtual reality, and advanced motor analyses can be used to improve specific motor activities (e.g., Holden, 2005; Nef and Riener, 2005; Howard, 2017). The effective application of such technology for cognitive rehabilitation is currently less common, but is quickly evolving (see e.g., Mantovani et al., 2020). Within cognitive rehabilitation, technology can be applied to both the content and the format of treatment. In terms of content, cognitive exercises can be digitized, for instance (Schatz and Browndyke, 2002), whereas the format can benefit from communication solutions such as audio or video chat functions to provide care remotely (Kampik et al., 2015). The development of digital treatments is benefitting from widely accessible tools such as virtual reality applications. Recent studies demonstrate the value of such treatment approaches (Edwards et al., 2014; Claessen et al., 2016; van der Kuil et al., 2018), especially in terms of ecologically valid and controllable environments. The traditional approach to rehabilitation involves a team of healthcare professional that provide exercises and instructions for everyday cognitive activities. Commonly, pen and paper workbooks are used to instruct patients, monitor progress, and communicate between healthcare professionals. Notable advantages of digitally based treatments as compared to these traditional counterparts include the automatic and secure storage of test data, highly reliable administration of stimuli, improvements in standardization, and the possibility to administer treatments remotely (Schatz and Browndyke, 2002; Edwards et al., 2014; Kampik et al., 2015). Moreover, the current Corona pandemic situation has accelerated the demand and development of these techniques, which allow for online continuation of treatment (e.g., Hosey and Needham, 2020). Despite the fast increase in the popularity of this form of treatment and its obvious advantages, the implementation of digital cognitive rehabilitation can still be challenging due to various obstacles. Furthermore, this form of rehabilitation extends to a range of clinical applications, including treatment of neurodevelopmental disorders (e.g., Yerys et al., 2018; Voss et al., 2019) Lack of endorsement and lack of acceptance for digital treatment methods among health care providers may pose such obstacles, as their attitude clearly plays a crucial role in the adoption process (Chismar and Wiley-Patton, 2002; Mora et al., 2008). One factor that could affect health care provider attitude is a critical evaluation of earlier methods of digital cognitive rehabilitation, which often focus on restoration of isolated cognitive functions. However, newer methods are currently introduced, which use a more holistic approach, aimed at increasing participation and offering blended care (e.g., Van Heugten et al., 2016; Cogollor et al., 2018). Therefore, the current study is aimed at identifying the attitude of healthcare providers toward digital cognitive rehabilitation, in order to gain insight in this important factor for success of implementing digital cognitive rehabilitation techniques and to pinpoint potential obstacles toward its implementation.

The identification of an individual's attitude toward a specific form of technology can be accomplished by using the "Technology Acceptance Model" (TAM; Davis, 1989). This scale was originally designed to discover the underlying factors causing a negative attitude toward technology. It is based on the notion that the degree of technology acceptance depends on multiple constructs (Davis, 1989). In 2000, the scale has been updated (Venkatesh and Davis, 2000). Subjective norm, perceived usefulness, and perceived ease of use contribute to the intention to use, which ultimately leads to actual use. Additionally, subjective norm, an evaluation of the preferences of an individual's peers and superiors, is directly related to perceived usefulness (Chismar and Wiley-Patton, 2002; Dalcher and Shine, 2003; Venkatesh et al., 2003; Cheon et al., 2012; Surendran, 2012).

Individual differences might additionally influence the constructs of the TAM and technology use. Demographic information such as gender and age of potential users had an effect on their degree of acceptance (Venkatesh et al., 2003; Abu-Dalbouh, 2013; Gartrell et al., 2015; Khalifa and Alswailem, 2015; Moore et al., 2015; Almeida et al., 2017). Given the specificity of the current focus on cognitive rehabilitation and the incongruence in the literature, gender, age, and professional background will be considered in our examination of the attitude of healthcare providers toward digital cognitive rehabilitation.

In our use of the TAM, the mean ratings across the different subscales were explored to assess the current state of healthcare providers' attitude toward digital cognitive rehabilitation. Next, individual items of the questionnaire used were studied in order to identify potential obstacles toward technology acceptance and eventually actual system use. In literature, impact of age, gender, and professional background has been found in some but not all cases, therefore, no clear hypotheses can be formulated and an exploratory approach will be used. Lastly, the outcomes of this study will provide information about the current degree of acceptance for digital cognitive treatments among healthcare providers working in the field of cognitive rehabilitation. The degree of acceptance along with the identification of potential obstacles can be consulted in future implementation of such digital treatment solutions.

MATERIALS AND METHODS

Participants

The target population for the questionnaire consisted of healthcare providers administering cognitive treatment to patients suffering from cognitive complaints. This particularly includes healthcare providers not only working in care facilities with a specialization in cognitive rehabilitation, such as neurological rehabilitation centers, but also more general facilities such as hospitals. In order to answer the questionnaire adequately, a fluent understanding of the Dutch language was required. No requirements for participation were made based on gender or age. Participants were selected and contacted by the researchers, through professional networks concerning rehabilitation, relevant professional social media groups, and email to direct professional contacts. Dutch as well as Belgian practitioners took part in the questionnaire. Ethical approval for the study was provided by the local ethical committee.

Measures

A questionnaire was used to assess the attitude of healthcare providers toward digital cognitive rehabilitation. The questionnaire was designed based on the core constructs of the TAM and TAM2 (Davis, 1989; Venkatesh et al., 2003). This included the subjective norm construct as well as this has been shown to directly predict the intention to use technology. Each construct is measured with a separate subscale. In order to answer the main question of the attitude of healthcare providers toward digital cognitive rehabilitation, we examined the scores of each of the subscales of the TAM2 (perceived usefulness – six items, perceived ease of use – six items, subjective norm – three items, and intention to use – two items; for a complete list of questions, see **Table 1**). To avoid confusion and to ease comparability to other studies based on the TAM, we defined the constructs in the terms of Venkatesh and Davis (2000). As such, the construct of perceived usefulness was defined as the belief the participant has about the extent the use of the cognitive rehabilitation program will enhance their job performance. The construct of perceived ease of use was defined as the extent to which the participant believes the use of the program will be effortless. The construct of subjective norm was defined as the participants' impression that the use of the program would be or would not be encouraged by peers or superiors important to the respondent. Intention to use referred to the intention to use the technology, provided it is available.

The questionnaire was supplemented by demographic and job related questions to additionally explore the potential impact of age, gender, and professional background on the attitude toward digital cognitive rehabilitation. Questions were selected and rephrased based on relevance to healthcare providers working in the field of cognitive rehabilitation. We expected the Cronbach's alpha scores of the constructs used in this questionnaire to be similar to the ones found in the originals. This entailed a Cronbach's alpha score of approximately 0.86–0.98 for the perceived usefulness, 0.79–0.98 for the perceived ease of use, 0.81–0.95 for the subjective norm, and 0.82–0.97 for the intention of use (Davis, 1989; Hu et al., 1999; Venkatesh and Davis, 2000; Chismar and Wiley-Patton, 2002; Liang et al., 2003; Yi et al., 2006; Van Schaik et al., 2010; Asua et al., 2012). The possible professional backgrounds of the participants were grouped into meaningful response options. Five categories were determined based on the most likely options within our target demographic. These job categories were occupational therapist, physiatrist, healthcare psychologist (post-graduate level), psychologist, and cognitive therapist. An additional "other" category was added to make the item exhaustive.

Procedure

At the beginning of the questionnaire, the participants were given a brief explanation of the purpose of the study. Next, the participants were asked to digitally give their informed consent. First, demographic information including their gender, age, professional background, years as a healthcare professional, years of experience with cognitive rehabilitation, and self-reported internet skills were collected. This was followed by 17 questions to measure the participants' perceived usefulness, perceived ease of use, their subjective norm, and their intention to use the program. These questions were all measured on a 7-point Likert scale following an item phrased as a statement. The scores ranged from 1 (complete disagreement) to 7 (complete agreement), with 4 as the neutral center of the range. Finally, participants were asked additional questions to indicate their preference for several specific design related aspects of a digital cognitive rehabilitation tool developed by the researchers. These last questions were not part of the current study.

Statistical Analysis

The program IBM SPSS Statistics version 25 was used to conduct the analyses. Cronbach's alpha for all subscales was determined by conducting a reliability analysis on all items of the subscale. All mean scores were compared to the neutral center of the response options (4.0) to evaluate whether or not participants significantly showed agreement or disagreement for each subscale, using Bonferroni corrected one-sample *t*-tests. Additionally, the individual scores per item were evaluated in the same way, in order to identify potential specific obstacles to the acceptance and use of digital cognitive treatment. Lastly, for gender, age

TABLE 1 | List of individual items of the questionnaire with mean scores of all participants grouped together.

Subscale	Item	Mean (*SD*)	*t*
Perceived usefulness	Using digital cognitive treatments would improve the care I provide	4.80 (1.16)	8.42**
	Using digital cognitive treatments would increase my productivity	4.54 (1.22)	5.42**
	Using digital cognitive treatments would make the care I provide more effective	4.82 (1.18)	8.50**
	Using digital cognitive treatments would be useful for my work	4.99 (1.28)	9.37**
	Using digital cognitive treatments would enable me to provide care for my patients more quickly	4.72 (1.47)	5.95**
	Using digital cognitive treatments would make it easier to provide care for my patients	4.70 (1.32)	6.43**
Perceived ease of use	My interaction with digital cognitive treatments would be clear and understandable	4.27 (1.11)	2.89*
	Interacting with digital cognitive treatments would not require a lot of effort	4.35 (1.11)	3.87**
	I would find digital cognitive treatments easy to use	4.43 (1.08)	4.82**
	I would find it easy to apply digital cognitive treatments for what I want them to do	4.08 (1.36)	0.73
	Learning to provide digital cognitive treatments would be easy for me	5.30 (1.11)	14.16**
	It would be easy for me to become skillful at using digital cognitive treatments	5.29 (1.17)	13.44**
Subjective norm	Most of my patients would welcome me using digital cognitive treatments	4.07 (1.47)	0.56
	My superior(s) think(s) that I should use digital cognitive treatments	4.06 (1.66)	0.45
	Colleagues who are important to me think I should use digital cognitive treatments	3.78 (1.52)	–1.72
Intention to use	If I had access to digital cognitive treatments, I would intend to use them	5.37 (1.36)	13.44**
	If I had access to digital cognitive treatments, I predict I would use them	5.37 (1.29)	12.87**

*Each score was contrasted with the neutral value of 4.0 with a Bonferroni corrected one-sample t-test (score range 1–7). SD = standard deviation. *p < 0.01; **p < 0.001.*

group, and professional background, the nonparametric Kruskal-Wallis H test was performed to identify potential significant differences between groups. For age, participants were divided into three age groups of similar size: younger (<31), middle (31–40), and older (>40). An alpha below 0.05 was considered significant in all analyses and Bonferroni correction was applied in case of multiple comparisons.

RESULTS

Participants

In total, 147 participants completed the questionnaire, with a mean age of 38.2 (*SD* = 10.2, range 22–63). A description of the demographic characteristics and self-reported internet skills of the sample is provided in **Table 2**. The sample was skewed in terms of gender, had a sufficiently varied age range, and covered all professional groups included. However, there was only one cognitive therapist among the participants; therefore, this individual was grouped with the "other" category. All participants indicated at least an average level of internet skills.

Subscale Scores

Table 1 depicts all mean scores for all items included and the outcome of the one-sample *t*-tests, comparing the mean scores to 4.0, the neutral center of the scale used. **Table 3** depicts mean scores for each subscale, along with Cronbach's alpha, and the outcome of the one-sample *t*-tests, comparing the mean scores to 4.0. Results indicate that Cronbach's alpha was well within the expected ranges for perceived usefulness, perceived ease of use, and intention to use. For all three subscales, the mean score was significantly higher than neutral. Subjective norm, however, showed a lower Cronbach's alpha than expected and did not significantly differ from neutral. Therefore, it is more appropriate to assess scores for the three individual items rather than the subscale as a whole.

Identification of Possible Obstacles

All individual items were included in a two-tailed, one-sample *t*-test, corrected for multiple comparisons (alpha: 0.05/17 = 0.0029; see **Table 1**). All individual items of the subscales perceived usefulness and intention to use had mean scores significantly above 4.0, the neutral center of the scale. For the perceived ease of use, all individual items were significantly higher than 4.0, with the exception of "I would find it easy to apply digital cognitive treatments for what I want them to do." This specifies that general use is perceived as eas, with the exception of the application of the treatment in practice. Furthermore, all three items of the subjective norm were not significantly different from 4.0, indicating that the subjective norm as presented by patients, superiors, or colleagues is not favorable.

Individual Differences

Lastly, the impact of individual differences on the subscale scores was assessed. In **Table 4**, all means scores per subgroup are provided for each of the four subscales. As gender was skewed, a Mann-Whitney U test was used as a nonparametric alternative. No significant differences between males and females were found ($p > 0.10$ in all cases).

To assess the impact of age, the participants were grouped into three age groups, roughly based on the distribution of participants: younger (22–30), middle (31–40), and older (41–63). A one-way ANOVA on the mean scores of the four subtasks did not reveal any significant differences between the three age groups.

A nonparametric approach was also appropriate for the analysis of different professional categories. An independent samples Kruskal-Wallis test was performed and showed that for perceived ease of use, subjective norm, and intention to use, no significant differences were found between professional categories. In contrast, the scores for perceived usefulness were significantly different

TABLE 2 | Demographic variables of the sample.

Variable	Response option	N (%)
Gender	Female	128 (87.1)
	Male	19 (12.9)
Professional background	Occupational therapist	45 (30.6)
	Psychologist	28 (19.0)
	Healthcare psychologist	30 (20.4)
	Physiatrist	24 (16.3)
	Cognitive therapist	1 (0.7)
	Other*	32 (21.8)
Years as healthcare worker	1–5 years	35 (23.8)
	6–10 years	35 (23.8)
	11–20 years	50 (34.0)
	>20 years	27 (18.4)
Experience cognitive treatment	1–5 years	62 (42.2)
	6–10 years	48 (32.7)
	11–20 years	30 (20.4)
	>20 years	7 (4.8)
Internet skills	Very poor	0
	Poor	0
	Average	19 (12.9)
	Good	69 (46.9)
	Very good	59 (40.1)

**For example, clinical psychologist, clinical neuropsychologist, and physical therapist.*

TABLE 3 | Mean scores for each of the technology acceptance subscales and for all participants grouped together.

Subscale	N items	Mean (*SD*)	Cronbach's alpha	*t* (comparison to 4.0)
Perceived usefulness	6	4.76 (1.01)	0.884	9.13*
Perceived ease of use	6	4.62 (0.88)	0.851	8.56*
Subjective norm	3	4.00 (1.20)	0.664	–0.30
Intention to use	2	5.37 (1.25)	0.975	13.31*

*Reliability was assessed by calculating Crohnbach's alpha, and each score was compared to the neutral value of 4.0 with a Bonferroni corrected one-sample t-test (score range 1–7). SD = standard deviation. Two-tailed, corrected for multiple comparisons (alpha = 0.0125). *p < 0.001.*

TABLE 4 | Mean scores for each subscale divided by the subgroups of the sample, based on gender, age group, and professional background.

Factor	Subgroup	N	Perceived usefulness	Perceived ease of use	Subjective norm	Intention to use
Gender	Males	19	4.74 (1.05)	4.60 (1.00)	4.16 (1.12)	5.66 (0.99)
	Females	128	4.77 (1.01)	4.62 (0.86)	3.94 (1.21)	5.33 (1.28)
Age group	Younger (22–30)	41	4.85 (0.87)	4.83 (0.75)	4.01 (1.19)	5.56 (1.19)
	Middle (31–40)	50	4.64 (1.01)	4.55 (0.91)	3.86 (1.33)	5.24 (1.33)
	Older (41–63)	56	4.81 (1.11)	4.52 (0.92)	4.04 (1.09)	5.35 (1.22)
Professional background	Occupational therapists	45	4.33 (1.12)	4.37 (0.87)	3.61 (1.25)	5.06 (1.46)
	Psychologists	28	4.70 (0.97)	4.64 (0.92)	3.92 (1.27)	5.48 (1.19)
	Healthcare psychologists	30	5.05 (0.84)	4.62 (0.86)	4.06 (1.11)	5.42 (1.21)
	Physiatrists	24	5.06 (0.93)	4.76 (0.86)	4.36 (1.01)	5.52 (0.99)
	Other	20	5.04 (0.87)	5.00 (0.79)	4.25 (1.17)	5.68 (1.09)

Standard deviations in parentheses.

between professional categories ($p = 0.014$). A Bonferroni-corrected *post hoc* analysis showed that the scores of the occupational therapists were significantly lower than those of the healthcare psychologists and the physiatrists ($p < 0.05$ in both cases).

DISCUSSION

There is an ongoing increase in the availability of digital cognitive rehabilitation tools with digital applications both in terms of format and content. Technology acceptance is a key in the successful implementation of such treatment protocols as it has been shown to accurately predict actual system use. Here, we studied technology acceptance among healthcare providers in order to answer the main question, concerning the attitude of healthcare providers toward digital cognitive rehabilitation. First, the mean ratings across the different elements of the TAM were explored. Next, individual items of the questionnaire used were studied in order to identify potential obstacles toward technology acceptance and eventually actual system use. Lastly, the impact of individual characteristics including age, gender, and professional background was examined.

First of all, with regard to digital cognitive rehabilitation, health care providers showed convincing levels of agreement with perceived usefulness, perceived ease of use, and the intention to use. In contrast, for the subjective norm subscale, the mean scores showed that this factor is regarded neutrally by our participants. Furthermore, Cronbach's alpha was rather low for this particular subscale. Therefore, it is informative to also consider each individual item. This analysis revealed that for all three sources of subjective norm included – patients, superiors, colleagues – a neutral attitude is present. This presents a potential obstacle toward technology acceptance and eventually actual system use and is therefore an important element in the implementation of digital cognitive rehabilitation tools. The interpretation of this effect could be 2-fold: either subjective norm is not as high as it needs to be to stimulate system use or the subjective norm is neutral because the attitude of peers and superiors is not known. In the first case, establishing a more positive attitude toward digital cognitive rehabilitation, established by, e.g., visible use of such technology and exchange of positive experiences, could promote system use. In the latter case, a more explicit discussion of attitude concerning digital cognitive rehabilitation would be appropriate, e.g., by discussion this in formal meetings and with patient organizations (e.g., Ploeg et al., 2007; Andreassen et al., 2015). In line with this finding, it should be noted that only few effective methods are currently in use, due to recent improvements in terms of content and required technology. A number of methods have been available for longer, but have not been able to show clear positive results as they often focus on restoration of isolated cognitive functions. In contrast, newer methods use a more holistic approach, in which participation and blended care are focused on (e.g., Van Heugten et al., 2016; Cogollor et al., 2018). Only a limited number of studies are currently available for effective cognitive digital cognitive rehabilitation due to its novelty and the need of follow-up study (e.g., Larson et al., 2014; Mansbach et al., 2015). The process of creating a positive subjective norm is hindered by the scarcity of successful and commendable methods. Furthermore, there is substantial variation in the application of cognitive rehabilitation, in terms of, e.g., pathology, patient characteristics, and specifications of cognitive deficits. Combined with the observation that scores are especially high for the intention to use items, this suggests that health care providers are highly willing to use effective novel methods for digital cognitive rehabilitation, which are not yet widely available. In line with this, implementation strategies that target subjective norms are recommended, e.g., gradual implementation of novel technology, starts with a small group of enthusiastic users (e.g., De Veer et al., 2011).

In the creation of the TAM2, demographic factors were included, with a direct relationship to perceived ease of use (Venkatesh et al., 2003). However, findings on the impact of these factors have been contradictory. Gender may affect the overall acceptance of technology, with a higher level of acceptance of digital therapeutic tools for males, in comparison to females (Mora et al., 2008). In contrast, Khalifa and Alswailem (2015) found that gender did not have a significant influence on the satisfaction of a system. With regard to age, Mora et al. (2008) report a specific age effect for digital chat sessions replacing tradition face-to-face treatment. Psychologist with an older age was more accepting. Similarly, Gartrell et al. (2015) found that older nurses' approval of an electronic health record for patients was higher in comparison to younger nurses. However, Schnall and Bakken (2011) found no significant relationship between the age of the user and their acceptance for health information technology. In addition to age and gender, professional background can be of impact in acceptance of healthcare technology. Khalifa and Alswailem (2015) found that especially pharmacists and physicians were less inclined to endorse health information technology, while nurses, technicians and administrators did not differ from one another. Van der Vaart et al. (2016) found that mental health counselors tended to have a higher use as well as intention to use online interventions than primary care psychologists. In contrast, Schnall and Bakken (2011) have found no relationship between the professional backgrounds of several different employment classes working in healthcare. These different professional backgrounds included several management positions, social workers, and case follow-up workers. In short, literature is unclear about the impact of demographic variables; therefore, an examination of individual differences was performed. It should be noted that gender did not affect any of the subscales included. Therefore, gender is not expected to have a substantial contribution to actual system use. Age of the health care provider also did not show any effect on the degree of agreement to any of the four subscale of the TAM. Lastly, professional background affected only perceived usefulness. It was found that occupational therapists responded with less agreement to perceived usefulness, in comparison to healthcare psychologists and physiatrists. In terms of task description, the healthcare psychologists and physiatrists are concerned more with an overview of treatment plans for individual patients and generally more involved with management tasks, where occupational therapists are more hands-on in their daily activities and executing the selected treatment plans.

It should be noted that our sample was of sufficient size to accurately assess technology acceptance at group level, but that the individual characteristics of gender and professional background were rather skewed in the sample. Non-parametric statistics were selected to accommodate the sample composition in the analyses. It should be noted that the current questionnaire was focused on the perspective and the opinions of healthcare providers. Another limitation could be that all questions were phrased positively, which could stimulate more positive responses. However, we aimed to use the TAM in the original format, as this has been validated in a range of studies (Davis, 1989; Venkatesh and Davis, 2000). Other potential threats toward successful implementation like policy, insurance, and financial considerations are not considered, but could have a significant impact as well. This may be a prominent cause of why there is currently no common use of this technology. However, such potential barriers should be surveyed among managers and directors, rather than healthcare providers. Lastly, a potential threat of insufficient computer skills was addressed by verifying the level of internet skills in our sample, and we found that all participants indicated at least average internet skills.

To conclude, technology acceptance for digital cognitive rehabilitation is considerable among a sample of healthcare providers with experience in cognitive rehabilitation. Our findings indicate that one potential obstacle toward technology acceptance and eventually actual systems use lies with the subjective norm as perceived by health care providers. Overall, they consider the norms as implied by patients, superiors, and colleagues as neutral. To reach successful implementation, we advise to specifically address this issue in the implementation process, with, e.g., starting with a small group of enthusiastic users, followed by gradual expansion of use. Lastly, systematic individual variation seems limited, and the age and gender do not appear to have an impact. Only professional background, most likely linked to a difference in focus on execution vs. policy affects perceived usefulness to some extent. Overall, the current results indicate that healthcare professionals hold a positive attitude toward digital cognitive rehabilitation tools. The combination of this receptive attitude, technological advances, and increasing strain on healthcare provide ample opportunities for the development and implementation of evidence-based rehabilitation tools.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee of Ethics Psychology, Leiden University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, MK, and IH performed data processing and written the manuscript. AM and IH performed data analyses. AV and RV critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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The Michelangelo Effect: Art Improves the Performance in a Virtual Reality Task Developed for Upper Limb Neurorehabilitation

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The vision of an art masterpiece is associated with brain arousal by neural processes occurring quite spontaneously in the viewer. This aesthetic experience may even elicit a response in the motor areas of the observers. In the neurorehabilitation of patients with stroke, art observation has been used for reducing psychological disorders, and creative art therapy for enhancing physical functions and cognitive abilities. Here, we developed a virtual reality task which allows patients, by moving their hand on a virtual canvas, to have the illusion of painting some art masterpieces, such as The Creation of Adam of Michelangelo or The birth of Venus of Botticelli. Twenty healthy subjects (experiment 1) and four patients with stroke (experiment 2) performed this task and a control one in which they simply colored the virtual canvas. Results from User Satisfaction Evaluation Questionnaire and the NASA Task Load Index highlighted an appropriate level of usability. Moreover, despite the motor task was the same for art and control stimuli, the art condition was performed by healthy subjects with shorter trajectories ($p = 0.001$) and with a lower perception of physical demand ($p = 0.049$). In experiment 2, only the patients treated with artistic stimuli showed a reduction in the erroneous movements performed orthogonally to the canvas ($p < 0.05$). This finding reminds the so-called Mozart effect that improves the performance of subjects when they listen to classic music. Thus, we called this improvement in the performance when interacting with an artistic stimulus as Michelangelo effect.

Keywords: virtual reality, art, psychophysics, stroke, rehabilitation, cognition, aesthetics, neuroscience

INTRODUCTION

The human capacity to experience the beauty of things is particularly evident in the creation and appreciation of works of art. Experiencing the aesthetics of artworks is a very intriguing and controversial subject dealt with by philosophers and then by psychologists and neuroscientists (Di Dio et al., 2016). The processes involved in such a capacity include three different levels of aesthetic experience which have been evaluated and discussed: a perceptual, a cognitive and an emotional stage (Di Dio et al., 2016). It has opened a new field of research named neuroaesthetics

(Zeki, 2002). Surprisingly, the aesthetic experience of artworks depicting both human subjects and nature scenes seems to involve also brain motor areas. Indeed, it has been demonstrated that the dynamic human figures seem to activate more precuneus, fusiform gyrus, and posterior temporal areas, with respect to nature scenes that activate more occipital and posterior parietal cortex, both involved in visuospatial exploration and pragmatic coding of movement, as well as central insula (Di Dio et al., 2016). Static nature paintings further activated central and posterior insula, probably because they evoke aesthetic processes requiring an additional proprioceptive and sensorimotor component implemented by "motor accessibility" to the represented scenario, which is needed to judge the aesthetic value of the observed painting (Di Dio et al., 2016). It is important to highlight that further results also showed the involvement of the cortical motor system even in the viewing of static abstract artworks (Umilta' et al., 2012).

The sensorimotor networks activated by viewing an art masterpiece could be related to the recognition of emotions displayed by expressions of painted persons (Adolphs et al., 2000), to the mirror neuron networks activated by the actions performed by painted persons (Freedberg and Gallese, 2007), to the ideal possibility to walk in the scene (Di Dio et al., 2016), and even to the empathetic engagement activating simulation of the motor program that corresponds to the gesture implied by the trace done by the painter into the observer (Knoblich et al., 2002; Freedberg and Gallese, 2007).

Artworks would feed into a general feeling of pleasure, motivation, and arousal (Duckworth et al., 2014). Brain arousal and motivation are two fundamental aspects also in neurorehabilitation, together with active participation and treatment intensity (Paolucci et al., 2012). Based on these principles, music-therapy, for example, has been proposed in neurodegenerative diseases such as Parkinson's disease (De Bartolo et al., 2020a) or stroke (Verna et al., 2020). Furthermore, it was observed that listening to Mozart music improves the performance of subjects during the execution of a task, and it was called "Mozart effect" (Victorino et al., 2020). If Music-therapy could be performed by listening or generating music, Art-therapy was often limited to asking patients to paint, and not to observe art masterpieces. Action-observation neural mechanisms, based on the activations of mirror neuron networks, have been exploited in rehabilitation showing to patients some videos, but it does not involve the above described wide brain activations. The ideal scenario for combining the potential sensorimotor benefits of painting and the wide brain arousal induced by art would be to require the patient to copy a masterpiece. Unfortunately, very few humans are able to do it, so it seems practically impossible for a patient with an affected upper limb. However, virtual reality technology may provide valid support in simulating this task. Furthermore, technological sensors may also provide reliable measures of the subject's performance during the task (Iosa et al., 2016; Tieri et al., 2018).

Virtual reality (VR) is a new technology that can give the illusion to be in another place, thanks to the so-called sense of presence (Sanchez-Vives and Slater, 2005), and to respond in a realistic way to virtual stimuli, including both physiological (Meehan et al., 2002; Tieri et al., 2015; Fossataro et al., 2020) and neural reactivity (Vecchiato et al., 2015a,b; Pavone et al., 2016), the so-called sense of agency, and even to do impossible or uncommon things, living unusual experiences, in a safe and controlled situation (Tieri et al., 2015), as often occurs in immersive videogames. Virtual reality has been suggested also as a useful tool in neurorehabilitation of patients because it may increase motivation and enjoy during therapy process (Cho et al., 2013). Undoubtedly, technologically-assisted therapy should favor gaining maximum advantage from the opportunities provided by VR-technology for obtaining significant benefits in terms of rehabilitative outcomes (Tieri et al., 2018). Indeed, VR showed promising results in the therapy process thanks to interactive and direct training opportunities given to patients affected by neurodegenerative diseases, such as those with multiple sclerosis (Calabró et al., 2017). So, despite sometimes VR is used just to replicate the activities of daily living, it can provide the possibility to give the illusion to do something otherwise impossible, such as painting a masterpiece of the history of art. Even though the experience of standing in front of an authentic work of art cannot be replaced in terms of explicit hedonic attributed values by virtual reproductions, it has been shown as faithful high-quality virtual reproductions of artworks could be as arousing as the original works of art (Siri et al., 2018).

In the present study, we immersed healthy participants and a group of patients with stroke in a virtual environment where they had the illusion to paint famous masterpieces. Furthermore, during the task, their performance was assessed by measuring kinematic parameters related to the hand trajectory with respect to the virtual canvas. We also evaluated the acceptability and usability of this VR-system.

The main aim of this study was to validate the hypothesis that the performance of subjects could be improved when they interact with an art masterpiece, with respect to control stimuli, during the execution of the task performed in VR. This approach could open a novel way for rehabilitation programs for multiple users and can be helpful in administering to patients with stroke an art therapy for upper limb recovery.

MATERIALS AND METHODS

The study was divided in two experiments, one conducted on healthy subjects and one involving a group of four patients with stroke. The research protocol was designed in accordance with the 2013 Declaration of Helsinki and approved by the Ethics Committee of the Santa Lucia Foundation. Each volunteer provided written informed consent to participate in the study.

Hardware and Software Equipment

Each subject sat wearing the Oculus Rift Head Mounted Display and taking into his/her hand (the preferred one for healthy subjects, the paretic one for patients with stroke) an Oculus Controller joystick which allowed to interact with the virtual stimuli. The virtual environment, designed by using 3ds MAX 2018 and implemented in Unity 2018 game engine software, consisted of a large and comfortable room (with a door, a window, two lamps, a sofa; Scale 1:1) in the middle of which there was a canvas on an easel. The subject could interact with the canvas with a virtual sphere, displayed in VR in the same place of the real hand, which could be controlled with the Oculus Controller by means of a customized script in C# (see **Supplementary Video 1**).

Each virtual canvas was 60 cm × 40 cm and appeared white at the beginning of the task. Subjects were instructed that the sphere can color the canvas when put in contact with it, forming a painting. The illusion is given thanks to a white thin virtual panel (composed by 19 × 13 = 247 pixels, pixel area: 10 cm^2) placed in front of the canvas which occluded the visibility of an underlying image. When the subject touched the virtual panel with the sphere, the target pixels were automatically deleted allowing to see a part of the underlay picture. To overcome the missing tactile information concerning the real touch of the virtual canvas, we included visual feedback about the shadow of the virtual sphere on the canvas itself (in order to enhance the visual information about its position in the 3D-space) and also a change in the color of the sphere, from grey to green, when the virtual sphere touched the canvas colliding the panel's pixels, or becoming red if an erroneous movement was performed beyond the canvas. The dimension of canvas and pixels were chosen according to preliminary tests involving other patients with stroke (not included in the present study). Before the experiment, each participant underwent to a calibration task. Then the participant was asked to color the entire canvas in the shorter time possible, but without missing any pixel. The performance of the subject was recorded through a customized C# script implemented in Unity which allowed to track and record in real-time the position of the virtual sphere/real hand in space. Each subject was also instructed to move their upper limb without moving the trunk. Each trial was controlled by a researcher who monitored what happened into the virtual environment on the computer's monitor and by a physiotherapist who monitored the movements of the subjects, especially for avoiding trunk compensation strategies of patients. Each experimental session was composed of 10 trials, that could be 10 artistic paintings or 10 control stimuli, during which the participants painted the canvas. After each trial, the colored canvas disappeared and a new white canvas appeared on the easel.

The artistic paintings were chosen according to three criteria: to cover different époques (starting from Renaissance up to the twentieth century), to cover different styles (realism, baroque style, impressionism, post-impressionism, Ukiyo-e style, expressionism, and cubism), and especially to have similar proportions each other that could be matched by the size of the canvas. The following paintings were chosen: The Annunciation (Da Vinci, 1475), The Birth of Venus (Botticelli, 1485), The creation of Adam (Michelangelo, 1511), The Vocation of Saint Matthew (Caravaggio, 1600), The great wave of Kanagawa (Hokusai, 1831), Rowers Breakfast (Renoir, 1882), The bedroom (Van Gogh, 1888), The Night Café (Van Gogh, 1888), The Dance (Matisse, 1910), The Three Musicians (Picasso, 1921). For avoiding possible bias, the same colors and the same amount of brightness of the art masterpieces were maintained into the control stimuli; each masterpiece, was realized by blur-filter for control painting, and then reversing both left-right and up-down the image (GIMP software, Gnu Image Manipulation Program, version 2), as shown in **Figure 1**.

Self and Instrumented Assessment

A crucial aspect of the present study was to assess the acceptability and usability of the implemented VR task. In fact, to gain valid and reliable data, it is fundamental to assess usability and mental workload of the used tools and methods. Thus, User Satisfaction Evaluation Questionnaire (USEQ) and Nasa Task Load Index (NASA-TLX) were administered to subjects after the execution of the VR session. Both scales test six domains of the self-perception about the usability and the perceived load demand of the tool. In particular, USEQ has six questions (for example: "Did you enjoy your experience with the system?") with a five-point Likert Scale for each one of this item with a score going from 1 to 5, and hence a total score ranging from 6 (poor satisfaction) to 30 (excellent satisfaction). The six items test the self-perceived satisfaction, efficacy, efficiency, easiness-to-use, fatigue and self-perceived utility about the performed exercise. NASA-TLX has six questions with a ten point numerical rating scale for each one of the item (for example: "How physically demanding was the task?") with a score ranging from 1 to 100. It tests the self-perceived mental demand, physical demand, time demand, effort, performance, and stress. For patients enrolled in the experiment 2, the participation at each session was assessed also using the Pittsburgh Rehabilitation Participation Scale (PRPS) (Lenze et al., 2004; Kokini et al., 2012). Patients were also clinically evaluated at baseline using the Fugl-Meyer scale, the Box and Blocks test, and 9-hole peg test. Fugl-Meyer assessment scale is designed to assess motor functioning, balance, sensitivity, proprioception and joint functioning in patients with post-stroke hemiplegia. It includes 63 items, each one using a 3-point ordinal scale (score: 0 inability, 1 deficit, 2 no deficit), with a maximum total score of 126. The Box and Block Test measures unilateral gross manual dexterity, counting the number of blocks the patient is able to move, one by one, from a compartment of a box to the other one, within 60 s. The Nine-Hole Peg Test is used to measure hand dexterity, by measuring the time need to take nine pegs from a container, one by one, and place them into the holes on a specific board having nine holes. For each trial, the subject's performance was also quantitatively assessed starting from the spatio-temporal data of the joystick position with respect to the canvas. So, the following parameters have been computed: Time to Complete the Trial (TCT, from the moment in which the new white canvas appears to that in which the last pixel was colored), Length of Trajectory of the sphere on the canvas (LoT, evaluated in meters of the pathway performed on the frontal plane in which laid the canvas), root mean square of depth errors (RMSe, it was compute as the root mean square of the orthogonal distance of the sphere with respect to the canvas, considering the perfect contact as zero: it was a measure of erroneous movements performed along the axis orthogonal to the plane of the canvas).

Experiment 1

In the Experiment 1, 20 healthy subjects were involved (mean age: 30.2 ± 7.1 years, 10 males and 10 females, without any

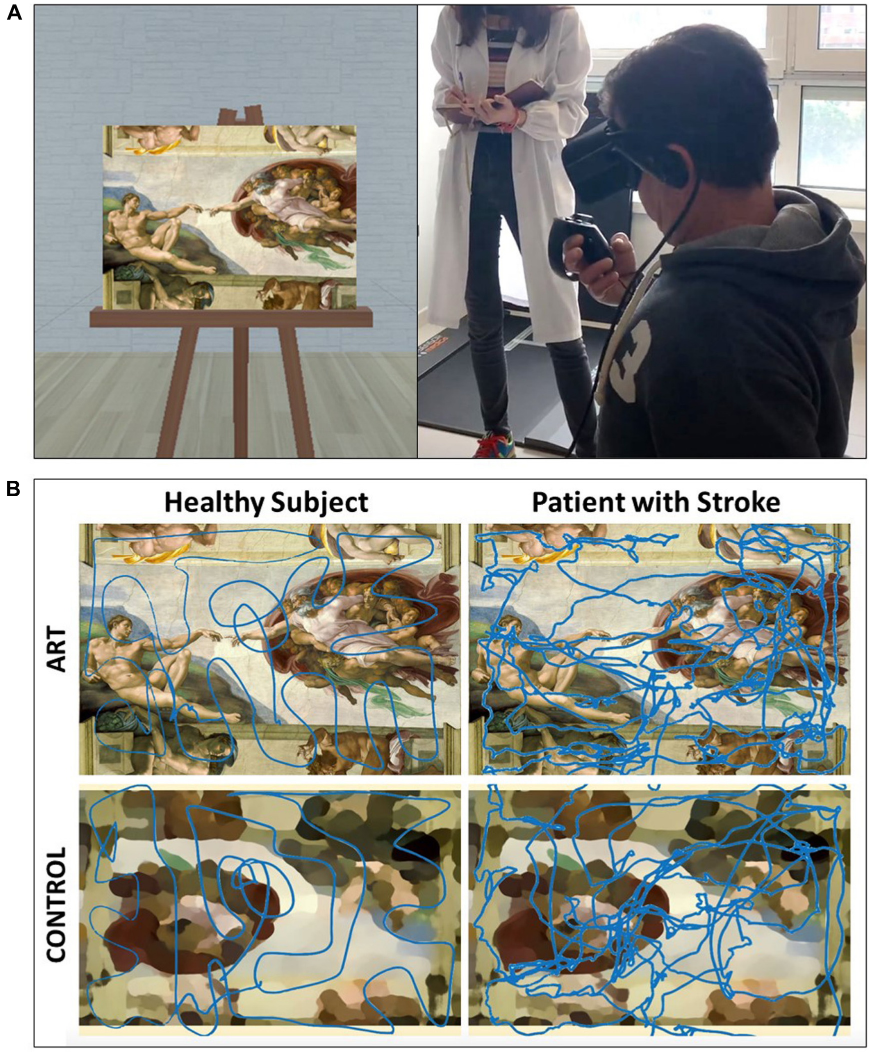

FIGURE 1 | (A) Experimental setup; Left-side represents an example of the art masterpieces (the Creation of Adam of Michelangelo) presented during the task; Right-side shows a patient with the experimental setting of Oculus Headset and Controller, under the supervision of experimenter. **(B)** Example of an experimental stimulus of the art masterpieces (the Creation of Adam of Michelangelo) and the relevant control stimuli (below), with superimposed the hand trajectories for a healthy subject (on the left) and a patient (on the right).

neurological disease or orthopedic problems at the upper limb). Healthy participants performed in the same day two sessions: one with 10 paintings and one with 10 control stimuli. Half of subjects firstly saw the paintings and then the control stimuli, the reverse for the other half of participants. After each session, USEQ and NASA-TLX were administered to the subjects.

Experiment 2

In the experiment 2, we enrolled 4 patients with stroke (3 males, 1 female, mean age: 59.5 ± 12.8 years, time from acute event longer than 3 months). Each patient performed 4 sessions of 10 stimuli each one, in 8 days. Two patients interacted with the same art-masterpieces of experiment 1 in all the four sessions while the other two patients interacted with the same control stimuli of experiment 1 in all the four sessions. All the patients had cognitive skills adequate to understand and to try to execute the task.

Statistical Analysis

Data are reported in terms of mean and standard deviation. In the experiment 1, the kinematic continuous measures were compared using Repeated Measure Analysis of Variance (RM-Anova) using as the main factors art (vs. control stimuli), and paintings. Effect size was computed as the partial eta squared. Ordinal scale scores were compared using Wilcoxon test. In the experiment 2, for each patient the parameters recorded during the fourth session were compared to the relevant values computed during the first session by means of paired t-test. Data of experiment 2 were also used to compute the required sample size of a further randomized control trial with an enrolment ratio

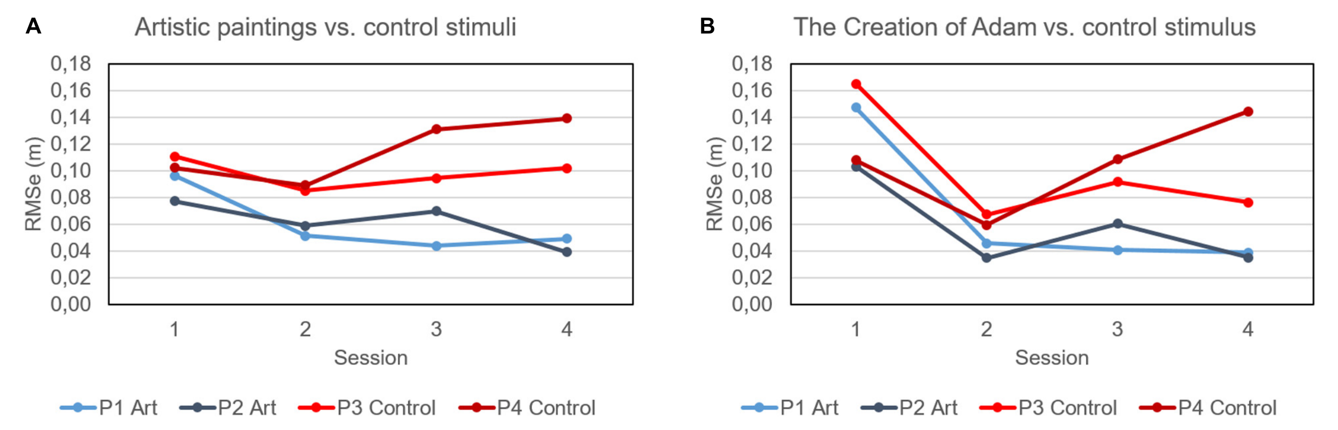

FIGURE 2 | Root mean square of hand position along the axis orthogonal to canvas (RMSe). **(A)** the average values of the 10 stimuli for each one of the four patients along the four sessions; **(B)** the RMSe computed for The Creation of Adam of Michelangelo (in P1 and P2) and the relevant control stimuli (in P3 and P4). In both panels, the patients treated with artistic stimuli were P1 (light blue) and P2 (dark blue), whereas those with control stimuli P3 (light red) and P4 (dark red).

1:1. The level of statistical significance was set at 5%, except for *post hoc* analysis performed applying the Bonferroni correction to the significance level.

RESULTS

Experiment 1

The length of trajectory was significantly lower for artistic paintings vs. colored canvas ($p = 0.001$). This main effect was not statistically significant for TCT. As shown by the significant interaction, the time significantly depended by the type of painting. *Post hoc* analyses showed a significant longer time for The Annunciation of Leonardo with respect to its control stimulus (6.7 ± 2.7s vs. 4.4 ± 0.9s, $p = 0.0025$), whereas shorter time for The Bedroom of Van Gogh with respect to its control (4.8 ± 1.0s vs. 8.0 ± 3.7s, $p = 0.0017$), but it was mainly due to the differences between the two control stimuli than between the two artistic paintings (3.0 ± 3.2s vs. 1.4 ± 2.7s, $p = 0.019$).

The self-reported assessment showed a slight but significant difference in terms of the perceived physical demand related to the task (NASA-TLX, second domain). In fact, despite the canvas are equal in dimension, a lower physical demand was perceived when subjects interact with paintings with respect to control stimuli (22.1 ± 21.7% vs. 27.1 ± 18.9% of the maximum load, $p = 0.049$). No significant differences were found for the other domains of NASA-TLX, nor for those of USEQ.

Experiment 2

Patients provided similar NASA-TLX and USEQ scores for both the conditions (art and control stimuli). They reported a mean score of 4.75 (on 5) about success in using the device, the minimum score of 1 for discomfort, and the highest score for the other domains of USEQ. Similarly, the mean scores for NASA-TLX were 9% for mental demand, 6% for physical demand, 4% for temporal demand, 93% for self-assessed performance, 5% for effort, 1% for frustration. The average score of Pittsburgh Rehabilitation Participation Scale ranged from 5.25 to 6 among the four sessions.

TABLE 1 | Experiment 1: mean ± standard deviation of the time to complete the task (TCT), the length of hand Trajectory (LoT) and the root mean square of hand trajectory in axis orthogonal to canvas (RMSe).

Parameters and statistics		TCT (s)	LoT (m)	RMSe (m)
Mean Art ± standard deviation		5.40 ± 1.97	6.74 ± 1.59	0.08 ± 0.05
Mean Control ± standard deviation		5.51 ± 2.55	7.71 ± 3.54	0.08 ± 0.03
Main effect Art vs. Control	*F*(1,190)	0.257	12.268	2.476
	p	0.613	**0.001**	0.117
	ES	0.001	0.061	0.013
Main effect Type of paint	*F*(1,190)	1.581	0.328	0.813
	p	0.123	0.965	0.605
	ES	0.070	0.015	0.037
Interaction	*F*(9,190)	4.419	0.760	0.172
	p	**<0.001**	0.654	0.997
	ES	0.173	0.035	0.008

Then the results of mixed analysis of variance: F-values (with degrees of freedom) and relevant p-values (in bold if statistically significant) and Effect Size (ES, computed as partial eta-squared).

Table 2 shows the baseline clinical assessment and the comparison of the first vs. fourth session for each patient. At the first session, patients showed a longer time to complete the task (TCT) and higher errors (RMSe) with respect to healthy subjects of experiment 1, as expected. Patients treated with artistic stimuli showed significant improvements for all the three computed parameters, especially halving the RMSe. Conversely, one patient treated with control stimuli just showed a significant reduction of length of trajectory,

TABLE 2 | Experiment 2: Baseline clinical assessment of patients mean ± standard deviation for the kinematic parameters (TCT: time to complete the task, LT: length of trajectory, RMSe: root mean square of erroneous movement orthogonal to the canvas) for the four Patients and relevant within-subject comparison.

Patients, parameters and statistics			**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**
Baseline Clinical Assessment	Gender		Male	Female	Male	Male
	Side of hemiparesis		Right	Left	Left	Left
	Type of stroke		Ischemic	Hemorrhagic	Hemorrhagic	Ischemic
	Fugl-Meyer total score		118	102	117	121
	Fugl-Meyer sensitivity		No deficit	No deficit	1 (arm)	No deficit
	Fugl-Meyer proprioception		1 (elbow)	No deficit	1 (elbow and wrist)	No deficit
	Box and Block test (blocks)		20	32	35	46
	9-hole peg test (s)		29.3	39.3	18.5	17.5
Type of stimuli during virtual reality task			**Art**	**Art**	**Control**	**Control**
Kinematic parameters recorded in the 1st and 4th sessions and relevant comparisons	TCT (s)	Session 1	17.6 ± 6.9	11.6 ± 1.9	7.7 ± 1.5	7.3 ± 2.5
		Session 4	7.0 ± 0.6	8.3 ± 0.9	7.3 ± 1.1	5.9 ± 1.4
		p-value	**0.008**	**<0.001**	0.465	0.125
	LoT (m)	Session 1	6.7 ± 1.5	7.8 ± 1.3	5.4 ± 0.7	7.6 ± 1.9
		Session 4	5.1 ± 0.3	6.2 ± 0.6	4.9 ± 0.4	8.4 ± 1.7
		p-value	**0.034**	**0.008**	**0.029**	0.385
	RMSe (m)	Session 1	0.10 ± 0.04	0.08 ± 0.03	0.11 ± 0.03	0.10 ± 0.02
		Session 4	0.05 ± 0.01	0.04 ± 0.01	0.10 ± 0.03	0.14 ± 0.04
		p-value	**0.041**	**0.007**	0.504	**0.022**

p-values in bold if statistically significant (<0.05).

but an increment of RMSe. This is a parameter related to erroneous movement along the axis orthogonal to the canvas, and **Figure 2** shows the values of this parameter for each patient in terms of average values among all the paintings (on the left), and also the specific trend for the Creation of Adam of Michelangelo, for which this effect was magnified (on the right).

Using the data of the length of trajectory in sessions 4 as pilot data to design a randomized controlled trial with 10 sessions for each patient, the required sample size to obtain statistically significant results in terms of length of trajectory was 10 patients for each one of the two groups.

DISCUSSION

In the present study, we capitalized on the power of immersive virtual reality to induce the illusion to paint famous masterpieces in order to evaluate whether the motor performance of healthy subjects and neurological patients could be affected by the observed masterpiece vs. a simple control canvas and whether the proposed VR task reaches a good level of acceptability and usability. In particular, based on previous evidences provided by neuroesthetic studies, we tested the hypothesis that the art masterpieces can improve the performance of subjects during virtual painting.

In general, USEQ and NASA-TLX scores obtained supported the idea of a good level of usability of the developed VR-system for both healthy subjects and patients, suggesting that this approach can be promising for future development of VR-based rehabilitative task.

Furthermore, kinematics analysis related to the performances suggested that the art masterpieces positively affect the execution of the exercises. Indeed, the results of experiment 1 showed that healthy subjects completed the task with shorter hand pathways and lower perception of physical demand when an art masterpiece appearing on the canvas. On the other side, in the experiment 2, only the two patients who interacted with art masterpieces showed significant improvements in all the three computed parameters as compared with the two patients who performed the task with the control stimuli, especially the reduction of errors orthogonal to the canvas, as also highlighted in **Figure 2** for the painting "The Creation of Adam" of Michelangelo.

These findings of paintings may have some in common with the so called Mozart-effect for music. In fact, previous studies found that listening to Mozart Sonata for two pianos in D major (K448) enhanced performance on spatial–temporal tasks (Hughes, 2001). It has motivated the scientific community in exploring the beneficial effects of musical stimuli on a variety of diseases over the past two decades (Hughes, 2001; Vinciguerra, 2017). The reported benefits of Mozart effect on neurophysiological activities include increased EEG power and coherence, increased correlations of neurophysiological activity on the left frontal and temporal areas, improved walking ability, and on neuropsychological abilities such as increased spatial–temporal reasoning after piano lessons in preschool children and improved IQ test results

(Escher and Evéquoz, 1999; Hughes, 2001; Trappe and Voit, 2016; De Bartolo et al., 2020b).

Similarly, we named as Michelangelo effect the improvement of subjects' performance in presence of an artistic masterpiece. This amelioration could be motivated by a general arousal of the brain, but more specifically, to the capacity of the beauty of art to activate specific brain areas, including sensorimotor ones, according to previous studies (Freedberg and Gallese, 2007; Umilta' et al., 2012; Di Dio et al., 2016). However, further studies are needed to deeper investigate whether it acts as a priming effect for the successive motor performance or if it works in parallel to the cognitive process related to psychological aspects such as the perceived load demand of the task and the level of participation.

Many factors concur in making a painting a masterpiece: colors, lines, elements, style, shadows, details and the general resulting overview. In this study, the control stimuli were balanced for colors and brightness, but they were blurred paintings, with less details than the artistic stimuli. Furthermore, the artistic stimuli included in this study were very different from each other in terms of number of details (i.e., few in The Dance of Matisse or many in The Night Café of Van Gogh), the presence of human figures (i.e., none in The Bedroom of Van Gogh, up to the 13 people in the Rowers Breakfast of Renoir), the curvatures of tracts (i.e., curve pathways characterize The great wave of Kanagawa whereas linear ones The Three Musicians of Picasso), and many other perceptual factors. However, the main effect of the type of paint was not statistically significant for the three kinematic parameters reported in **Table 1**. A higher variability in these parameters was even recorded for control stimuli, as shown by the higher standard deviations recorded for them, leading to a significant interaction effect. However, further studies are needed to investigate which elements of a masterpiece may affect the performance of subjects, planning balanced comparisons of specific features such as previous investigations did for exploring the effects of artwork content on brain activations.

Given the small sample size in the experiment two, the obtained results could be affected by the different clinical conditions of patients. For example, the patients treated with artistic stimuli showed worst performance at Box and Block test and 9-hole peg test and also longer TCT in the first sessions with respect to those treated with control stimuli. However, by observing LoT and RMSe values at the first session, we could compare the performance of patient 1 (art) with that of patient 3 (control), as well as that of patient 2 (art) with that of patient 4 (control). Patients treated with artistic stimuli (1 and 2) had a significant reduction in both these parameters. Conversely, patient 3 showed a reduction only in LoT, and patient 4 even showed a significant increment in RMSe.

It is important to mention the limits of the present study: first of all the limited sample size of patients enrolled in the experiment 2, then the age difference between subjects involved into the two experiments, the eventual bias related to our arbitrary selection of paintings (their styles, their contents, if landscape paintings or with human figures, and so on), the difference in details of these paintings and their modified control versions (we only balanced artistic and control stimuli for colors and brightness, but losing details in control stimuli), to absence of measures of physiological data of subjects during the task execution, and the absence of data about their artistic knowledge and/or sensitivity. At the same time, this study has also some strengths: first of all its novel approach to upper limb rehabilitation in patients with stroke using art-therapy combined with virtual reality, the high ecological validity of the motor task, the high engagement and motivation of patients, the robust measures of performance (based on kinematic, behavioral and self-reported assessment), and the promising results for patients with stroke and perhaps other neurological diseases. However further studies are necessary to confirm and extends these results, especially regarding the interpretation of the significant effect in the physical demand that deserves caution at the moment (given the *p*-value of 0.049).

This study was a first step for testing the usability of a VR system to allow subjects to interact with an art masterpiece, for analyzing if the artistic content could increase motivation and performance, and to compute the required sample size for designing a randomized controlled trial in which the Michelangelo effect can be tested if effective for improving the neurorehabilitation outcomes. This approach could open a novel way for rehabilitation program for multiple users and can be helpful in administering to neurological patients an art therapy for upper limb recovery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Santa Lucia Foundation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MI conceptualized the study. GM, MI, and GT wrote the first draft of this manuscript. GT and CC designed the 3D models and implemented the VR setup. MA, CC, and NC programmed the experimental tasks, collected the data, and computed the kinematic values. MI and FB performed all the statistical data analysis. GA, FM, and SP supervised the study. All authors revised the manuscript and provided important contributions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.611956/full#supplementary-material

Supplemental Video 1 | For an example of the experimental task can be seen at this link: https://youtu.be/Y4hP_t6bEH4.

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Using Virtual Reality as a Tool in the Rehabilitation of Movement Abnormalities in Schizophrenia

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Movement abnormalities are prevalent across all stages of schizophrenia contributing to poor social functioning and reduced quality of life. To date, treatments are scarce, often involving pharmacological agents, but none have been shown to improve movement abnormalities effectively. Virtual reality (VR) is a tool used to simulate virtual environments where behavioral performance can be quantified safely across different tasks while exerting control over stimulus delivery, feedback and measurement in real time. Sensory information is transmitted *via* a head mounted display allowing users to directly interact with virtual objects and bodies using gestures and body movements in the real world to perform different actions, permitting a sense of immersion in the simulated virtual environment. Although, VR has been widely used for successful motor rehabilitation in a variety of different neurological domains, none have been exploited for motor rehabilitation in schizophrenia. The objectives of this article are to review movement abnormalities specific to schizophrenia, and how VR can be utilized to restore and improve motor functioning in patients with schizophrenia. Constructing VR-mediated motor-cognitive interventions that can help in retaining and transferring the learned outcomes to real life are also discussed.

Keywords: movement abnormalities, schizophrenia, virtual reality, gestures, communication

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INTRODUCTION

Schizophrenia is a severe disorder with devastating symptoms affecting approximately 2–3% of the general population. These symptoms can be positive (hallucinations and delusions) and/or negative (reduced social drive and affective flattening) in nature, and include disorganized behavior and thinking, impaired cognitive and social functioning, anxiety, and lack of in-sight and self-awareness (Mccutcheon et al., 2020). As a result, schizophrenia causes tremendous individual burden, reduced quality of life, occupational performance and life expectancy (between 10 and 20 years), as well as, substantial costs to society. Although movement abnormalities are a part of the earliest descriptions of schizophrenia (Walther and Strik, 2012), their relevance was often reduced and attributed to pharmacological side effects (Walther and Mittal, 2017). Over the last decade clinicians and researchers alike have renewed their interest in movement abnormalities in schizophrenia as biological relatives, clinical high-risk individuals and non-medicated patients' also exhibit unusual movements (Mittal et al., 2006, 2008; Walther and Mittal, 2017; Walther et al., 2020e).

MOVEMENT ABNORMALITIES IN SCHIZOPHRENIA

Movement abnormalities in schizophrenia can occur spontaneously, may continue for several hours of the day and can also come and go. Clinicians have separated movement abnormalities in schizophrenia into six distinct categories (Walther and Strik, 2012). The first known as dyskinesia, is abnormal involuntary movements, which occurs as high frequent repetitive movements (Gervin et al., 1998). The second is classified as parkinsonism and includes akinesia, rigor, and tremor in the absence of an idiopathic Parkinson's syndrome (Waddington, 2020). The third is akathisia, characterized as restlessness and inner tension. The fourth is neurological soft signs (NSS), which are a set of tests evaluating patients' motor coordination, sequence of motor acts, and sensory integration, which are often performed worse compared to healthy controls (Whitty et al., 2009). The fifth is catatonia, which is a complex psychomotor syndrome that includes decreased, increased, and abnormal movements, disturbances of volition, and autonomous instability (Walther et al., 2019). Finally, the sixth is psychomotor slowing and it affects both fine (writing) and gross (walking) movements, facial expressions, and speech production (Morrens et al., 2007; Osborne et al., 2020). Patients with schizophrenia often suffer from multiple movement abnormalities during the course of their illness, and are thought to be predictors in the risk of developing psychosis (Walther and Mittal, 2017).

Movement abnormalities are prevalent across all stages of schizophrenia although the symptoms are not consistent across the different stages (Walther and Strik, 2012). During the early stages, there seems to be a link between the severities of movement abnormalities with the increase risk of developing the disorder. For example, at least one movement abnormality is present in 2/3rd of non-medicated first episode psychosis patients (Peralta and Cuesta, 2010). It increases drastically in chronically medicated patients, and affects almost all elderly patients with schizophrenia (Quinn et al., 2001; Walther and Strik, 2012). In addition, increased levels of dyskinesia are reported in children who exhibit symptoms of psychosis, while individuals with increased risk of psychosis have been reported to present both dyskinesia and psychomotor slowing (Kindler et al., 2016; Damme et al., 2020). Overall, these observations suggest a crucial role of movement abnormalities in the development of schizophrenia, and its importance in successfully screening and staging their presence during the course of the disorder.

THE RAMIFICATIONS OF MOVEMENT ABNORMALITIES

Besides movement abnormalities being predictors for the risk of developing schizophrenia, they are also indicative of poor social and cognitive functioning, affecting the overall quality of life of patients (Putzhammer et al., 2005). For example, NSS, parkinsonism, catatonia, dyskinesia, and akathisia reported in patients with the first episode of psychosis were strongly associated with the emergence of negative symptoms, executive dysfunctioning, and poor memory abilities (Cuesta et al., 2014, 2018a,b; Walther et al., 2015; Fritze et al., 2020; Sambataro et al., 2020; Schroder and Toro, 2020). This was true in both medicated and non-medicated patients. In addition, the presence of movement abnormalities are strongly linked to impaired gesture performance in schizophrenia, an important aspect of social communication, and were shown to be directly related to poor social functioning even at 6-month's follow-up (Walther et al., 2016). Errors during gesture performance are very frequent and consistent in schizophrenia patients (Walther et al., 2020d), as measured using the well-established Test of Upper Limb Apraxia (TULIA; Vanbellingen et al., 2010), developed along the principal domains and semantic traits of gesture performance. Gestural errors in schizophrenia often involve spatial and temporal configurations. Minor errors include movements that are too slow or hesitant and appear almost robotic-like, with reduced amplitudes, while major errors include omissions, body-part-as-object errors, extra movements, and errors in spatial orientation (Walther et al., 2013a,b, 2020b). In addition, schizophrenia patients tend to use fewer gestures during interactions with their psychiatrist or during casual conversations (Lavelle et al., 2013, 2015). Moreover, clinical high-risk patients for psychosis not only use fewer gestures during clinical interviews, they also tend to use mismatch gestures (Millman et al., 2014). This suggest that abnormal gesturing in schizophrenia is highly relevant for communication (Walther et al., 2020d).

Likewise, impaired gesture performance in schizophrenia is also associated with cognitive impairments, such as executive dysfunction (Walther et al., 2013b, 2015). In addition, schizophrenia patients also have deficits in perceiving and interpreting gestures (Bucci et al., 2008; White et al., 2016) and this deficit is linked to movement abnormalities (Walther et al., 2015). Hence, amelioration of movement abnormalities in schizophrenia has the potential to improve both social and cognitive functioning and expand patients' quality of life.

TREATMENT OPTIONS FOR MOVEMENT ABNORMALITIES

To date, the standard treatment to alleviate movement abnormalities in schizophrenia exclusively relied on pharmacology. However, treatment effects have been heterogeneous. For example, some forms of movement abnormalities, such as catatonia and dyskinesia improved following the administration of antipsychotics and benzodiazepines (Peralta and Cuesta, 2010; Walther et al., 2019), while akathisia worsened (Peralta and Cuesta, 2010). This suggests that pharmacological treatments may not be ideal candidates and offer no long-term solution in taming movement abnormalities. Preliminary findings suggest non-invasive brain stimulation (NIBS) is a potential candidate in alleviating movement abnormalities in schizophrenia patients (Walther et al., 2020a,c). Several ongoing clinical trials are currently administered to further assess the efficacy of NIBS (Lefebvre et al., 2020); Personalized Non-invasive

Neuromodulation by rTMS for Chronic and Treatment-Resistant Catatonia trial (RETONIC, NCT03116425), Overcoming Psychomotor Slowing in Psychosis trial (OCoPS-P, NCT03921450), and Brain Stimulation And Group Therapy to Improve Gesture and Social Skills in Psychosis trial (BrAGG-SoS, NCT04106427). Developing alternative interventions in tackling movement abnormalities may offer a better and long-term solution while addressing the concerns regarding usage of medication and their related side effects (Lieberman et al., 2005; Stegmayer et al., 2018). Successful movement production depends on the multisensory integration of different processes, thus better rehabilitative results are more likely to ensue when combining motor-socio-cognitive processes together with multimodal sensory feedback.

VIRTUAL REALITY AS A TOOL FOR MOTOR NEUROREHABILITATION

In recent years, Virtual Reality (VR) has become a popular tool in neurorehabilitation, as it promotes motor learning (ML) and neuroplasticity (Kleim and Jones, 2008; Cho and Lee, 2013). VR provides clinicians and researchers alike with the unique ability to simulate real world scenarios. It engages multiple senses, allows complete immersion within the virtual environment using a head-mounted display, and provides users with the opportunity to interact with virtual objects and/or other virtual characters, allowing the manipulation of a controlled and flexible setting while providing rapid online feedback, optimizing ML (Slater, 2009; Perez-Marcos et al., 2012; Parsons et al., 2017). ML is a process that examines the acquisition of newly developed motor skills *via* practice and experience and evokes a permanent change in the ability to execute a movement (Levac and Sveistrup, 2014). Thus, VR as a multi-facet system, has the potential to enrich conventional therapies and provide its users with a more intensive and enjoyable alternative that can help in retaining and transferring ML to real life (Weiss et al., 2014; Perez-Marcos, 2018; Perez-Marcos et al., 2018).

Optimization of ML in VR is highly dependent on the manipulation of testing conditions that explicitly apply (i) external focus of attention, (ii) intensity, (iii) implicit learning, (iv) diversity, (v) task specificity, and (vi) real-time feedback (**Table 1**; Wulf et al., 1998; Levac and Sveistrup, 2014; Perez-Marcos et al., 2018). These conditions support the acquisition, retention and transfer phase of newly developed movement skills (Willingham, 1998), and provide encouraging results in the motor rehabilitation of patients with neurological disorders. We discuss the importance of each condition below and provide their effectiveness in VR motor rehabilitation.

External focus of attention involves directing an individual's attention to the effect of the performed movement in their environment such as: "lift your arm to touch a mark on the wall", and has been effective in enhancing movement performance in gait, balance, and postural training (Wulf et al., 1998; Johnson et al., 2013; Park et al., 2015). In VR, Mirelman et al. (2009) opted to teach post stroke patients how to navigate a plane or a boat within a virtual environment by moving their feet, rather than teaching patients' how to move their feet. The use of these external cues directed patients' attention within the virtual environment and away from the performed movements improving their overall therapeutic outcome.

TABLE 1 | Movement learning principles for VR rehabilitation treatment.

Movement learning principles	Examples
External focus of attention	Navigating a virtual boat (Mirelman et al., 2009).
Intensity	Multiple sessions, repetitions of task (Perez-Marcos et al., 2017).
Implicit learning	Walking on treadmill while avoiding obstacles (Yang et al., 2008).
Variance	Increasing length and height of obstacles (Jaffe et al., 2004).
Task specificity	Shopping in virtual supermarket (Rand et al., 2009).
Real-time feedback	Auditory feedback when the chosen response is incorrect (Adery et al., 2018).

Treatment intensity is highly recommended to maximize therapeutic effects, as it can induce structural neural changes. Animal studies report that functional tasks repeated a minimum of 400 times prompt such changes (Birkenmeier et al., 2010). In a recent study, VR-mediated upper limb training in chronic stroke delivered a training intensity that was 10–15 times higher than that delivered in a standard clinical training (Perez-Marcos et al., 2017). Thus, VR provided large amounts of active training time and repetitions for each session, further highlighting VR's efficiency in treatment outcomes.

Implicit learning is a form of learning that occurs without the person's awareness (Reber, 1967). In VR rehabilitative treatments, implicit learning is often achieved using motor-cognitive dual-task training, and shown to enhance ML more efficiently in patients with neurological disorder (Fritz et al., 2015). Such tasks include walking while counting backwards, or walking while trying to avoid obstacles, and appear to be more effective than walking alone (Yang et al., 2008; Mirelman et al., 2016) while giving a more realistic approach in including the multiple processes (i.e., motor, cognitive, and social) necessary for daily functioning (Faria et al., 2016, 2018; Perez-Marcos, 2018). Studies implementing VR motor-cognitive tasks in post stroke, Parkinson's, and multiple sclerosis patients report significant improvements in both the motor and cognitive (memory, attention and visual-spatial abilities) domains (Maggio et al., 2019), with effects in the motor domain reportedly retained at follow-up (Mendes et al., 2012; Mirelman et al., 2016; Cano Porras et al., 2018; Faria et al., 2018).

Task variation is introduced by varying the difficulty of a performed task. Once the simple tasks are accomplished, complex tasks are introduced. This gradual level of learning sanctions a sense of triumph over the task, promoting self-efficacy and ML while increasing patients' motivation and enjoyment (Levac et al., 2019). For example, Jaffe et al. (2004) changed the difficulty level of their task by increasing the length and height of the obstacles in a virtual training course while poststroke hemiplegia patients walked on a treadmill.

While, Yang et al. (2008) increased the speed of the treadmill 5% after each training session, and introduced different walking scenarios. Such VR programs provide a more affluent training environment that involves adapting to unpredictable scenarios, which more reflect real-life scenarios more.

Task-specific training is one of most important aspects for treatment rehabilitation as it postulates that ML is promoted when the acquired movement skills are as close as possible to those expected to perform the task in the real world (Levac and Sveistrup, 2014). VR is the ideal candidate for such practice as it can simulate daily living challenges in a safe environment that with time translate to the real world. For example, Rand et al. (2009) placed post stroke patients in a virtual shopping mall, and measured multitasking abilities over a period of 3 weeks. Patients improved their multitasking abilities from 20.5 to 51.2% following this VR intervention.

Finally, real-time feedback is extremely important in ML as it provides some information as to how a task is being performed allowing the possibility to adapt the training accordingly, and reinforce movement control and reduce movement compensation (Subramanian et al., 2013). In a recent study, Van Gelder et al. (2017) measured gait performance of children suffering from cerebral palsy as they walked on a VR instrumented treadmill. They performed three conditions: one condition provided no feedback while the other two conditions provided feedback on hip and knee angle. Significant improvements were observed in hip and knee extensions following real-time feedback. Whereas, Mirelman et al. (2009) used real time feedback to encourage their patients whenever they successfully navigated their target by changing the target color from yellow to green along with the word "GREAT." Providing VR real-time feedback provides patients with the opportunity to become aware of their shortcomings, as well as, their progress, motivating them to continue towards the road to autonomy, improving activities in their daily living, and improving their overall quality of life.

Taken together, VR has the ability to implement all elements of ML and can improve performance of movement skills important for real world functioning in patients suffering from different neurological disorders.

DISCUSSION

To our knowledge, no study to date has utilized ML in VR specifically for motor rehabilitation in patients with schizophrenia. However, patients with schizophrenia have been mastering VR trainings in previous research (Valmaggia et al., 2016; Rus-Calafell et al., 2018). Specifically, VR studies using elements of ML outside the motor domain, show promising results in enhancing and maintaining interpersonal social skills, as well as, reducing auditory hallucinations and paranoia in schizophrenia patients (Rus-Calafell et al., 2018). VR settings designed to allow schizophrenia patients to interact with different virtual characters while encouraging progressive learning of social skills and providing both positive and negative reinforcement showed significant improvements in emotion perception, assertive and conversational behavior, as well as, negative symptoms, psychopathology, social avoidance, discomfort, and functioning (Park et al., 2011; Rus-Calafell et al., 2014; Adery et al., 2018). Most of these gains were also maintained at 4-month follow-up (Rus-Calafell et al., 2014). In addition, schizophrenia patients undergoing a 10 h VR job interview training significantly improved their virtual interview and role-playing performance scores across increasing levels of difficulty and had greater odds of receiving a job offer at 6-month follow-up (Smith et al., 2015). Furthermore, VR therapy designed to have schizophrenia patients confront and interact with a visual representation of their most distressed auditory hallucination produced significant improvements in auditory verbal hallucination severity, depressive symptoms, as well as, quality of life that remained at 3-month follow-up (Du Sert et al., 2018), while, error-feedback during social perception judgments reduced paranoid ideation in patients with schizophrenia (Moritz et al., 2014).

Overall, these studies show VR's efficacy and feasibility in improving symptoms associated with schizophrenia. The use of ML elements in these paradigms shows patients' ease in responding and adapting to the ever changing and increasingly challenging virtual environments reinforcing overall learning outcome. Patients have also recognized their enjoyment and increase motivation when using VR therapy where its use in combination with conventional therapy can have significant and everlasting benefits that can greatly influence patients' quality of life (Adery et al., 2018; Du Sert et al., 2018; Rus-Calafell et al., 2018).

Since, schizophrenia patients respond well to VR-therapy, and are able to adapt to different scenarios, we can apply ML in VR to ameliorate movement abnormalities in these patients by restoring, retaining, and transferring the learned movement skills, similarly to that done with neurological patients. Why is it important to do so? Movement abnormalities are ubiquitous across all stages in schizophrenia patients. These movement deficits are linked to socio-cognitive impairments, such as gesture performance, an integral part of communication, which can have devastating consequences on patients clinical outcome and overall functioning (Walther et al., 2020d). Designing a VR paradigm that encompasses motor and socio-cognitive domains, where for example, communicative gestures are mastered and are then applied during social interactions, can improve patients' overall communication. This can have substantial benefits in how they express themselves to their therapist or doctor, how they navigate daily tasks, while promoting autonomy and overall functioning.

FUTURE OUTLOOK AND CONCLUSION

Although movement abnormalities are prevalent in schizophrenia affecting overall communication and social functioning very little has been done to treat and alleviate these deficits. Psychopharmacology has proven to have very little effects on psychomotor abnormalities, while NIBS has some promise (Lefebvre et al., 2020). In this perspective paper, we highlight VR's success in effectively combining all elements of ML in improving motor abnormalities in neurological disorders, and advocate its potential use in ameliorating, restoring, and improving movement abnormalities in schizophrenia patients. Using ML, we can combine motor and socio-cognitive domains to establish personalized simulated real-life scenarios tailored to each patient's individual needs promoting autonomy that can greatly improve their quality of life, such as gesture performance. In addition, combining VR with NIBS can further benefit patients with schizophrenia as, neuromodulation of the affected cortical areas while being placed in a safe virtual environment, could allow for direct translation to the real world (Gainsford et al., 2020; Lefebvre et al., 2020).

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

AP drafted the manuscript. SW revised the manuscript. AP and SW edited the manuscript. Both the authors contributed to the article and approved the submitted version.

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A Multidimensional Virtual Reality Neurorehabilitation Approach to Improve Functional Memory: Who Is the Ideal Candidate?

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Aims: We aimed to identify the significant predictors of ecological memory amelioration after the Human Empowerment Aging and Disability (HEAD) rehabilitation program, a multidimensional treatment for chronic neurological diseases.

Materials and Methods: Ninety-three patients with Parkinson disease ($n = 29$), multiple sclerosis ($n = 26$), and stroke ($n = 38$) underwent a multidimensional rehabilitation. We focused on changes after treatment on ecological memory (outcome measure) evaluated by Rivermead Behavioral Memory Test, Third Edition (RBMT-3). Minimal clinically important difference (MCID) after treatment were calculated for RBMT-3. The change score on RBMT-3 was categorized in positive effect, stabilization, or no effect of the treatment. Random forest classification identified who significantly benefited from treatment against who did not in terms of ecological memory functioning. Accordingly, logistic regression models were created to identify the best predictors of the treatment effect. A predicted probability value was derived, and the profile of the ideal candidate of HEAD protocol was shown by combining different ranks of significant predictors in a 3 $\times$ 3 matrix for each pair of predictors.

Results: A significant number of cases reported positive effect of the treatment on ecological memory, with an amelioration over the MCID or a stabilization. The random forest analysis highlighted a discrete accuracy of prediction (>0.60) for all the variables considered at baseline for identifying participants who significantly benefited and who did not from the treatment. Significant logistic regression model (Wald method) showed a predictive role of Montreal Cognitive Assessment (MoCA; $p = 0.007$), 2-Minute Walk Test (2MWT; $p = 0.038$), and RBMT-3 ($p < 0.001$) at baseline on HEAD treatment effect. Finally, we observed a high probability of success in people with higher residual cognitive functioning (MoCA; odds ratio = 1.306) or functional mobility (2MWT; odds ratio = 1.013).

Discussion: The HEAD program is a rehabilitation with effects on multiple domains, including ecological memory. Residual level of cognitive and/or motor functioning is a significant predictor of the treatment success. These findings confirm the intrinsic relationship subsisting between motor and cognitive functions and suggest the beneficial effects of physical activity on cognitive functions and *vice versa*.

Keywords: rehabilitation, telerehabilitation, virtual reality, multiple sclerosis, stroke, Parkinson disease, digital health, cognition

INTRODUCTION

Recent reports alarmingly pointed out the age-related increment of years of life with diseases (1). Since 1990, mortality rates declined concomitantly with the growth of non-fatal diseases, leading people to cope with chronic conditions and consequently chronic care needs throughout life. Parkinson disease (PD), multiple sclerosis (MS), and post-stroke are the most prevalent chronic neurological conditions (2–4) that weigh heavily on the personal burden and the healthcare costs (5). Especially, Global Burden of Diseases' studies recently reported a global prevalence of more than 6 million PD cases (1), more than two million of MS patients (6), and about 1 million adults living with stroke (2). Although these conditions are characterized by different epidemiology and etiopathology, they are united by a high level of motor and cognitive disability accounting for a consistent loss of quality of life. Regarding the cognitive profile, cognitive deficits are heterogeneous, but memory and executive dysfunctions are frequently reported in all of them (7–9). It is of great importance to cope with the cognitive deficits considering their significant impact on daily living (10). Specifically, everyday memory difficulties are frequent and common in MS, PD, and stroke diseases (11–13). Intact memory skills are required to complete many everyday activities; thus, impairments in memory functioning can have important negative effects on the individual ability to live independently and negative implications for quality of life. Given the chronic course of the disease, people living with these conditions must cope with disability for the remainder of their lives. For this reason, new rehabilitative solutions for such individuals to preserve or improve cognitive status and everyday functioning are crucial; especially, it is important to evaluate their efficacy adopting an ecological assessment. Recent evidence suggests (1) the extensive beneficial effects of multidimensional rather than unidimensional treatment, (2) the positive results from the integration of virtual reality (VR) systems into the conventional rehabilitation in people with chronic neurological diseases, and (3) the importance of characterizing the profile of the ideal candidate for these novel approaches.

First, because of the multidimensional pathology-related difficulties, often impacting motor, cognitive, and behavioral functionality, multidisciplinary models of care are taken in consideration (14–17). Recently proposed integrated treatments involve a multidisciplinary team to offer a personalized systemic care for the disabled person. This holistic approach provides beneficial effects in everyday living, and, for this reason, tools to detect changes in daily functioning after treatments need to be considered. In fact, in the last few years, it has become increasingly clear that standard paper-and-pencil neuropsychological tests are limited in predicting what occurs in patients' everyday life. Only weak associations were reported between results on classical tests and subjects' complaints of everyday problems (18–21). To overcome these difficulties and to better describe how cognitive deficits may affect daily functioning, an innovative approach has been proposed, which entails the administration of more ecological tasks (22, 23).

The second evidence regards the adoption of VR solutions. Rehabilitation with these tools seems to be promising in terms of patient involvement and treatment efficacy (24, 25). The utilization of these VR tools helps facilitate engagement and increase patient satisfaction during the training (26–31), by creating a virtual environment eliciting realistic perceptions and reactions (32). In this framework, the Human Empowerment Aging and Disability (HEAD) protocol is a VR multidimensional rehabilitation intervention for people with chronic neurological conditions conceived for both clinical and home settings (i.e. telerehabilitation). A previous study demonstrated its feasibility (33) and its efficacy in PD populations (24). However, as an integrated treatment proposed for different pathologies and grades of disabilities, a secondary investigation on the predictors of treatment success on everyday functions can provide extensive information on the population target for the HEAD rehabilitation.

The last consideration focused on the lack of clinical consensus regarding the characteristics of the population for targeting these types of VR treatments. It is extremely useful to identify which clinical features are prognostic of treatment success. Along these lines, a new field of investigation aims to individualize significant predictors of treatments (34, 35). This approach establishes the profile of the ideal candidate for a given rehabilitation intervention. This strategy will facilitate the possibility to *a priori* differentiate between patients who will potentially benefit from the treatment and those who will not. The implications of these studies are large and favor the personalization of intervention targeted for the patient, by ensuring a high probability of treatment success.

The present study aims to characterize the profile of the ideal candidate for the VR-multidimensional treatment who will benefit the most with a high probability on ecological measures. Accordingly, we performed a secondary analysis on a large cohort of patients who completed a VR multidimensional treatment (the HEAD program) by adopting an ecological measure of cognitive functioning, one of the more disabling aspects of the chronic neuropathological conditions.

METHODS

This study consists of a secondary analysis on data related to a multicenter interventional protocol of integrated rehabilitation for people with chronic neurological diseases whose efficiency and efficacy findings are described elsewhere (24, 33). In this context, we focus on the first part of the study design in which patients underwent a 1-month rehabilitation period in and outpatient setting, consisting in 45-min sessions three times per week, for a total of 12 sessions (ClinicHEAD). The entire dataset from the three recruiting centers of the original study (Valduce Hospital Villa Beretta Rehabilitation Center in Lecco, IRCCS Don Carlo Gnocchi Foundation in Milan and the District Clinic San Camillo in Turin) was utilized for the present work. The study was carried out under the norms of the Declaration of Helsinki; it was approved by the local ethics committees; each participant was adequately informed about the study and offered their collaboration and signed a written informed consent.

Participants

The sample of the present study consists of people with chronic neurological conditions meeting the following inclusion criteria: diagnosis of MS with an Expanded Disability Status Scale score $\leq$5.5, or diagnosis of PD with a Hoehn and Yahr score $\leq$2, or diagnosis of chronic stroke at least 6 months after the event; ages between 18 and 80 years; Mini-Mental State Examination score $>$20; absence of disabling pain; severe deficit of visual acuity or auditory perception or in communication; and absence of severe dysmetria.

Patients were enrolled during their periodical clinical visit by the neurologists, periodically receiving neurological follow-up.

All subjects took part in an experimental clinical trial between 2016 and 2017 consisting of multidimensional rehabilitation with VR activities in the clinic, lasting 1 month, 3 times a week for 12 sessions. The intervention, extensively detailed elsewhere (33), took place in the clinic, with the presence of clinical professionals: the neurologist, the physiotherapist, and the neuropsychologist. Motor and cognitive rehabilitation activities were proposed while interacting with virtual scenarios and watching short video clips. The rehabilitation dimensions targeted by the treatment included balance, endurance, speed and strength of both upper and lower limbs, executive functions, memory, language, and dual-task capabilities.

Measurements for the Analysis

Cognitive performance outcome was obtained by the Montreal Cognitive Assessment [MoCA; (36)] and the Rivermead Behavioral Memory Test, Third Edition [RBMT-3; (37)]. The MoCA (36), is a sensitive tool for global cognitive level assessment, by screening different domains, such as executive functions, memory, language, visual–spatial abilities, attention, calculation, abstraction, and spatial and temporal orientation (scores range from 0 to 30). Two parallel forms of this instrument (38) were utilized for the assessment at T0 and T1. Following Santangelo et al. (39) scores correction procedure, we obtained a age and education adjusted score of the MoCA subdomains: visuospatial abilities (AVS), executive functions (EF), memory (ME), attention (ATT), language (LANG), and orientation (OR).

RBMT-3 is an ecological battery for the assessment of everyday memory performance with relatively short times of administration, and parallel forms and is applicable to patients with motor deficits (37). The RBMT-3 consists of 14 subtests (scores range from 51 to 147): names (remembering the first and second names of two portrait photos), belongings (remembering to ask for two personal belongings at the end of the evaluation session), appointments (asking two questions when an alarm rings 25 min later), picture recognition (delayed recognition of line drawings against distractors), story (immediate and delayed recall of a short story), faces (delayed recognition of photographs of faces against distractors), route (immediate and delayed recall of a short route in the examination room), message (immediate and delayed remembering to pick up an envelope and book), orientation and date (orientation to person, place and time), and novel task (immediate and delayed recall of puzzle pieces positioned in a specific order within a template). In addition to the scaled scores on the subtests, the Global Memory Index (GMI) was calculated as an overall memory performance measure.

Motor performance outcome was evaluated by the Berg Balance Scale [BBS; (40)], 10-Meter Walk Test [10MWT; (41)], and 2-Minute Walk Test [2MWT; (42)]. The BBS is a measure of static balance and the risk of falling. It consists of a 14-item 4-point scale, with a total score ranging from 0 to 56. 10MWT is a quantitative analysis of the walking speed, measuring the speed in meters per second over 10 m. It is considered an assessment of functional mobility. The 2MWT provides a quantitative analysis of gait speed and endurance. The walking distance walked in 2 min is registered as a functional mobility measure.

Measures of quality of life and affectivity were also considered: the Positive Affect and Negative Affect Schedule [PANAS; (43)]. The PANAS scale consists of 20 items that evaluate two independent dimensions: positive affect and negative affect. The range for each scale (10 items on each) is from 10 to 50.

Statistical Analyses

Statistical analyses on outcome measures were performed with IBM SPSS Statistics software (version 24) and JASP (JASP Team 2020, JASP version 0.11.1).

Means, frequencies, and standard deviations were computed to describe sample characteristics. χ^2-test and univariate analysis of variance were used to verify whether the three pathologies included in the sample were balanced for age, education, and sex distribution.

For each outcome measure, changes scores (Δ change) from T1 to T0 were calculated. Minimal Clinical Important Difference (MCID) was derived separately for each pathology computing one-half of the deviation standard, according to Katajapuu et al. (44) and Shikiar et al. (45). After that, each change score was categorized into one of three categories: positive effect of the treatment (Δ change $>$ MCID), stable after treatment (–MCID $\leq \Delta$ change $\leq$ MCID), and no effect of the treatment (Δ change $<$ MCID). Frequencies and χ^2-test were run to show effectiveness results of the treatment on the whole sample and separately for each pathology.

Random forest (RF) classification was applied to the data as an exploratory analysis including all demographic and clinical variables assessed at the baseline, as an overall prediction approach in identifying subjects who significantly benefited from treatment in the RBMT-3 (Δ change > MCID). For this purpose, the RBMT-3 outcome was considered dichotomously (Δ change > MCID vs. Δ change ≤ MCID). We built RFs with the default parameter values in JASP (version 0.11.1), with the exception of the data split for which we partitioned the data set into a training (50%), validation (20%), and test set (30%). In relation to the number of trees, we selected an optimal number of trees [Ntrees (maximum) = 100], optimized with respect to the out-of-bag accuracy. Classification accuracy represents the proportion of the instances that were classified correctly.

Performance of the classification model was also evaluated by carrying out a receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) provides a measure of overall prediction accuracy and corresponds to random chance when AUC is equal to 0.5 and represents perfect accuracy when AUC be 1. Precision represents the proportion of true positives among all the instances classified as positive; F1 score indicates the harmonic mean of precision and recall, and recall is the proportion of cases that were classified as positive, among all instances that truly were positives.

To further explore the link between the dichotomic variable of the outcome RBMT-3 and possible predictors at baseline, point-biserial correlation analyses were performed for continuous variables and χ^2-test for categorical variables to select variables for insertion in the following regression model. A $p < 0.10$ was preferred to the conventional threshold $p < 0.05$ to avoid excluding potential significant predictors.

A logistic regression model was utilized to identify the best predictors of treatment effect. Regardless the statistical significance of association in the previous phase (χ^2-test), the pathology (PD, SM, stroke) was cautiously considered in the regression model as a possible predictor. Wald forward option was used as a stepwise selection method. A predicted probability value was derived from the logistic model for each subject. Finally, significant baseline predictors were organized in three-tile ranks, and the mean predicted probability values were shown by combining the different ranks of predictors (in a 3 × 3 matrix for each pair of significant predictors).

RESULTS

Participants

Ninety-three of the 112 subjects of the original dataset were considered for the present study as they had no missing data (29 with PD, 26 with MS, and 38 with a stroke in the chronic phase). The three pathologies were balanced in terms of sex distribution and level of education. The age of the MS group significantly differed from PD and stroke (**Table 1**).

The global cognitive level at the Mini-Mental State Examination was comparable between the three groups. However, when considering the MoCA total score, patients with PD showed higher global cognitive functioning than stroke. Moreover, the memory profile at RBMT-3–GMI was slightly different between MS and the other two conditions (MS < PD/stroke). The specific profile on MoCA and RBMT-3 subscores is detailed in **Table 2**.

The three groups showed an equal level of affectivity, whereas a major impairment in motor functioning was observed in stroke (**Table 1**).

Treatment Effects

Changes between T1 and T0 were classified in one of three categories: patients who significantly benefited from treatment (Δ change > MCID), patients who substantially remained stable after treatment (–MCID ≤Δ change ≤ MCID), and patients with a significant worsening over time (Δ change < MCID).

Percentages of treatment success for each outcome measure are reported in **Table 3**. The results showed a significantly higher number of cases with treatment success and who remained stable after treatment vs. patients with a significant worsening over time in all outcomes related to cognitive and motor functioning, and affectivity. **Table 4** reports percentages of treatment success separately for each pathology.

The RF analyses revealed an overall good accuracy (77.8 %) of the classification model built to identify subjects who significantly benefited from treatment in the RBMT-3 (Δ change > MCID vs. Δ change ≤ MCID). **Table 5** shows the predictive performances of RF in terms of Precision, Recall, F1 Score and AUC. Precision was above 60% for both classes of patients who benefited and did not benefit from treatment.

Possible Predictors of Treatment

By adopting an explorative approach, point-biserial correlations (*rpb*) and χ^2-test, as appropriate, were run between the dichotomic variable of the outcome RBMT-3–GMI (Δ change > MCID vs. Δ change ≤ MCID) and clinical and demographic data in order to detect potential predictors at baseline.

Results highlighted a link between Δ RBMT-3–GMI (Δ change > MCID vs. Δ change ≤ MCID) and MoCA at baseline ($rpb = 0.178$, $p = 0.087$), visuospatial subdomain (AVS) of MoCA at baseline ($rpb = 0.211$, $p = 0.042$), attention subdomain (ATT) of MoCA at baseline ($rpb = 0.210$, $p = 0.043$), RBMT-3–GMI at baseline ($rpb = -0.250$, $p = 0.016$) (2MWT ($r = 0.274$, $p = 0.008$), BBS at baseline ($r = 0.196$, $p = 0.060$), and 10MWT at baseline ($r = -0.264$, $p = 0.011$).

Regression Models for the Identification of the Best Predictors of the Treatment

Two logistic regression models were computed considering significant results of correlations and the pathology (PD, SM, stroke) as possible predictors of the outcome RBMT-3–GMI (Δ change > MCID vs. Δ change ≤ MCID). In the first model, the following variables were included in the logistic regression: 2MWT, RBMT-3–GMI, MoCA, BBS, and 10MWT. Instead, in the second model, the MoCA was substituted by the subdomains that resulted significantly associated to RBMT-3–GMI Δ change in the preliminary correlation analysis: AVS and ATT. With respect to the first regression, the final third step (Cox and Snell $R^2 = 0.247$, Nagelkerke $R^2 = 0.334$) correctly classified 73.12% of patients. Variables excluded from the third final step were BBS and 10MWT scores at baseline. The binary logistic regression

TABLE 1 | Description of sample characteristics at baseline.

	PD	MS	Stroke	All	Groups comparison *p*-value	Pairwise comparisons
n	29	26	38	93	—	
Sex (Ma:F)	15:14	13:13	21:17	49:44	0.911^	
Age (mean ± s.d.)	66.21 ± 9.09	50.96 ± 11.41	59.66 ± 12.29	59.27 ± 12.49	**<0.001**§	MS < PD/stroke
Education (mean ± s.d.)	11.86 ± 4.42	11.50 ± 3.20	12.89 ± 3.97	12.18 ± 3.93	0.347#	
2MWT (mean ± s.d.)	133.17 ± 35.77	95.25 ± 37.67	78.49 ± 44.88	100.23 ± 46.14	**<0.001**§	MS/stroke < PD
MMSE (mean ± s.d.)	27.52 ± 1.92	27.27 ± 2.11	26.84 ± 2.84	27.17 ± 2.38	0.506^	
MoCA (mean ± s.d.)	22.33 ± 2.65	20.08 ± 3.38	20.02 ± 4.29	20.76 ± 3.71	**0.021**§	PD > stroke
RBMT-3–GMI (mean ± s.d.)	85.07 ± 17.89	60.73 ± 14.61	80.66 ± 17.29	78.70 ± 17.84	**0.002**§	MS < PD/stroke
BBS (mean ± s.d.)	48.93 ± 6.39	42.81 ± 9.98	40.13 ± 15.36	43.62 ± 12.19	**0.018**#	MS/stroke < PD
10MWT (mean ± s.d.)	6.94 ± 4.97	8.51 ± 4.10	15.12 ± 12.02	10.72 ± 9.17	**<0.001**#	stroke>PD/MS
PANAS-PA (mean ± s.d.)	33.52 ± 8.21	34.69 ± 6.10	35.34 ± 7.84	34.59 ± 7.48	0.529#	
PANAS-NA (mean ± s.d.)	17.90 ± 7.02	17.08 ± 7.23	15.95 ± 7.65	16.87 ± 7.31	0.343#	

2MWT, 2-Minute Walk Test; 10MWT, 10-Meter Walk Test; BBS, Berg Balance Scale; F, females; M, mean; Ma, males; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; N, number; PANAS-PA, Positive Affect and Negative Affect Schedule—positive affect; PANAS-NA, Positive Affect and Negative Affect Schedule—negative affect; PD, Parkinson disease; RBMT-3–GMI, Rivermead Behavioral Memory Test, Third Edition—Global Memory Index; s.d., standard deviation. ^χ^2-test computed; §univariate analysis of variance computed; #Kruskal–Wallis test computed. $p < 0.05$ are reported in bold.

TABLE 2 | Description of sample cognitive profile at baseline.

	PD	MS	Stroke	All	Groups comparison *p* value	Pairwise comparisons
n	29	26	38	93	—	
MoCA subscore [median (IQR)]						
AVS	2.96 (1.46)	3.65 (1.52)	3.15 (1.70)	3.23 (1.58)	0.738	
EF	2.78 (1.96)	2.44 (2.63)	2.19 (1.73)	2.57 (2.37)	0.331	
ME	1.00 (3.50)	2.00 (3.00)	2.00 (3.25)	2.00 (3.00)	0.875	
ATT	6.00 (0.68)	6.00 (1.16)	5.87 (1.60)	6.00 (1.12)	0.237	
LANG	5.42 (1.55)	5.03 (1.65)	4.65 (2.08)	4.90 (1.75)	0.072	
OR	6.00 (0.00)	6.00 (0.00)	6.00 (0.95)	6.00 (0.00)	0.381	
RBMT subscores [median (IQR)]						
N	8.00 (6.00)	5.50 (4.00)	6.00 (4.50)	6.00 (6.00)	**0.016**	MS < PD
B	9.00 (7.50)	11.00 (4.25)	11.00 (5.50)	11.00 (7.00)	0.828	
A	8.00 (6.50)	5.50 (6.25)	8.50 (8.00)	8.00 (7.00)	**0.015**	MS < PD/stroke
PR	12.00 (2.00)	12.00 (4.00)	12.00 (3.00)	12.00 (3.00)	0.475	
SI	7.00 (3.00)	5.00 (5.25)	7.00 (6.00)	7.00 (4.50)	0.112	
SD	6.00 (3.00)	4.00 (4.00)	6.00 (4.25)	5.00 (3.00)	0.050	
FR	11.00 (4.50)	7.00 (5.00)	9.00 (5.00)	9.00 (6.00)	**0.005**	MS < PD
RI	10.00 (6.00)	7.50 (6.50)	10.00 (6.00)	9.00 (7.00)	**0.012**	MS < PD/stroke
RD	9.00 (6.50)	6.50 (7.25)	8.00 (7.50)	8.00 (7.50)	0.088	
MI	11.00 (4.00)	6.50 (10.00)	11.00 (6.50)	11.00 (7.00)	**0.022**	MS < PD/stroke
MD	12.00 (4.00)	11.00 (10.25)	11.50 (7.00)	11.00 (7.00)	0.060	
O	8.00 (5.50)	7.50 (5.00)	9.00 (4.50)	9.00 (4.00)	0.110	
NI	6.00 (5.50)	2.00 (5.00)	4.00 (6.00)	5.00 (6.00)	**0.004**	MS < PD
ND	6.00 (2.50)	1.00 (2.00)	4.00 (5.00)	4.00 (4.50)	**0.001**	MS < PD/stroke

Differences between the three groups were tested with Kruskal–Wallis test. PD, Parkinson disease; MS, multiple sclerosis; MoCA, Montreal Cognitive Assessment; AVS, visuospatial abilities; EF, executive functions; ME, memory; ATT, attention; LANG, language; OR, orientation; RBMT-3, Rivermead Behavioral Memory Test, Third Edition; IQR, interquartile range; N, Names–Delayed Recall; B, Belongings–Delayed Recall; A, Appointments–Delayed Recall; PR, Picture Recognition; SI, Story–Immediate Recall; SD, Story–Delayed Recall; FR, Face Recognition–Delayed Recall; RI, Route–Immediate Recall; RD, Route–Delayed Recall; MI, Messages–Immediate Recall; MD, Messages–Delayed Recall; O, Orientation and Date; NI, Novel Task–Immediate Recall; ND, Novel Task–Delayed Recall. $p < 0.05$ are reported in bold.

TABLE 3 | Changes between T0 and T1 and comparison results of treatment effect vs. no effect cases.

		Δ change (mean ± SD)	% no treatment success	% stable after treatment	% treatment success	χ^2 ($df = 2$)	% success *p* value
Cognitive functioning	MoCA	1.25 ± 2.43	8.60	51.60	39.78	27.548	**<0.001**
	AVS	0.13 ± 1.04	20.43	46.24	33.33	9.290	**0.010**
	EF	0.63 ± 1.31	12.90	38.71	48.39	18.774	**<0.001**
	ME	0.57 ± 1.48	20.43	31.18	48.39	11.097	**0.004**
	ATT	0.03 ± 1.02	18.28	64.52	17.20	40.710	**<0.001**
	LANG	0.02 ± 1.10	29.03	44.09	26.88	4.903	**0.086**
	OR	0.01 ± 0.77	6.45	81.72	11.83	98.387	**<0.001**
	RBMT-3–GMI	5.94 ± 10.85	9.68	50.54	39.78	25.032	**<0.001**
	RBMT-3 subtests						
	N	1.32 ± 3.55	18.28	40.86	40.86	9.484	**<0.009**
	B	0.75 ± 4.29	15.05	52.69	32.26	19.806	**<0.001**
	A	0.92 ± 3.73	15.05	51.61	33.33	18.645	**<0.001**
	PR	−0.40 ± 3.44	23.66	62.37	13.98	36.581	**0.002**
	SI	1.31 ± 2.98	17.20	29.03	53.76	19.419	**<0.001**
	SD	1.20 ± 2.87	15.05	38.71	46.24	14.774	**0.001**
	FR	−0.76 ± 3.63	34.41	40.86	24.73	3.677	**0.159**
	RI	−0.20 ± 4.41	29.03	45.16	25.81	6.000	**0.050**
	RD	0.40 ± 4.26	23.66	49.46	26.88	11.032	**0.004**
	MI	−0.60 ± 5.21	31.18	48.39	20.43	11.097	**0.004**
	MD	0.04 ± 4.91	21.51	56.99	21.51	23.419	**<0.001**
	O	1.48 ± 3.01	10.75	49.46	39.78	22.645	**<0.001**
	NI	1.97 ± 3.99	19.35	22.58	58.06	25.742	**<0.001**
	ND	1.77 ± 4.16	20.43	36.56	43.01	7.548	**0.023**
Motor functions	2MWT	6.90 ± 19.38	7.53	69.89	22.58	59.097	**<0.001**
	10MWT	−0.86 ± 3.04	1.08	89.25	9.68	131.871	**<0.001**
	BBS	1.61 ± 4.53	3.23	84.95	11.83	112.516	**<0.001**
Affectivity	PANAS-PA	0.20 ± 7.31	29.03	43.01	27.96	3.935	0.140
	PANAS-NA	−2.06 ± 7.02	10.75	58.06	31.18	31.419	**<0.001**

%, percentage; Δ, delta change between T0 and T1; 2MWT, 2-Minute Walk Test; 10MWT, 10-Meter Walk Test; BBS, Berg Balance Scale; M, mean; PANAS-PA, Positive Affect and Negative Affect Schedule—positive affect; PANAS-NA, Positive Affect and Negative Affect Schedule—negative affect; RBMT-3–GMI, Rivermead Behavioral Memory Test, Third Edition—Global Memory Index; SD, standard deviation. N, Names–Delayed Recall; B, Belongings–Delayed Recall; A, Appointments–Delayed Recall; PR, Picture Recognition; SI, Story–Immediate Recall; SD, Story–Delayed Recall; FR, Face Recognition–Delayed Recall; RI, Route–Immediate Recall; RD, Route–Delayed Recall; MI, Messages–Immediate Recall; MD, Messages–Delayed Recall; O, Orientation and Date; NI, Novel Task–Immediate Recall; ND, Novel Task–Delayed Recall. $p < 0.05$ are reported in bold.

revealed a significant link between RBMT-3–GMI change after rehabilitation and outcome measure at baseline, which was confirmed with a predictive effect for the RBMT-3–GMI, MoCA and 2MWT scores. β-value indicated an inverse relation between the outcome RBMT-3–GMI (Δ change) and the RBMT-3–GMI at baseline, whereas a direct relation was observed between the outcome RBMT-3–GMI (Δ change) and the MoCA and 2MWT scores at baseline the variables (see **Table 6** for details).

In the second regression, the final third step (Cox and Snell $R^2 = 0.235$, Nagelkerke $R^2 = 0.318$) correctly classified 73.12% of patients. Variables excluded from the third final step were BBS, 10MWT, and ATT scores at baseline (see **Table 7** for details).

Finally, when considering three-tile ranks of significant baseline predictors (RBMT-3–GMI, MoCA, and 2MWT scores–**Figure 1**), the ideal candidate for the HEAD treatment in the clinical setting was a person with higher residual cognitive functioning (predicted probability of success: 0.856, **Figure 1**, panel A) or functional mobility (predicted probability of success: 0.733, **Figure 1**, panel C). Moreover, an ideal candidate is a person with a higher functional mobility with a moderate level of cognitive decline (predicted probability of success: 0.583, **Figure 1**, panel B).

DISCUSSION

In the present study, we aimed to identify predictors of the HEAD treatment success considering changes in RBMT-3, an ecological measure of functional memory, and to characterize the profile of the ideal candidate for HEAD treatment.

TABLE 4 | Changes within each pathology between T0 and T1 and comparison results of treatment effect vs. no effect cases.

	PD			MS			Stroke				
	% no treatment success	**% stable after treatment**	**% treatment success**	**% no treatment success**	**% stable after treatment**	**% treatment success**	**% no treatment success**	**% stable after treatment**	**% treatment success**	χ^2	***p***
MoCA	17.2	41.4	41.4	7.7	50.0	42.3	2.6	60.5	36.8	5.445	0.245
AVS	24.1	48.3	27.6	23.1	50.0	26.9	15.8	42.1	42.1	2.416	0.660
EF	6.9	44.8	48.3	11.5	34.6	53.8	18.4	36.8	44.7	2.437	0.656
ME	17.2	41.4	41.4	23.1	30.8	46.2	21.0	23.7	55.3	2.587	0.629
ATT	20.7	65.5	15.8	15.4	65.4	19.2	18.4	63.2	18.4	0.521	0.971
LANG	31.0	41.4	27.6	38.5	46.2	15.4	21.1	44.7	34.2	3.790	0.435
OR	6.9	82.8	10.3	0.0	84.6	15.4	10.5	79.0	10.5	3.117	0.538
RBMT-3–GMI	13.8	51.7	34.5	0.0	46.2	53.8	13.2	52.6	34.2	5.433	0.246
RBMT-3 subtests											
N	17.2	44.8	37.9	11.5	38.5	50.0	23.7	39.5	36.8	2.179	0.703
B	24.1	34.5	41.4	11.5	65.4	23.1	10.5	57.9	31.6	6.569	0.161
A	13.8	41.4	44.8	11.5	38.5	50.0	18.4	68.4	13.2	12.026	**0.017**
PR	37.9	55.2	6.9	19.2	69.2	11.5	15.8	63.2	21.1	6.660	0.155
SI	10.3	17.2	72.4	15.4	38.5	46.2	23.7	31.6	44.7	6.773	0.148
SD	10.3	31.1	58.6	11.5	57.7	30.8	21.0	31.6	47.4	7.228	0.124
FR	37.9	48.3	13.8	30.8	34.6	34.6	34.2	39.5	26.3	3.330	0.504
RI	34.5	41.4	24.1	23.1	38.5	38.5	28.9	52.6	18.4	3.882	0.422
RD	34.5	31.0	34.5	15.4	57.7	26.9	21.0	57.9	21.1	6.295	0.178
MI	27.6	48.3	24.1	15.4	61.5	23.1	44.7	39.5	15.8	6.678	0.154
MD	13.8	62.1	24.1	11.5	61.5	27.0	34.2	50.0	15.8	6.432	0.169
O	13.8	44.8	41.4	3.8	53.8	42.3	13.2	50.0	36.8	1.979	0.740
NI	20.7	13.8	65.5	19.2	30.8	50.0	18.4	23.7	57.9	2.397	0.663
ND	20.7	34.5	44.8	11.5	53.8	34.7	26.3	26.3	47.4	5.518	0.238

%, percentage; Δ, delta change between T0 and T1; RBMT-3–GMI, Rivermead Behavioral Memory Test, Third Edition—Global Memory Index; SD, standard deviation; N, Names–Delayed Recall; B, Belongings–Delayed Recall; A, Appointments–Delayed Recall; PR, Picture Recognition; SI, Story–Immediate Recall; SD, Story–Delayed Recall; FR, Face Recognition–Delayed Recall; RI, Route–Immediate Recall; RD, Route–Delayed Recall; MI, Messages–Immediate Recall; MD, Messages–Delayed Recall; O, Orientation and Date; NI, Novel Task–Immediate Recall; ND, Novel Task–Delayed Recall. $p < 0.05$ are reported in bold.

Overall, in line with our previous reports (24), the present work clearly showed that a relatively large number of patients benefited from the HEAD treatment in the clinical setting, with a stable condition or a significant improvement, above the MCID, in all cognitive, motor, and affective domains. It is worth noting that participants were people with chronic diseases who tend to have a stable or worsening disease course over time.

Our findings on predictors of treatment success highlighted the role both of cognitive and motor abilities on the improvement in functional memory. In more detail, when delineating the profile of the ideal candidate for the HEAD treatment in clinic, we found that the prototypical patient who can report beneficial effects with a high probability is a person with more preserved general cognitive functioning and/or higher functional mobility.

Patients with higher MoCA score at baseline are not only patients with more global residual cognitive abilities, but also people with greater cognitive control. In fact, the MoCA test is a screening test highly sensitive to executive functioning, attention and visuospatial abilities (46). Individuals with higher MoCA scores should present with higher capability in representing and maintaining information about goals to be achieved over time, such as rehabilitation goals (47, 48). On the contrary, patients with less cognitive control are likely to encounter difficulties in maintaining representations of task objectives

TABLE 5 | Evaluation Metrics of RF classification.

Evaluation metrics

	Precision	**Recall**	**F1 Score**	**AUC**
Patients who did not benefit from treatment	0.938	0.750	0.833	0.682
Patients who benefited from treatment	0.545	0.857	0.667	0.746
Average/Total	0.836	0.778	0.790	0.714

rea Under Curve (AUC) is calculated for every class against all other classes.

TABLE 6 | Binary logistic regression model to test best predictors of the RBMT-3–GMI change after rehabilitation.

		β	**SE**	**Wald**	***p*-value**	**Odds ratio (*B*)**
Step 1	2MWT T0	0.013	0.005	6.582	**0.010**	1.013
	Constant	−1.747	0.576	9.187	0.002	0.174
Step 2	2MWTT0	0.018	0.006	9.932	**0.002**	1.019
	RBMT-3–GMI T0	−0.046	0.015	8.844	**0.003**	0.955
	Constant	1.216	1.127	1.164	0.281	3.374
Step 3	2MWT T0	0.013	0.006	4.316	**0.038**	1.013
	MoCA T0	0.267	0.099	7.328	**0.007**	1.306
	RBMT-3–GMI T0	−0.075	0.020	13.921	**<0.001**	0.928
	Constant	−1.510	1.607	0.883	0.347	0.221

2MWT, 2-Minute Walk Test; MoCA, Montreal Cognitive Assessment; RBMT-3–GMI, Global Memory Index; SE, standard error. p < 0.05 are reported in bold.

TABLE 7 | Binary logistic regression model to test best predictors of the RBMT-3–GMI change after rehabilitation.

		β	**SE**	**Wald**	***p*-value**	**Odds ratio (*B*)**
Step 1	2MWT T0	0.013	0.005	6.582	**0.010**	1.013
	Constant	−1.747	0.576	9.187	0.002	0.174
Step 2	2MWTT0	0.018	0.006	9.932	**0.002**	1.019
	RBMT-3–GMI T0	−0.046	0.015	8.844	**0.003**	0.955
	Constant	1.216	1.127	1.164	0.281	3.374
Step 3	2MWT T0	0.017	0.006	8.400	**0.004**	1.017
	AVS T0	0.648	0.268	5.859	**0.015**	1.911
	RBMT-3–GMI T0	−0.059	0.017	11.237	**0.001**	0.943
	Constant	0.325	1.294	0.063	0.802	1.384

2MWT, 2-Minute Walk Test; AVS, visuospatial abilities; RBMT-3–GMI, Global Memory Index; SE, standard error. p < 0.05 are reported in bold.

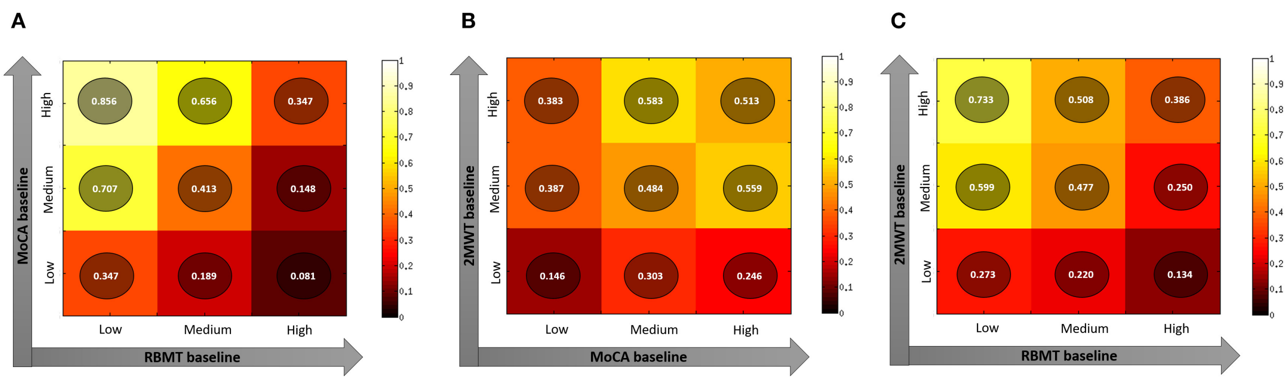

FIGURE 1 | Plots representing predicted probability of different combination of best predictors (Panel **A**: MoCa and RBMT; Panel **B**: 2MWT and MoCA; Panel **C**: 2MWT and RBMT) of the RBMT-3–GMI change after rehabilitation. Panel **(A)** MoCA value at baseline and RBMT value at baseline; Panel **(B)** 2MWT value at baseline and MoCA value at baseline; Panel **(C)** 2MWT value at baseline and RBMT value at baseline. 2MWT, 2-Minute Walk Test; MoCA, Montreal Cognitive Assessment; RBMT-3–GMI, Rivermead Behavioral Memory Test-3–Global Memory Index.

and also in shifting attention between different stimuli in the same task or between different tasks (task-shifting). Therefore, ultimately, they are unfortunately likely to benefit less from a rehabilitative treatment. Similarly, best responders in regaining functional memory after the HEAD treatment are patients with better functional mobility. In fact, persons with higher 2MWT scores at baseline are also persons with higher aerobic capacity and endurance, which represent other relevant prerequisites to perform HEAD activities and thus to achieve rehabilitation goals.

Interestingly, we observed that a high level of residual abilities in one of the two domains (cognitive or motor functioning) was sufficient to compensate the initial decay in the other one. Especially, the best treatment responders were participants with high residual level of motor abilities and a moderate residual level of cognitive functions, especially visuospatial abilities. *Vice versa*, people with high level of residual cognitive functions but moderate motor abilities benefited from the treatment with a considerable probability of success. This cognitive–motor balance underlines the critical role of the rearrangement mechanisms of the residual resources in the pathological conditions.

Our results also shed light on the intrinsic relationship subsisting between motor and cognitive functions, as well as reported in the literature. In fact, evidence showed the beneficial effects of physical activity on cognitive functions in healthy and pathological conditions (49, 50), indicating also the motor enhancement as a protective factor against cognitive impairment. The underlying biological mechanisms comprise the increment of neurotrophin level (51), the neurogenesis (52), the vascularization and angiogenesis (53), and increased activation in the frontoparietal network and a decreased activation in the default-mode network (54).

Accordingly, high cognitive control and motor abilities allowed performing motor–cognitive dual-task activities included in the HEAD treatment, demanding a discrete level of residual motor and cognitive resources. Although the potential of dual-task training has been demonstrated in different clinical populations (55, 56), potential downsides have been noted in terms of motor and cognitive interference in people with moderate disability, such as increased episodes of falls and sway (57). Moreover, motor–cognitive interference is particularly frequent in some clinical conditions, such as MS (58).

Finally, the VR devices of HEAD rehabilitation required patients to carry out quite sophisticated movements during cognitive activities, as well as visual exploration during motor and cognitive tasks. It is well-known that VR treatments particularly engage visuospatial abilities (59). This aspect could have represented a practical limitation for people with a severe disability. In fact, although there are numerous advantages related to these innovative tools, a recent study indicated also some possible barriers (60), including the need of adaptation of the technological devices to the patient's disability and the patient's additional effort in learning how to interact with the technological system.

The fact that demographic characteristics, such as age and pathology, were not significant predictors was unexpected. The lack of significant impact of age and pathology as predictors could be related to the intrinsic nature of HEAD. This treatment was conceived and developed to ensure a good level of personalization in terms of activities' contents, types, and difficulty level in clinic and at home (i.e. telerehabilitation). This aspect of the treatment allowed adapting the program session-to-session according to the patient's profile and performance. Especially, the personalization of the treatment was designed also on the basis of the pathology, in terms of the activities most effective for the specific clinical conditions (such as "finger-tapping" task for PD patients), and age, in terms of VR contents to be selected for the task (e.g., more or less up-to-date video clips). The selection of the activity's multimedia content could also be tailored to engage the patients by considering motivational aspects. Accordingly, positive outcomes related to VR rehabilitation have been reported, giving the opportunity to set numerous parameters through technological systems (61) in favor of the personalization of rehabilitation.

This work is not without limitations. We considered three clinical populations, and therefore the selection of the outcome measures for this study purposely excluded tests and scales mainly sensible to particular characteristics of a single clinical population (such as Box and Block Test for stroke). Moreover, our results are only related to cognitive outcomes and to the application of the VR in the clinical context. Future studies could adopt this approach and apply it to compare different rehabilitation settings (clinic vs. home), for detecting the impact of VR on different outcomes (i.e., quality of life, gait, affectivity…) and different cognitive domains.

To conclude, our findings will support clinical decision by identifying patients who can be targeted with high probability of VR rehabilitation success on ecological memory functioning. The ideal candidate for HEAD treatment is a person with residual capabilities on motor or cognitive domain, confirming the considerable importance of a prompt multidimensional rehabilitation and the intrinsic relationship subsisting between motor and cognitive functions. Especially, when a domain is impaired, the residual capability allows a compensative mechanism to help facilitate a successful outcome of the rehabilitation process, confirming the beneficial effects of physical activity on cognitive functions and *vice versa*.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committees of IRCCS Don Gnocchi Foundation, the province of Lecco, Como and Sondrio Ethics Committees, and Città della Salute e della scienza of Turin Ethics Committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FB, FM, and MS conceived the study. CG, JJ, and PG carried out the study. CC, CP, and SC collected data. SD, SI, and FB performed statistical analysis and interpreted results. SD, FB, and SI wrote the first draft of manuscript. All authors reviewed and approved the final manuscript.

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OPINION
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Multi-Modal Dual-Task Measurement: A New Virtual Reality for Assessment

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Keywords: virtual reality, attention assessment, multimodal assessments, dual-task, psychometric development

INTRODUCTION

This *Opinion Paper* considers the role of Virtual Reality (VR) as a viable platform for the clinical utility of dual-task assessments. VR has emerged as a promising tool for the diagnosis, treatment and cognitive improvement of neurological conditions, stroke, sport-related concussion, and dementia (Büttner et al., 2020; Sobral and Pestana, 2020). VR can be used in isolation for specific assessments of cognitive functions (Hørlyck et al., 2021), or can be combined with neuroimaging techniques and ancillary methods to offer insight into how target brain regions respond *in-vivo* to neurorehabilitation and/or cognitive stimulation (Ansado et al., 2020). The specific development of VR-based cognitive assessments and therapeutic interventions in neurological conditions is growing (Schultheis et al., 2002; Bell et al., 2020; Clay et al., 2020; De Luca et al., 2020; Diaz-Orueta et al., 2020; EbrahimiSani et al., 2020; Gamito et al., 2020; Vass et al., 2020). Within clinical practice, cognitive assessments rely on high levels of experimental control, and this is congruent with assessment paradigms in VR, while VR also potentially provides greater ecological validity than clinic-based assessments can provide (Parsons, 2015). The application of VR is becoming more commonplace in clinical trials and trial-based design (Clay et al., 2020; Escamilla et al., 2020; Hsieh et al., 2020), with some challenges reported in translating clinical trial outcomes to clinical practice (Brown et al., 2020).

Ideally, traditional neuropsychological assessments are developed using incremental levels of difficulty (Benson et al., 2010), to recruit additional cognitive processes as the test continues, or as serial stages of the test are administered to participants (Radua et al., 2014). For VR, this model of assessment has been mirrored with examples of VR-based tests including variable executive and functional levels of difficulty (Chang et al., 2020), which are also used as ecologically valid functional capacity assessments e.g., the Virtual Reality Functional Capacity Assessment Tool (Ruse et al., 2014). VR has shown clinically meaningful potential to provide opportunity for assessment and observation of motor function, gait analysis, motor imagery, and spatial aspects of cognition. While such assessment paradigms have been developed and used in neurodevelopmental conditions e.g., developmental co-ordination disorder (EbrahimiSani et al., 2020), there are exponential avenues for the development of clinical assessment for neuromuscular neurodegenerative diseases (Bekkers et al., 2020). Certainly, this is an emerging area within neurodegenerative movement disorders, such as Parkinson's Disease, or Multiple Sclerosis, where dual-task assessments are commonly used (Bekkers et al., 2020; Maggio et al., 2020; Saldana et al., 2020).

Dual-task assessments can be particularly useful from a clinical perspective, especially where a person who has difficulties with their gait, balance, and/or co-ordination, also presents with concurrent cognitive impairment or difficulties (Kalyani et al., 2019). Typically, people are able to perform motor and higher order cognitive tasks at the same time e.g., walking and holding a conversation. For some people with neurological conditions or brain injury, simultaneous performance of two such tasks often leads to performance deficits in one or both. This effect,

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known as dual-task interference, is thought to be evidence of deficits in selection and resourcing of cognitive function, at a given time. There are a number of proposed reasons for this; specific neurological conditions or head injury may result in domain-specific cognitive impairment due to the brain-behavior relationships associated with a specific neuroanatomical region (Bayot et al., 2018). This modular view of cognitive processing is challenged, however, by a more network-based approach to cognitive processing. For example, in isolation a person may be able to perform each individual task well e.g., walking without talking, though the capacity required to complete simultaneous tasks well, may be impaired. The extent to which the deficits are common to all tasks serves to indicate how general or specific the cognitive decline.

During the earlier stages of recovery from head or traumatic brain injury, performing a motor task may only be possible if the full computational resources of central cognitive capacity are available to direct and control movement. This would mean that the additional capacity available for any concurrent cognitive task is diminished, producing a dual task cognitive decrement. Similarly, for people with neurodegenerative movement disorders like Parkinson's Disease, dual-task interference can manifest in the everyday difficulties observed with executing both cognitive and motor tasks simultaneously (Raffegeau et al., 2019).

LITERATURE GAP

In current dual-task paradigms, there appears to be a high level of sophistication with motor assessment and outcomes, with non-specific cognitive measures being used to supplement the motor assessment (Veldkamp et al., 2019). Typically, to facilitate this assessment, headphones are used to administer the test stimuli, which allows for a motor assessment e.g., walking, concurrent with an attention task e.g., auditory digit-span. To that end, attention assessments to date during dual-task assessments have been restricted to auditory input, with little to no assessments of spatial span. Pragmatically, this is intuitive as the participant is required to use visual scanning to navigate their environment for safety while completing the task. Notwithstanding, the development of a multi-modal dual-task assessment is needed to overcome this current clinic-based limitation, allowing for a valid assessment of spatial span during a movement task. This in turn, could provide more sophisticated technologically supported assessments of auditory attention which may be more informative for clinical trials.

DISCUSSION

Emerging technology, such as virtual reality, can provide cognitive assessments with number of important benefits. VR assessments are flexible so they can be tailored with precise adjustment to meet the exact needs for a specific person, yet standardized for benchmarking performance. In this way they can powerfully inform individual rehabilitation support needs and strategies. In addition, their multi-modal nature offers a broad range of neuropsychological domains, within which assessment can take place and offers a way to mimic real world environments so as to embed the assessments in contextualized and meaningful activities. Through the use of a VR assessment-based model, one could tailor a motor task to the person and their current capacity, then concurrently administer a graded measure of auditory or visual attention, tailored to the person. Through the use of VR, the interaction between motor control and cognitive demand can be assessed with high levels of experimental control for the clinician-scientist, without compromising the ecologically-validating assessment experiences that support rehabilitating patients. On the other hand, an assessment paradigm such as this may also provide useful clinical markers for neurodegenerative conditions where dual-tasks are routinely used, such as Parkinson's Disease. Thus, this *Opinion Paper* supports the consideration of not only dual-tasks to be considered within VR, but for multi-modal and cross-modal cognitive-motor assessment paradigms to be considered. This has implications for clinical assessment and intervention, as the degree of interference between motor and cognitive tasks may be a potential indicator of the functional state of the motor system, cognitive function, and indeed the integration of both, during rehabilitation.

The development of a multimodal dual-task VR assessment which is underpinned by cognitive models of attention and working memory will be a great strength to cognitive assessment through the use of VR going forward with aging populations and the development of technology. Such an assessment paradigm would allow the facilitation of attention and working memory tasks, through multi-modal delivery e.g., auditory digit span and visual spatial span. To date, few studies, have specifically investigated the fractionation of attention and working memory processes stratified by input modality (Ettenhofer et al., 2016). Yet such an approach is of great importance when considering neurological conditions or brain injury. For example, previous research has demonstrated relatively independent patterns of performance on the standard Spatial Span and digit span tasks (Wilde and Strauss, 2002; Flaks et al., 2014). This lends support to the vast work demonstrating the relative separation of multimodal processing in theories of attention and working memory (Baddeley and Hitch, 1994; Baddeley, 1996, 2000, 2001, 2003, 2012; Bruyer and Scailquin, 1998; Repovs and Baddeley, 2006; Baddeley et al., 2011, 2019). While on a cursory methodological level, traditional versions of these tasks may show analogous properties, there is doubt about whether they show similar operating characteristics and measure the same cognitive process.

To elaborate, from a cognitive model perspective, where a task requires target stimuli of increasing length to be reproduced in the order they were presented, the task evaluates attention through modality-specific systems i.e., the phonological loop and the visuo-spatial sketchpad for verbal and visual or spatial data, respectively. Whereas if a task requires stimuli to be manipulated (e.g., reversed prior to reproduction), then this task primarily implicates executive function, as part of the same modality-specific systems, and is consequently considered a working memory task. For this reason comprehensive assessments require specific tasks matched on equivalency. Here, we propose that VR can provide a novel avenue to consider a multimodal cognitive assessment. Importantly, this can be combined with a motor task to develop a VR-specific dual-task assessment.

Potential dissociation between impaired attention (verbal and/or visuospatial) and short-term memory may be of most importance when assessing impairment in early stages of a disease, prior to impairment of the wider executive system. A VR-based multi-modal dual-task could assess whether patients' patterns of scoring on dual-tasks, are equivalent on measures of attention and working memory, regardless of the modality used i.e., auditory (digit-span) or visual (spatial span). From a clinical perspective, such a measure allows for a person to complete an assessment as they present to a clinic at one timepoint, and then reliably repeat the assessment over time. Importantly, the modality could be changed in light of any progressive motor impairment e.g., using a spatial task rather than one relying on verbally responding to tasks. The conceptualization of this task has not only clinical importance for dual-task development, but also for the development of cross-modal tasks. It is expected that tasks such as this will provide valid, reliable, and clinically meaningful results for conditions where dual-task paradigms are currently being used, in a more traditional modality. The technologically-supported VR dual-task, with multimodal components, can also be designed to collect a range of performance and outcome metrics such as rapid response latency, accuracy, error monitoring, and recordings of data relating to the relationship between motor and cognitive outcomes. These data may uncover more reliable indices of functioning, diagnosis and prognosis. Notwithstanding, there are a number of potential limitations for consideration which may have a secondary influence of participants' performance, which are related to the use of VR, over and above a clinical syndrome. Potential negative affects need due consideration, and these may include health and safety risks e.g., visually-induced motion sickness (cybersickness; Arcioni et al., 2019), challenges to performance e.g., discomfort with head mounted displays and equipment (Zhdanov et al., 2019), or social implications e.g., the acceptability of VR and VR-based assessments (Stanney et al., 1998). Consequently, clinician scientists need to ensure gold standard assessments and cross-validations occur with the introduction of new VR-based assessments, in order to provide reliable and valid metrics, as well as VR-alternatives should a person find it challenging or comfortable to engage with VR.

This article forms part of a special issue on the use of neuropsychological and cognitive assessment in neurodegenerative diseases, through the use of VR. From a clinical perspective, attention and working memory tasks have an important role to play in the cognitive assessment of neurodegenerative disorders, especially where motor function is a core feature e.g., Huntington's disease. The combination of verbal and visuospatial span tasks are of great importance when examining attention and working memory, yet traditionally, a single test modality is often chosen. Clinically, measures of attention, executive function, and short-term memory have important prognostic value in neurodegenerative syndromes, and a multimodal dual-task such as this will have particular utility in motor conditions involving cortico-striatal-thalamo-cortical pathways e.g., Parkinson's Disease (Peters et al., 2016). To integrate a VR-based assessment paradigm into clinical practice, a novel measure is required to have cross-modal interchangeability to support dynamic patient presentations in neurodegenerative movement disorders. From a usability perspective, it is also required to be portable, and cost-effective. There is vast scope for dual-task assessments through the use of VR in neurodegenerative and neurological conditions, and this *Opinion Paper* highlights some of the cognitive and neuropsychological considerations to be made, as well as potential avenues for outcomes specific to assessing auditory and visual attention.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this Opinion Paper.

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The Smart Aging Platform for Assessing Early Phases of Cognitive Impairment in Patients With Neurodegenerative Diseases

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Background: Smart Aging is a serious game (SG) platform that generates a 3D virtual reality environment in which users perform a set of screening tasks designed to allow evaluation of global cognition. Each task replicates activities of daily living performed in a familiar environment. The main goal of the present study was to ascertain whether Smart Aging could differentiate between different types and levels of cognitive impairment in patients with neurodegenerative disease.

Methods: Ninety-one subjects (mean age = 70.29 ± 7.70 years)—healthy older adults (HCs, $n = 23$), patients with single-domain amnesic mild cognitive impairment (aMCI, $n = 23$), patients with single-domain executive Parkinson's disease MCI (PD-MCI, $n = 20$), and patients with mild Alzheimer's disease (mild AD, $n = 25$)—were enrolled in the study. All participants underwent cognitive evaluations performed using both traditional neuropsychological assessment tools, including the Mini-Mental State Examination (MMSE), Montreal Overall Cognitive Assessment (MoCA), and the Smart Aging platform. We analyzed global scores on Smart Aging indices (i.e., accuracy, time, distance) as well as the Smart Aging total score, looking for differences between the four groups.

Results: The findings revealed significant between-group differences in all the Smart Aging indices: accuracy ($p < 0.001$), time ($p < 0.001$), distance ($p < 0.001$), and total Smart Aging score ($p < 0.001$). The HCs outperformed the mild AD, aMCI, and PD-MCI patients in terms of accuracy, time, distance, and Smart Aging total score. In addition, the mild AD group was outperformed both by the HCs and by the aMCI and PD-MCI patients on accuracy and distance. No significant differences were found between aMCI and PD-MCI patients. Finally, the Smart Aging scores significantly correlated with the results of the neuropsychological assessments used.

Conclusion: These findings, although preliminary due to the small sample size, suggest the validity of Smart Aging as a screening tool for the detection of cognitive impairment in patients with neurodegenerative diseases.

Keywords: virtual reality, serious games, cognitive impairment, global cognitive functions, neurodegenerative disease

INTRODUCTION

A growing interest in the development of accessible and easily administered neuropsychological screening tools for detecting cognitive impairment in aging, also driven by the technological advances of recent years, has resulted in excellent opportunities for improving neuropsychological evaluation in clinical practice. In this setting, virtual reality (VR) gaming and interactive video gaming have emerged as promising new ways of assessing cognitive mechanisms in a more ecological manner (e.g., Christiansen et al., 1998; Rizzo et al., 1998; Davies et al., 1999; Riva et al., 1999; Rose et al., 1999; Jack et al., 2001; Zhang et al., 2001; Kang et al., 2008; Zucchella et al., 2014a; Fabbri et al., 2019; Realdon et al., 2019). In particular, serious games (SGs), which can be defined as innovative computer games designed for purposes other than leisure (Charsky, 2010), constitute a young VR gaming subfield. These games can vary greatly in structure, but most of the ones used in neuropsychological assessment involve the generation of realistic 3D scenarios that simulate the demands of daily life and, therefore, have greater ecological validity than traditional cognitive assessments. SGs can also be self-administered (possibly after minimal training); furthermore, they provide a pleasant experience and reduce the psychological stress that can be caused by traditional screening tools (Ismail et al., 2010). Finally, being computer-based assessments, they can allow better standardization of both administration and data collection (Parsons, 2014). All these aspects are particularly useful in the diagnosis of early cognitive impairments. SGs can detect impairments in multiple cognitive domains while, thanks to the advantages outlined above, overcoming the limitations of traditional pen-and-paper tests. Therefore, they could potentially be used in place of traditional assessments to perform large-scale, low-cost screening campaigns aimed at earlier detection of cognitive impairments in aging, which in turn would allow earlier enrollment in rehabilitation programs.

As already highlighted in the literature, SGs have been successfully used for assessment purposes both in normal aging and in clinical populations, such as mild cognitive impairment (MCI) and Alzheimer's disease (AD) cohorts. Manera et al. (2015) used a cooking pot-based SG to compare groups with MCI and AD vs. healthy controls (HCs). They found the cooking game to be sensitive to between-group differences in performance, which depended on the level of cognitive impairment. Other authors, too, have provided evidence of the validity of SG-based assessments in MCI and AD (e.g., Tarnanas et al., 2014; Valladares-Rodríguez et al., 2016; Ouellet et al., 2018). To date, however, these aspects have been little explored in the field of Parkinson's disease (PD). One of the few exceptions was a study using the Virtual Multiple Errands Test (VMET), which aims to test different aspects of executive functioning (EF) by having patients explore a virtual supermarket. The authors (Cipresso et al., 2014a) compared VMET performances with performances recorded on traditional pen-and-pencil tests in cognitively normal PD patients, PD patients with MCI (PD-MCI), and HCs. The results showed that the VMET was more sensitive than traditional EF assessments in detecting EF deficits. More recently, Serino et al. (2017) used the 360° version of the Picture Interpretation Test (PIT) to compare EF in cognitively normal PD patients and HCs, and found that it seemed able to distinguish between these two groups. Together, the aforementioned studies highlight the potential of VR environments and SGs in cognitive assessment. However, more research is necessary to investigate, in detail, how they might be used for cognitive assessment in pathological aging. Given the importance, from a therapeutic perspective, of early differential diagnoses, previous studies have evaluated the ability of single assessment tools to discriminate between different forms of early cognitive impairment. To date, however, only traditional pen-and-paper tests, and not SG tools, have been evaluated (e.g., Kwak et al., 2010; Yamamoto et al., 2017; Allone et al., 2018).

Smart Aging is an SG technology-based platform developed by our group for the assessment of global cognition and specific aspects of cognition, such as memory and EF, in normal aging (Pazzi et al., 2014; Tost et al., 2014, 2015). Essentially, it integrates various games that reproduce, in 3D, different everyday life tasks. In a previous work (Bottiroli et al., 2017), we compared the results of cognitive screening performed by means of Smart Aging with the scores obtained on a traditional standardized screening test, i.e., the Montreal Overall Cognitive Assessment (MoCA), in a sample of 1,086 healthy older adults stratified by MoCA score. We found significant between-group differences in each Smart Aging task, and thus demonstrated the validity of this platform as a screening tool for cognitive functioning in normal aging. More recently, Smart Aging (Cabinio et al., 2020a) was tested for its ability to identify individuals with amnesic MCI vs. HCs, and the overall score derived from this platform (i.e., the Smart Aging total score) performed comparably, in this regard, to traditional neuropsychological tests (i.e., MoCA, Free and Cued Selective Reminding Test, Trail Making Test). In addition, Smart Aging has been shown (Zucchella et al., 2014b) to be easily administrable, even in patients unfamiliar with computerized tests. This may be explained by the fact that movements in its VR environments are performed by means of a touch screen monitor, which is easier and more intuitive to use than a mouse, even for individuals with some cognitive impairment (Cernich et al., 2007). It is, in fact, important to limit as much as possible any influence of manual skills on test results. Hence, on the basis of our previous experience, we argue that Smart Aging may complement the traditional assessment of cognitive function, and indeed serve to broaden access to neuropsychological testing.

In the present study, we set out to establish whether Smart Aging can differentiate between different types and levels of cognitive impairment in patients with neurodegenerative diseases, and whether it might therefore be used as a screening tool in these patients. Our ultimate intention is the development of an SG-technology-based assessment tool for the evaluation of cognition as a whole in an ecological context. Pathological aging can present in many different forms, and it is important to develop screening tools able to distinguish between them and, therefore, able to identify factors that may affect a patient's disease course and increase opportunities for interventions designed to delay or prevent progression to dementia. In the present study, we tested the Smart Aging platform in patients with different types of MCI (single-domain amnesic MCI—aMCI—and single-domain executive MCI—PD-MCI) and in patients with mild AD. A sample of healthy older adults was included as the control group. We expected that patients with different cognitive profiles would show different Smart Aging performance trends. Performances across groups were evaluated in terms of accuracy, time spent performing tasks, and distance covered within the virtual environment. We also considered the Smart Aging total score (obtained from the difference between accuracy, time, and distance), which could represent a final index of performance and reflect global functioning. Giving that SGs use automated systems for scoring performances (Clauser et al., 2002), it might therefore capture the complexity of cognitive functioning in everyday situations, better than traditional assessments do (Fortin et al., 2003). In particular, evaluation of indices such as time and distance, in addition to accuracy, may better reveal whether individuals are able to use skills and strategies effectively in order to facilitate their responses to environmental demands. Finally, we also evaluated associations between Smart Aging scores—i.e., the global scores recorded for three indices (accuracy, time, and distance) and the Smart Aging total score—and performances on traditional neuropsychological tests. Given that this platform was expected to reflect global cognitive functioning, correlations were first carried out with traditional screening tests (i.e., MMSE and MoCA), and then with measures of specific cognitive functions.

MATERIALS AND METHODS

Design of the Comparative Study

This study was designed to compare cognitive performance in normal aging and early cognitive impairment using the Smart Aging platform. To this end, we evaluated four groups of subjects: aMCI, PD-MCI, and mild AD patients, and a group of HCs.

Participants

A total sample of 91 subjects (mean age = 70.29 ± 7.70 years) took part in this study. It comprised patients diagnosed with aMCI (n = 23), mild AD (n = 25), and PD-MCI (n = 20), who were recruited and enrolled from the Neuropsychology/Alzheimer's Disease Assessment Unit and Neurorehabilitation Unit of the IRCCS Mondino Foundation.

The inclusion criteria were:

- a diagnosis of mild AD, aMCI, or PD-MCI according to widely accepted diagnostic criteria (McKhann et al., 2011, for mild AD; Albert et al., 2011, for aMCI, and Litvan et al., 2012, for PD-MCI);
- a Mini-Mental State Examination (MMSE) score > 20 in patients with mild AD;
- age between 60 and 85 years;
- educational level ≥5 years.
- The exclusion criteria were:
- other causes of cognitive impairment due to preexisting conditions (e.g., aphasia, neglect);
- concomitant severe psychiatric diseases or other neurological conditions (e.g., depression and behavioral disorders);
- severe sensory or motor disturbances liable to interfere with the assessment;
- deep brain stimulation.

A group of age-, gender-, and education-matched community-dwelling healthy older adults (HCs, n = 23) was also included. HCs were recruited among patients' caregivers. They were native Italian speakers and received no tangible incentive to participate.

Written informed consent was obtained from all the participants; the consent document and study protocol had local ethics committee approval. Participant characteristics are reported in **Table 1**.

Traditional Neuropsychological Assessment

In all cases, before the participants performed the Smart Aging test, their global cognitive functioning was assessed using the following traditional cognitive screening tests: MMSE (Magni et al., 1996) and MoCA (Conti et al., 2015).

Participants were also administered a neuropsychological battery including (a) phonological (Carlesimo et al., 1996) and semantic fluency (Novelli et al., 1986) tests, to assess logical-executive functions and language; (b) the Trail Making Test (TMT, parts A and B) (Giovagnoli et al., 1996), to assess executive functions, mental flexibility, visual search ability, and processing speed; and (c) the Free and Cued Selective Reminding Test (FCSRT) (Frasson et al., 2011), focusing on immediate and delayed free and total recall, to evaluate encoding and retrieval phases of the memorization processes.

The Smart Aging Platform

As described elsewhere (Pazzi et al., 2014; Tost et al., 2014, 2015; Zucchella et al., 2014b; Bottiroli et al., 2017), Smart Aging is an SG platform based on a first-person paradigm and administered in the presence of a neuropsychologist. The virtual 3D environment is a loft apartment that brings together, in a small space, the basic elements of the environmental interactions that occur in the setting of a private home: a kitchen corner, a bedroom corner, and a living room corner (see **Figure 1**). Participants use a touch screen monitor to navigate and interact with the environment. The Smart Aging platform has been designed to

TABLE 1 | Demographic characteristics and traditional neuropsychological assessment scores of study participants.

	HCs (*n* = 23)	Mild AD (*n* = 25)	aMCI (*n* = 23)	PD-MCI (*n* = 20)	*p*
Age	69.43 (6.83)	73.52 (6.86)	69.74 (9.27)	67.85 (6.84)	0.08
Gender (F)	12 (52%)	13 (52%)	12 (52%)	9 (45%)	0.96
Education (years)	10.39 (2.55)	8.84 (4.36)	10.44 (4.64)	9.20 (3.61)	0.38
MMSE	26.99 (2.58)$^{*+}$	22.79 (2.05)$^{*\circ\#}$	25.09 (2.78)$^{\circ+}$	25.44 (2.16)$^{\#}$	<0.001
MoCA	26.60 (3.47)$^{*+z}$	17.84 (2.94)*	19.08 (2.73) $^{+}$	16.74 (2.43)^{z}	<0.001
Fluency§					
Phonological	−0.11 (0.58)$^{*+z}$	−0.67 (0.65)*	−0.68 (0.73)$^{+}$	−0.89 (0.77)^{z}	0.002
Semantic	−0.15 (0.92)$^{*+z}$	−1.78 (0.90)*	−1.29 (0.72) $^{+}$	−1.63 (0.55)^{z}	<0.001
TMT§					
Part A	0.31 (2.84)^{*z}	2.81 (2.26)$^{*\circ}$	1.18 (1.54)$^{\circ}$	2.13 (1.49)^{z}	0.001
Part B	−0.12 (1.06)^{*z}	2.41 (2.09)*	1.15 (1.60)	1.93 (2.05)^{z}	<0.001
FCSRT§					
Immediate free recall	−0.12 (1.17)$^{*+z}$	−3.08 (0.97)$^{*\circ\#}$	−1.93 (1.32)$^{\circ+}$	−1.74 (1.37)$^{\#z}$	<0.001
Immediate total recall	−0.94 (1.29)$^{*+}$	−3.75 (2.52)$^{*\#}$	−2.20 (2.11)$^{+}$	−1.67 (2.85)$^{\#}$	<0.001
Delayed free recall	−1.00 (1.16)*	−3.07 (1.13)$^{*\circ\#}$	−1.43 (2.97)$^{\circ}$	−1.42 (1.27)$^{\#}$	<0.001
Delayed total recall	−0.16 (1.42)$^{*+}$	−3.20 (2.95)$^{*\#}$	−2.45 (2.38)$^{+}$	−1.17 (2.10)$^{\#}$	<0.001

**Significant differences between HC and mild AD.* $^{+}$*Significant differences between HC and aMCI.* ^{z}*Significant differences between HC and PD-MCI.* $^{\circ}$*Significant differences between mild AD and aMCI.* $^{\#}$*Significant differences between mild AD and PD-MCI. TMT = Trial Making Test; FCSRT = Free and Cued Selective Reminding Test.* §*, Z scores.*

engage participants in task-specific scenarios where they perform five tasks, related to everyday life activities, that evaluate several cognitive functions (e.g., EF, attention, memory, and visuo-spatial orientation) (see **Table 2** for a description of the tasks). Execution of the whole game takes from 10 to 30 min. As the participant experiences the virtual environment and performs the tasks, the system records various data (positions, times, and actions). The scores provide a picture of the participant's cognitive functions. In particular, the system computes separate sets of indices for each task. For four of the five tasks, we considered accuracy, time, and distance; for task 4, a 2D task not entailing navigation in the environment, we considered only accuracy and time. Accuracy was measured as the total number of correct actions while completing each of the tasks. In particular, for tasks 1, 4, and 5, it referred to the total number of objects correctly remembered, whereas for tasks 2 and 3, it corresponded to the total number of correct actions performed while completing each of these tasks. For task 3, we also considered correct recall of the telephone number needed to make the phone call, as well as performance of the prospective memory action, i.e., remembering to switch on the TV at the end of the task. Time, on the other hand, referred to the time taken to accomplish each task, from start to finish. Distance was the number of meters covered in the loft while performing each task, from start to finish. More information is available in Bottiroli et al. (2017).

Statistical Analysis

In accordance with previous research (Bottiroli et al., 2017), for each Smart Aging task, we considered accuracy, time, and distance, which were converted into *z*-score units. We then computed a global score per index, in each case obtained as the sum of the scores recorded over the five tasks. Finally, we computed the Smart Aging total score, obtained by calculating the sum of (or difference between, in the case of reverse scores, i.e., time and distance) the scores of all five tasks. We used univariate analysis of variance (ANOVA) in order to compare normally distributed variables between groups. The Tukey *post-hoc* test with 0.05 level of significance was applied to evaluate between-group differences. As the distribution of the Smart Aging data was not normal, group comparisons were performed using non-parametric Kruskal–Wallis tests followed by Mann–Whitney *U*-tests corrected for multiple comparisons. A series of receiver operating characteristic (ROC) analyses was performed to evaluate the relationship between sensitivity and specificity of the global accuracy, time, and distance scores on each of the five tasks, and of the Smart Aging total score, for identifying the four groups. The area under the ROC curve (AUC) gives the proportion of cases that are correctly discriminated by the considered variables. To this end, we compared each group with the other three (i.e., HCs vs. mild AD + aMCI + PD-MCI; mild AD vs. HCs + aMCI + PD-MCI; aMCI vs. HCs + mild AD + PD-MCI; and PD-MCI vs. HCs + mild AD + aMCI). For the Smart Aging total score, we also performed the ROC analysis comparing HCs vs. mild-AD alone, and mild AD vs. aMCI and PD-MCI separately, in order to avoid biases related to the differences between the clinical entities considered. This analysis was restricted to the Smart Aging total score as this was expected to be indicative of the presence/absence of cognitive impairment. Effect sizes were calculated by using G*Power 3 (Faul et al., 2007). Finally, Pearson's correlations were used to detect associations between Smart Aging scores and neuropsychological tests. These

FIGURE 1 | An example of the virtual scenarios used in the Smart Aging platform.

analyses were carried out first on MMSE and MoCA, as these are our gold standard traditional screening tests, and then using the rest of the neuropsychological battery. We set the significance level alpha at 0.05 for parametric tests, while a value of 0.0125 (0.05/4) was applied for non-parametric tests involving the four groups. The SPSS 23.0 statistical software package was used to perform all the statistical analyses.

RESULTS

Participant Characteristics

The four groups were similar (**Table 1**) in terms of age, $F_{(3,90)} = 2.37$; $p = 0.08$, and years of education, $F_{(3,90)} = 1.03$; $p = 0.38$. The proportion of female and male participants was similar across the groups, $\chi^2_{(3)} = 0.32$; $p = 0.96$.

Traditional Neuropsychological Evaluations

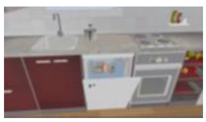
MMSE scores differed significantly between the four groups, $F_{(3,90)} = 12.46$, $p < 0.001$ (**Table 1**). Specifically, the score was lower in the mild AD group than in the other three groups, while the aMCI group scored lower than the HCs. No other comparisons of MMSE scores showed differences. Significant differences between groups were also found in the MoCA scores, $F_{(3,90)} = 52.19$, $p < 0.001$. In this case, the HCs outperformed the three other groups, which all performed similarly to each other.

The HCs recorded significantly higher scores than the three other groups both on phonological and on semantic fluency tests, $F_{(3,87)} = 5.42$, $p = 0.002$ and $F_{(3,87)} = 19.78$, $p < 0.001$, respectively, whereas the three patient groups performed similarly to each other.

On the TMT part A, $F_{(3,86)} = 6.16$, $p = 0.001$, the mild AD patients were outperformed by the HCs and the aMCI group, while the HCs outperformed the PD-MCI group. No other significant between-group differences were found. On the TMT part B, $F_{(3,68)} = 8.35$, $p < 0.001$, the HCs outperformed both the mild AD and the PD-MCI patients, but no other significant differences emerged between the groups.

On FCSRT immediate free recall, $F_{(3,86)} = 23.75$, $p < 0.001$, the HCs outperformed the three patient groups, and the mild AD patients were outperformed by the aMCI and PD-MCI groups, which performed similarly to each other. On FCSRT immediate total recall, $F_{(3,86)} = 10.56$, $p < 0.001$, HCs outperformed the mild AD and aMCI groups; the mild AD patients were outperformed by the PD-MCI group. The other groups performed similarly to each other. On FCSRT delayed free recall, $F_{(3,86)} = 10.57$, $p < 0.001$, the mild AD group was outperformed by the other three groups, which all performed similarly to each other. Finally, on FCSRT delayed total recall, $F_{(3,85)} = 7.99$, $p < 0.001$, the HCs outperformed the mild AD and aMCI patients, and the mild AD group was also outperformed

TABLE 2 | The Smart Aging tasks.

Task	Picture
Task 1—Object search After exploring the kitchen, the subject is asked to look for a list of objects.	
Task 2—Water flowers while listening to the radio The subject is asked to turn on the radio and press the spacebar every time the word "sun" is aired, while watering the flowers on the windowsill in the dining room.	
Task 3—Make a phone call The person is asked to make a phone call using the phone book and the phone placed on the bedside table. The subject is asked to remember to turn the TV on after dialing the number.	
Task 4—Choose the right object A 2D screen with 24 images of objects is shown. The subjects has to identify the 12 objects presented in task 1.	
Task 5—Find the objects The subject is positioned in front of the kitchen, and he/she is asked to find each of the objects that he looked for in task 1.	

by the PD-MCI patients. No other between-group differences were found.

Smart Aging Results

The means and standard deviations for accuracy, time, and distance (expressed in z scores) are reported in **Table 3** and the corresponding analyses in **Table 4**.

Accuracy

The four groups showed significant differences in accuracy scores on all the tasks (except Task 2, on which they scored similarly) and in global accuracy.

On Task 1, the HCs outperformed the mild AD ($d = 2.74$), aMCI ($d = 2.04$), and PD-MCI ($d = 2.45$) groups, which all performed similarly ($p > 0.09$).

On Task 3, the HCs recorded higher scores than the mild AD ($d = 0.96$), aMCI ($d = 0.69$), and PD-MCI ($d = 0.24$) patients, with no differences found between the three clinical groups ($p > 0.09$).

On Task 4, too, the HCs outperformed the mild AD ($d = 2.07$), aMCI ($d = 0.97$), and PD-MCI ($d = 0.77$) groups. The mild AD patients scored lower than the aMCI ($d = 0.86$) and PD-MCI ($d = 1.48$) ones, which instead performed similarly to each other ($p = 0.38$).

On Task 5, the HCs again outperformed the mild AD ($d = 3.71$), aMCI ($d = 2.60$), and PD-MCI ($d = 2.31$) groups. The mild AD patients scored lower than the PD-MCI ones ($d = 0.82$). No other between-group differences were found ($p > 0.09$).

The HCs recorded a higher global accuracy score than all three clinical groups: mild AD ($d = 2.55$), aMCI ($d = 1.67$), and PD-MCI ($d = 1.70$). The mild AD patients were outperformed by the aMCI ($d = 0.90$) and PD-MCI ($d = 1.17$) groups, which performed similarly to each other ($p = 0.63$).

The ROC curve and the AUC of global accuracy scores were first measured by comparing HCs vs. mild AD + aMCI + PD-MCI patients. The AUC was 0.975 (95% confidence interval, 0.828–1.00, $p < 0.001$). When comparing mild AD vs. HCs + aMCI + PD-MCI groups, the AUC was 0.168 (95% confidence interval, 0.082–0.253, $p < 0.001$). Global accuracy was not a significant predictor of aMCI vs. HCs + mild AD + PD-MCI (AUC: 0.437–95% confidence interval, 0.315–0.559, $p = 0.37$) or for PD-MCI vs. HCs + mild AD + aMCI (AUC: 0.496–95% confidence interval, 0.377–0.614, $p = 0.95$).

Time

The four groups showed significant differences both in the time scores recorded on each of the tasks (except Task 4, on which they scored similarly) and in the global time score.

On Task 1, the HCs were faster than the mild AD ($d = 1.48$), aMCI ($d = 1.01$), and PD-MCI ($d = 1.34$) patients. The three clinical groups did not differ from each other ($p > 0.10$).

On Task 2, the HCs were faster than the mild AD ($d = 1.80$), aMCI ($d = 1.20$), and PD-MCI ($d = 0.75$) groups, which again performed similarly ($p > 0.23$).

On Task 3, the HCs were faster than the mild AD ($d = 2.41$), aMCI ($d = 2.35$), and PD-MCI ($d = 1.63$) groups. The mild AD patients were slower than the aMCI ones ($d = 0.78$), but no other differences were found between the groups ($p > 0.11$).

As for Task 5, the HCs were faster than the mild AD ($d = 2.07$), aMCI ($d = 2.19$), and PD-MCI ($d = 1.89$) groups, which did not differ from each other ($p < 0.58$).

As regard the global time score, the HCs were faster than mild AD ($d = 2.86$), aMCI ($d = 2.32$), and PD-MCI ($d = 1.56$) groups, which all performed similarly ($p > 0.10$).

The ROC curve and the AUC of the global time score were initially measured by comparing HCs vs. mild AD + aMCI + PD-MCI patients; the AUC was 0.937 (95% confidence interval, 0.848–1.000, $p < 0.001$). We then measured the ROC curve by comparing mild AD vs. HC + aMCI + PD-MCI patients, and the AUC was 0.250 (95% confidence interval, 0.150–0.349, $p < 0.001$). The global time score was not a significant predictor of aMCI vs. HCs + mild AD + PD-MCI (AUC: 0.405–95% confidence interval, 0.283–0.527, $p = 0.18$) or PD-MCI vs. HCs + mild AD + aMCI (AUC: 0.421–95% confidence interval, 0.287–0.556, $p = 0.31$).

Distance

The groups differed significantly in terms of the distance covered in each of the four tasks and also in the global distance score.

On Task 1, the mild AD patients covered less distance than the other groups: aMCI ($d = 0.71$), PD-MCI ($d = 1.16$), and HCs ($d = 1.82$); the aMCI patients covered less distance than the HCs ($d = 0.74$). No other differences were found between the groups ($p > 0.22$).

TABLE 3 | Z scores—means and (standard deviations)—in the Smart Aging tasks as a function of group.

Smart Aging tasks	HCs ($n = 23$)	Mild AD ($n = 25$)	aMCI ($n = 23$)	PD-MCI ($n = 20$)	p
Accuracy					
Task 1	-0.02^{*+z} (1.06)	-2.67^{*} (0.86)	-2.16^{+} (1.04)	-2.46^{z} (0.93)	<0.001
Task 2	0.11 (1.31)	−0.47 (1.54)	0.00 (1.91)	0.33 (1.48)	0.15
Task 3	-0.07^{*+z} (1.78)	-1.86^{*} (1.93)	-1.07^{+} (0.99)	0.33^{z} (1.48)	<0.001
Task 4	-0.12^{*+z} (1.32)	$-2.74^{*\circ\#}$ (1.21)	$-1.53^{+\circ}$ (1.58)	$-1.05^{\#z}$ (1.07)	<0.001
Task 5	0.03^{*+z} (0.78)	$-3.44^{*\#}$ (1.07)	-2.68^{+} (1.25)	$-2.46^{\#z}$ (1.31)	<0.001
Global accuracy score	-0.26^{*+z} (4.41)	$-11.17^{*\circ\#}$ (4.14)	$-7.44^{+\circ}$ (4.23)	$-6.83^{\#z}$ (3.23)	<0.001
Time					
Task 1	0.51^{*+z} (1.29)	2.15^{*} (0.88)	1.60^{+} (0.80)	2.18^{z} (1.20)	<0.001
Task 2	0.20^{*+z} (1.12)	1.86^{*} (0.67)	1.92^{+} (1.69)	1.40^{z} (1.95)	<0.001
Task 3	-0.28^{*+z} (0.78)	$2.71^{*\circ}$ (1.57)	$1.71^{+\circ}$ (0.91)	1.71^{z} (1.54)	<0.001
Task 4	0.05 (0.82)	0.24 (0.97)	0.70 (2.12)	0.22 (1.39)	0.57
Task 5	0.01^{*+z} (1.00)	1.92^{*} (0.84)	1.94^{+} (0.74)	1.88^{z} (0.98)	<0.001
Global time score	0.50^{*+z} (3.26)	8.65^{*} (2.37)	7.17^{+} (2.42)	6.61^{z} (4.47)	<0.001
Distance					
Task 1	-0.09^{*+} (1.01)	$-1.99^{*\circ\#}$ (1.08)	$-1.05^{+\circ}$ (1.52)	$-0.18^{\#}$ (1.92)	<0.001
Task 2	-0.06^{*z} (0.89)	$-1.27^{*\circ}$ (0.56)	-0.34° (1.69)	-0.98^{z} (0.74)	<0.001
Task 3	-0.02^{*+z} (0.56)	$-2.32^{*\circ}$ (0.99)	$-1.27^{+\circ}$ (2.43)	-2.26^{z} (1.09)	<0.001
Task 5	-0.01^{*} (1.11)	$-0.86^{*\circ\#}$ (0.90)	-0.24° (1.18)	$0.54^{\#}$ (1.86)	0.01
Global distance score	0.17^{*+z} (2.27)	$-5.19^{*\circ\#}$ (2.39)	$-1.30^{+\circ}$ (5.70)	$-1.11^{\#z}$ (3.40)	<0.001
Smart Aging total score	1.22^{*+z} (4.14)	-15.23^{*} (5.86)	-15.18^{+} (6.43)	-13.19^{z} (6.55)	<0.001

Task 1 = Object search; Task 2 = Water flowers while listening to the radio; Task 3 = Make a phone call; Task 4 = Choose the right object; Task 5 = Find the objects. Distance is not reported for Task 4 because it is a 2D task not involving navigation. **Significant differences between HCs and mild AD. +Significant differences between HCs and aMCI. zSignificant differences between HCs and PD-MCI. °Significant differences between mild AD and aMCI. #Significant differences between mild AD and PD-MCI.*

On Task 2, the mild AD patients covered less distance than the aMCI ones ($d = 0.74$) and the HCs ($d = 1.63$). The PD-MCI patients covered less distance than the HCs ($d = 1.12$). No other between-group differences were found ($p > 0.20$).

On Task 3, the mild AD patients again covered less distance than the aMCI ones ($d = 0.56$) and the HCs ($d = 2.86$). In addition, the aMCI ($d = 0.71$) and PD-MCI ($d = 2.58$) groups covered more distance than the HCs. No other between-group differences were found ($p > 0.11$).

On Task 5, the mild AD patients covered more distance than the other three groups: aMCI ($d = 0.03$), PD-MCI ($d = 0.06$), and HCs ($d = 2.87$), which all performed similarly ($p > 0.28$).

The global distance score showed that the mild AD group covered less distance than the aMCI patients ($d = 0.89$), PD-MCI patients ($d = 1.39$), and HCs ($d = 2.30$); the aMCI ($d = 0.34$) and PD-MCI ($d = 0.44$) groups covered more distance than the HCs. No other between-group differences were found ($p = 0.21$).

When comparing HCs vs. the mild AD + aMCI + PD-MCI groups, the AUC of the global distance score was 0.237 (95% confidence interval, 0.140–0.333, $p < 0.001$). When measuring the ROC curve for mild AD vs. HCs + aMCI + PD-MCI, the AUC was 0.829 (95% confidence interval, 0.743–0.914, $p < 0.001$). The global distance score was not a significant predictor of aMCI vs. HC + mild AD + PD-MCI (AUC: 0.479–95% confidence interval, 0.317–0.640, $p = 0.76$), or of PD-MCI vs. HC + mild AD + aMCI (AUC: 0.409–95% confidence interval, 0.282–0.536, $p = 0.23$).

Smart Aging Total Score

As for this score, the HCs outperformed the mild AD ($d = 3.24$), aMCI ($d = 3.03$), and PD-MCI ($d = 2.63$) groups. The three clinical groups did not differ from each other ($p > 0.29$).

When measuring the ROC curve of the Smart Aging total score for HCs vs. mild AD + aMCI + PD-MCI, the AUC was 0.982 (95% confidence interval, 0.959–1.000, $p < 0.001$). On comparison of mild AD vs. HCs + aMCI + PD-MCI, the AUC was found to be 0.304 (95% confidence interval, 0.192–0.417, $p = 0.005$). Comparing aMCI vs. HC + mild AD + PD-MCI gave an AUC of 0.314 (95% confidence level, 0.201–0.427, $p = 0.009$). This index was not a significant predictor of PD-MCI vs. HC + mild AD + aMCI (AUC: 0.421–95% confidence interval, 0.288–0.554, $p = 0.30$).

We then performed separate ROC analyses. For HCs vs. mild AD, the AUC was 0.986 (95% confidence interval, 0.962–1.000, $p < 0.001$). Instead, this index was not a significant predictor of mild AD vs. aMCI (AUC: 0.484–95% confidence interval, 0.315–0.652, $p = 0.85$) and mild AD vs. PD-MCI (AUC: 0.414–95% confidence interval, 0.236–0.592, $p = 0.35$).

Correlations

As shown in **Table 5**, the Smart Aging global accuracy and global distance scores and the Smart Aging total score correlated positively with both MMSE and MoCA performances, whereas negative correlations were found between the global time score and MMSE and MoCA. When considering specific

TABLE 4 | Between-group comparisons of Smart Aging task performances using the Kruskal–Wallis test and then the Mann–Whitney test for significant differences.

Smart Aging tasks	Kruskal–Wallis test			HC vs. Mild AD		HC vs. aMCI		HC vs. PD-MCI		Mild AD vs. aMCI		Mild AD vs. PD-MCI	
	χ^2	df	*p*	*U*	*p*	*U*	*p*	*U*	*p*	*U*	*p*	*U*	*p*
Accuracy													
Task 1	37.34	3	<0.001	41.50	<0.001	57.50	<0.001	35.50	<0.001	–	–	–	–
Task 2	5.38	3	0.15	–	–	–	–	–	–	–	–	–	–
Task 3	34.70	3	<0.001	59.50	<0.001	77.00	<0.001	55.00	<0.001	–	–	–	–
Task 4	35.41	3	<0.001	51.00	<0.001	106.50	<0.001	90.00	0.001	159.00	0.008	76.50	<0.001
Task 5	49.41	3	<0.001	8.00	<0.001	20.00	<0.001	19.50	<0.001	–	–	151.0	0.022
Global accuracy score	44.43	3	<0.001	29.00	<0.001	51.00	<0.001	49.00	<0.001	152.50	0.005	95.00	<0.001
Time													
Task 1	29.87	3	<0.001	63.00	<0.001	94.00	<0.001	49.00	<0.001	–	–	–	–
Task 2	39.40	3	<0.001	33.50	<0.001	49.40	<0.001	67.00	<0.001	–	–	–	–
Task 3	46.42	3	<0.001	10.00	<0.001	28.00	<0.001	34.00	<0.001	161.00	0.009	–	–
Task 4	2.00	3	0.57	–	–	–	–	–	–	–	–	–	–
Task 5	25.20	3	<0.001	77.00	<0.001	71.00	<0.001	59.00	<0.001	–	–	–	–
Global time score	39.70	3	<0.001	24.00	<0.001	27.00	<0.001	49.00	<0.001	–	–	–	–
Distance													
Task 1	24.55	3	<0.001	50.00	<0.001	138.00	<0.015	–	–	171.50	0.016	90.50	0.001
Task 2	22.32	3	<0.001	46.00	<0.001	–	–	71.00	0.001	193.00	0.034	–	–
Task 3	32.75	3	<0.001	39.00	<0.001	85.00	<0.001	41.50	<0.001	202.00	0.032	–	–
Task 5	11.43	3	<0.001	141.00	0.007	–	–	–	–	178.00	0.022	112.00	0.005
Global distance score	39.79	3	<0.001	20.00	<0.001	27.00	<0.001	119.00	0.049	176.00	0.022	69.00	<0.001
Smart Aging total score	44.58	3	<0.001	7.00	<0.001	3.00	<0.001	15.00	<0.001	–	–	–	–

Task 1 = Object search; Task 2 = Water the flowers while listening to the radio; Task 3 = Make a phone call; Task 4 = Choose the right object; Task 5 = Find the objects. Distance is not reported for Task 4 because it is a 2D task not involving navigation. There is no column comparing the aMCI and PD-MCI patients as these two groups showed no significant differences.

TABLE 5 | Correlations of Smart Aging global task and total scores with traditional neuropsychological test performances.

	Accuracy	Time	Distance	Smart Aging total score
MMSE	0.36**	−0.42**	0.36**	0.37**
MoCA	0.27**	−0.63**	0.26**	0.64**
Phonological fluency	0.22*	−0.31**	0.10	0.30**
Semantic fluency	0.59**	−0.49**	0.39**	0.49**
TMT part A	−0.49**	0.50**	−0.33**	−0.39**
TMT part B	−0.48**	0.53**	−0.33**	−0.41**
FCSRT immediate free recall	0.67**	−0.65**	0.44**	0.58**
FCSRT immediate total recall	0.53**	−0.51**	0.46**	0.40**
FCSRT delayed free recall	0.49**	−0.37**	0.24*	0.40**
FCSRT delayed total recall	0.56**	−0.44**	0.41**	0.40**

***$p < 0.01$; *$p < 0.05$.*

neuropsychological tests (fluencies, TMT, and FCSRT), the same trend was found: positive associations with the Smart Aging global accuracy, global distance and total scores, but negative associations with the global time score. The only exception was the lack of an association between phonological fluency and the global distance score.

DISCUSSION

The main aim of the present study was to evaluate the Smart Aging platform as a potential screening tool for differentiating between patients with early neurodegenerative disease and different types and levels of cognitive impairment. To this end, we examined cognitive performances in patients with (a) single-domain amnesic MCI, (b) single-domain executive MCI (PD-MCI), and (c) mild AD, as well as in (d) healthy older adults. Using this tool, we calculated global accuracy, time, and distance scores, each calculated taking into account performances across the five Smart Aging tasks, as well as a composite total score (i.e., Smart Aging total score) calculated as the sum of (or difference between, in the case of reverse scores, i.e., time and distance) the scores recorded on each of the five tasks.

In general, the global accuracy, time and distance scores showed marked differences between the healthy older adults and the mild AD, aMCI, and PD-MCI patients, as well as between the mild AD patients and the other three study groups. We did not find differences between the aMCI and PD-MCI groups. A similar pattern was found when considering these performance indices within each of the five tasks (with the sole exceptions of accuracy on task 2 and time on task 4, in which the groups did not differ). Taken together, these findings seem to suggest that the Smart Aging platform is particularly sensitive as a means of detecting differences between the two opposite ends of the normal/impaired continuum of cognitive functioning in aging, but slightly less sensitive when it comes to distinguishing between the variants that lie along it; this was evident when considering both the global and the single task performances. The lack of between-group differences in accuracy on task 2, together with the fact that all the groups performed it well in comparison with the other four Smart Aging tasks, might indicate that it was comparatively easy. Instead, the lack of differences between the four groups in the time taken to perform task 4 could depend on the fact that this was a 2D task, and as a consequence, timing was not a crucial factor for comparing the groups. The ROC curves and AUC measurements for the performance indices considered in this study showed the platform to have good discriminative capacity in distinguishing healthy participants and mild AD patients from the other groups. Interestingly, we also found that the Smart Aging total score performed well in discriminating aMCI patients from the other three groups. The fact that no similar discriminative ability was found in a previous study using Smart Aging in normal aging participants stratified according to MoCA scores (Bottiroli et al., 2017) highlights the "true" discriminative power of this game platform when used in populations with neurodegenerative diseases.

Rather surprisingly, no differences in Smart Aging scores were found between the patients with different types of MCI, as might instead have been expected, considering that the two conditions reflect the involvement of anatomically and functionally diverse structures, with hippocampal atrophy (Evans et al., 2010) being found in aMCI, and basal ganglia degeneration (McKinlay et al., 2010) in PD-MCI. However, it is important to consider that the present study included only patients with single-domain MCI, which might be characterized by less functional impairment than multiple-domain MCI, as already suggested by others (Aretouli and Brandt, 2010). Future studies, also considering MCI patients with other subtypes of impairment, are needed to better clarify this issue.

In any case, our finding of more pronounced differences in HCs vs. mild AD participants than between aMCI vs. PD-MCI patients is similar to the trend we observed when using traditional neuropsychological screening tests (i.e., MMSE and MoCA), which give a dichotomous index of global cognitive functioning, indicating the presence/absence of cognitive impairment. In addition, the same pattern was found when considering specific neuropsychological tests. In a number of previous studies on this topic, authors devised SG assessment tools for evaluating specific aspects of cognition. For instance, Serino et al. (2017) developed an innovative measure for evaluating executive functions in cognitively normal PD, and Plancher et al. (2012) a test for assessing episodic memory in aMCI and AD, to mention just two. The SG devised in the present study aimed to provide an index of global functioning based on participant performance of several tasks, rather than on single aspects of cognition; the idea was to create a brief screening tool able to assess global cognitive functioning, as traditional neuropsychological screening tests do, but in ecologically relevant and standardized conditions (Rizzo et al., 2004; Saposnik and Levin, 2011). Therefore, the very fact that Smart Aging gave findings similar to those produced by conventional tools argues in favor of its use, as do the important advantages of SG-based assessment tools over traditional approaches. The fact that SGs are more user friendly, ecological, and motivating, as well as less time and resource consuming for the professionals involved are just some of these advantages (Bohil et al., 2011).

In previous research (Bottiroli et al., 2017), we have already shown that the five Smart Aging tasks pertain to different cognitive functions and engage the multi-domain skills involved in performing many real-life activities (Fortin et al., 2003). In particular, we showed that Smart Aging can be easily administered to evaluate memory, executive mechanisms, and visual–spatial processes, i.e., the abilities mainly supporting instrumental activities of daily living (Schmitter-Edgecombe et al., 2009). Hence, SGs like the Smart Aging platform, being devised as assessment tools, have added strengths, namely, they make it possible to assess how cognitive functions act together, as a whole, in a more ecological manner (Logan and Barber, 1985), and they used automated scoring systems (Clauser et al., 2002), which have several benefits for both patients and clinicians.

In Bottiroli et al. (2017), we considered cognitive functioning patterns across the five Smart Aging tasks, analyzing them in comparison with MoCA scores. In the present study, we decided to focus on accuracy, time, and distance across the tasks (i.e., to calculate and consider global accuracy, time and distance scores) as opposed to within each of them singly. There are two main reasons for this. As we already demonstrated (Bottiroli et al., 2017), it is not possible to separate the specific cognitive domains involved in performing individual tasks; instead, it is necessary to consider them acting as a whole, as they do during everyday life activities (Logan and Barber, 1985). In line with this, we indeed found the Smart Aging indices (global and total scores) to show significant correlations not only with MMSE/MoCA but also with all the specific neuropsychological tests considered. To further corroborate this point, it should be noted that considering each index within each single task would not have allowed us to capture the ecological added value of these platforms. In fact, researchers in the SG field usually consider performances in terms of global indices and not task by task (e.g., Raspelli et al., 2011; Cipresso et al., 2014; Ouellet et al., 2018). Second, we believe that each of the analyzed indices provides different information on participant performance. Accuracy is an index usually considered by traditional neuropsychological assessments, such as MMSE and MoCA, whereas time is usually considered in tests measuring attentional control, such as the Trail Making Test (Tombaugh, 2004). SG-based tools like Smart Aging offer additional indices, i.e., the distance covered while performing each activity in the virtual scenario, which may provide deeper insights on how individuals are able to effectively respond to environmental demands. According to the "stealth" approach (Shute et al., 2016), SGs are unique in that they allow performance to be measured by unobtrusively logging user behaviors, such as paths taken to reach destinations. In this context, the mild AD patients showed marked differences, compared with the other groups, in not only accuracy but also distance. The fact that the mild AD patients navigated the virtual scenario differently compared with HCs, and aMCI and PD-MCI patients may indicate that they were less able to be strategic and focused in responding to the task demands. Therefore, these features further support the view that SG assessment tools could provide a context for assessing a broader range of skills and constructs compared with traditional assessment approaches. Similarly, Cipresso et al. (2014) aimed to detect early executive function deficits in PD by considering indices such as task failure, time, strategies, and rule breaks during a VR-based test. Manera et al. (2015) on the other hand, considered time spent playing and number of errors in MCI and AD. Lee et al. (2014) devised the Virtual Radial Arm Maze in order to assess spatial working memory in aMCI and AD patients; they considered the number of times subjects reenter the same arm, the total time spent in the maze, and the total distance covered. Future studies should further explore the opportunities offered by the possibility of logging user behaviors in SG assessment tools. We suggest that the Smart Aging total score already represents a valuable parameter for evaluating individuals' global performances, given that it is based on simultaneous logging of user behaviors in terms of accuracy, time, and distance. After all, it could be that a subject obtains a high score in terms of accuracy, but takes a considerable amount of time, or does not cover an adequate distance within the virtual scenario, both findings that may reflect difficulties in strategic planning of responses to the demands. The Smart Aging total score efficiently discriminated not only HCs from mild AD patients but also aMCI patients from all the other groups, as shown by the ROC analyses. As a consequence, this index could be the one that best reflects participants' global cognition. Larger samples including individuals with/without cognitive impairment in early neurodegenerative disease, and with different types and levels of cognitive impairment, will allow more in-depth exploration of how each of the other indices—accuracy, time, and distance—may reflect different aspects of cognition in this population.

To date, the Smart Aging platform has been validated in a healthy population of older adults (Bottiroli et al., 2017). Cabinio et al. (2020) also tested it in aMCI patients compared with HCs and found significant differences between groups in all the indices considered (i.e., accuracy, time, and Smart Aging total score). In the present study, we confirmed and further extended those findings by also considering early AD and PD-MCI patients. To the best of our knowledge, this is the first study using an SG-based screening tool devised for assessing cognitive functioning in patients with different types and levels of cognitive impairment. Future studies are necessary to evaluate the performance of the Smart Aging platform in the screening of other neurodegenerative conditions. Another future challenge is to develop other scenarios and tasks with different levels of complexity, with a view to using this platform for remote monitoring of patient functioning and for rehabilitation purposes. For instance, this platform could be integrated into portable devices, such as tablets or laptops, and easily administered at patients' own homes. In recent years there has been a growing interest in telemedicine and telerehabilitation as means of providing rehabilitation remotely in chronic conditions, including ones related to aging, such as dementia and other neurodegenerative disorders (Nesbitt et al., 2000; Chirra et al., 2019). In this field, VR and SGs could allow remote delivery of different rehabilitation services in different medical conditions, benefiting patients and also healthcare systems in terms of cost effectiveness and feasibility for large-scale implementations (Zampolini et al., 2008; Peretti et al., 2017).

While we believe the findings we have reported are valuable and interesting, several limitations of the study suggest that they should be interpreted with caution. First, the number of participants ($n = 91$) may limit the generalizability of the results. In particular, the small sample size may explain why we were able to detect differences when they were marked, as in healthy controls and early AD patients, but not when they were more subtle, as when comparing amnesic and executive deficits in different types of MCI. This is, unfortunately, a limitation common to many studies conducted in clinical populations in this field (e.g., Cipresso et al., 2014; Lee et al., 2014; Manera et al., 2015; Tarnanas et al., 2015; Serino et al., 2017; Valladares-Rodriguez et al., 2018, 2019). Hence, a larger validation study should be performed. Second, the sample selection may constitute a further limitation of the present study. Our main aim was to differentiate between persons with different levels and types of cognitive impairment. To this end, we included patients at different points on the AD cognitive spectrum (i.e., mild AD, aMCI). Unfortunately, we did not cover the same range for the PD spectrum, as we included no Parkinson's disease with mild dementia patients. In addition, it would also be useful to consider patients showing comparable levels of global cognitive impairment, but the involvement of different cognitive domains (e.g., single-domain MCI vs. multiple-domain MCI) in order to further test the accuracy of the Smart Aging platform in identifying different types of early cognitive impairment. Third, in order to fully evaluate the full potential of Smart Aging as a screening tool for cognitive functioning, future studies are needed to assess its test–retest reliability and validity. The present study, however, provides initial evidence that an ecological evaluation of cognitive functioning performed with an SG-based assessment tool may offer a means of determining the presence/absence of cognitive impairment in neurodegenerative diseases.

Our study provides useful evidence that SG-based assessment tools may have a role to play in neuropsychological evaluation in the future. In particular, it suggests that the Smart Aging platform is a powerful screening tool for detecting the presence of cognitive deterioration. The many advantages offered by VR environments over traditional cognitive screening tests make this platform an innovative tool for clinicians and researchers interested in exploring cognitive mechanisms. We are now seeing a surge of interest in remote communication technologies as assessment tools (e.g., Geddes et al., 2020; Phillips et al., 2020; Scuteri et al., 2020) and treatment (Zucchella et al., 2018; Bloem et al., 2020; Maggio et al., 2020; Mantovani et al., 2020; Platz and Sandrini, 2020; Stasolla et al., 2020; Bernini et al., 2021) for use in all situations in which it is not possible to guarantee patients' continuity of care. In the context of the ongoing public health emergency, Smart Aging might be considered an innovative approach and valid support, making it possible to monitor cognitive function of individuals with neurodegenerative diseases remotely and safely in their own homes.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Zenodo. http://doi.org/10.5281/zenodo.4422021.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the San Matteo Hospital in Pavia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SBo designed the game, collected the data, carried out the statistical analyses, and wrote the manuscript. SBe assisted in collecting the data, statistical analyses, interpretation of the results, and manuscript writing. CZ and EC designed the game and assisted with the selection of the clinical assessments used in the study. SP and PC supervised the data collection and storage, and assisted in data analyses. DT developed the game. TV, ES, CT, and GS supervised the entire study. All authors did read and approve the final version of the manuscript.

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Remote Ischemic Conditioning With Exercise (RICE)—Rehabilitative Strategy in Patients With Acute Ischemic Stroke: Rationale, Design, and Protocol for a Randomized Controlled Study

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Objective: Exercise rehabilitation is an effective therapy in reducing the disability rate after stroke and should be carried out as early as possible. However, very early rehabilitation exercise exacerbates brain injury and is difficult to conduct in stroke patients due to their weakened and potentially disabled state. It is valuable to explore additional early rehabilitation strategies. Remote Ischemic Conditioning (RIC) is a novel therapy designed to protect vital organs from severe lethal ischemic injury by transient sublethal blood flow to non-vital organs, including the distal limbs, in order to induce endogenous protection. RIC has previously been conducted post-stroke for neuroprotection. However, whether combined early RIC and exercise (RICE) therapy enhances stroke rehabilitation remains to be determined.

Methods: This is a single-center, double-blinded, randomized controlled trial that will enroll acute ischemic stroke patients within 24 h of symptom onset or symptom exacerbation. All enrolled patients will be randomly assigned to either the RICE group (exercise with RIC) or the control group (exercise with sham RIC) at a ratio of 1:1, with 20 patients in each group. Both groups will receive RIC or sham RIC within 24 h after stroke onset or symptom exacerbation, once a day, for 14 days. All patients will begin exercise training on the fourth day, twice a day, for 11 days. Their neurological function [Modified Rankin Scale (mRS) score, National Institutes of Health Stroke Scale (NIHSS) score, Barthel Index, and walking ability], infarct volume (nuclear magnetic resonance, MRI), and adverse events will be evaluated at different time points in their post-stroke care.

Results: The primary outcome is safety, measured by the incidence of any serious RICE-related adverse events and decreased adverse events during hospitalization. The secondary outcome is a favorable prognosis within 90 days (mRS score < 2), determined by improvements in the mRS score, NIHSS score, Barthel Index, walking ability after 90 days, and infarct volume after 12 ± 2 days.

Conclusion: This study is a prospective randomized controlled trial to determine the rehabilitative effect of early RIC followed by exercise on patients with acute ischemic stroke.

Trial Registration: www.chictr.org.cn, identifier: ChiCTR2000041042

Keywords: acute ischemic stroke (AIS), exercise rehabilitation, remote ischemic conditioning (RIC), neuroprotection, intravenous thrombolysis

INTRODUCTION

Stroke is a leading cause of death and disability worldwide (1, 2), with an annual mortality rate of approximately 5.5 million (3). Through the application of evidence-based control measures, the burden of stroke death has declined in many developed countries—in the Western world, death from stroke declined by 30–50% from 1975 to 2005 (4). However, despite an increase in the rate of effective life-saving interventions, such as vascular recanalization by intravenous thrombolysis and intravascular therapy, over 50% of the survivors are left with new disabilities (5). Therefore, stroke remains as a disease of enormous public health importance, and the need for an effective stroke rehabilitation beyond mortality reduction is growing as an essential part of the continuum of stroke care. Acute ischemic stroke, in which an embolic or thrombotic event occludes an artery supplying the brain, accounts for 80% of all strokes (4) and thus represents an unmatched source of devastating disability (6).

Stroke protocols are carried out within hours of the cerebrovascular accident in order to maximize penumbral reperfusion and tissue recovery (7–9). Analogously, rehabilitation techniques, which can also enhance reperfusion and are an indispensable component of promoting the functional recovery of stroke patients, should be carried out as early as possible. Numerous clinical studies have demonstrated that exercise enhances motor function after a cerebrovascular accident (10). Therefore, national guidelines for improving stroke outcomes recommend early exercise rehabilitation (11). However, A Very Early Rehabilitation Trial (AVERT) demonstrated that very early mobilization (<24 h) after stroke actually exacerbated brain injury and reduced rates of favorable prognoses measured at 3 months (12, 13). Similar results were also found in our clinical study (14). Furthermore, patients at the early stages of recovery from stroke had unstable body conditions and poor endurance and found it difficult to adapt to exercise training, which limited the promotion of early exercise rehabilitation after stroke (15). Moreover, since patients differ in the nature of their cerebrovascular accidents and resulting disabilities; it is difficult to recommend and implement standardized rehabilitation protocols that are both safe and effective for all stroke patients. These findings point to a gap in the continuum of stroke care at its early recovery stages: theoretically, early exercise intervention is beneficial to stroke victims, but the practicality of exercise rehabilitation limits its clinical applications. This gap calls for exploration of different novel, simple, and feasible rehabilitation models to be implemented in the early stages of recovery—when exercise poses greater harm than good.

Remote ischemic conditioning (RIC) is a novel therapy that was initially developed in the realm of cardioprotection after myocardial infarction, where it was shown to reduce infarct size, minimize ischemia/reperfusion injury, and prevent the onset of heart failure (16). More recently, it has emerged for victims of cerebrovascular accidents due to its non-invasive, easy-to-administer, and low-cost nature (17). RIC involves the induction of transient sublethal ischemia *via* controlled blood flow restriction to the distal limbs, which induces endogenous protective effects against severe lethal ischemic injury to vital organs of the body, such as the heart, brain, and kidney (18). RIC has been shown to function by similar biochemical mechanisms as physical exercise, such as through the promotion of neurogenesis and angiogenesis, which are essential for post-stroke rehabilitation (19, 20).

Studies have demonstrated RIC to be an effective prophylactic therapy for acute ischemic stroke in patients with symptomatic intracranial arterial stenosis (SIAS) (21) and during carotid artery stent placements (22). In post-stroke therapy, RIC has been shown to enhance cognitive function, particularly in the domains linked to visuospatial, executive functioning, and attention (23). Furthermore, long-term application of RIC appears to have the same benefits to the human body as exercise (24) and has been shown to improve walking speed and to reduce neuromuscular fatigue in chronic stroke survivors (25). These studies and others suggest that the use of RIC in stroke patients enables a similar spectrum of benefits as exercise therapy without many of its associated drawbacks. In contrast to physical activity, RIC is administered to the patient passively and depends less on his or her motivation, level of physical activity, and degree of post-stroke disability, especially at the early stage. Indeed, RIC is performed through the basic application of a blood pressure cuff to the arm for sessions measured in minutes, and is thus feasible for patients irrespective of their clinical picture (26). However, research on RIC is in its infancy, and it is still unclear whether it can be used as a unique component, or eventually as the sole therapy, of early rehabilitation to improve neurological function after stroke.

In this study, we will evaluate the safety and feasibility of RIC with exercise (RICE) as a novel rehabilitation strategy in patients with acute ischemic stroke. RIC, a simple procedure, will be implemented as early as possible to initiate rehabilitation closer to the onset of the ischemic event and into the time frame in which early exercise rehabilitation was shown to exacerbate brain injury. It will be combined with exercise, implemented at the time at which it has been shown to promote functional recovery and improve long-term functional prognosis. Clinical improvement with very early RIC would highlight RIC as an effective rehabilitation method that could bridge the gap in the continuum of very early post-stroke care. Marked improvement in the dual therapy group could also point to an additive or synergistic effect of exercise and RIC therapy, namely, the RICE.

METHODS

Study Design

This is a single-center, double-blinded, randomized controlled trial that will enroll acute ischemic stroke patients within 24 h of the ischemic event or symptom exacerbation. All participants will be informed about the clinical study and the requirement to give informed consent. The study protocol and informed consent were approved by the regional ethics committee and have been registered with the Clinicaltrials.gov (ChiCTR2000041042).

After receiving informed consent, all enrolled patients will be randomly assigned to either the intervention group (RIC with exercise rehabilitation) or the control group (sham RIC with exercise rehabilitation) at a ratio of 1:1, with 20 patients in each group. Within 24 h of the ischemic event or symptom exacerbation, the groups will start either RIC or sham RIC in 45-min sessions, once a day, for 14 days. All patients will begin exercise rehabilitation training 4 days after the ischemic stroke event in 30-min sessions, twice a day, for 11 days. Brain imaging with MRI will be performed on the day of the stroke for a baseline and again at 12 days. Evidence of stroke severity and disability will be evaluated using the National Institutes of Health Stroke Scale (NIHSS) score and the Barthel Index, which will be administered by trained investigators blinded to the treatment assignment on the day of the stroke for a baseline and at 1, 3, 7, and 90 days after enrollment. Furthermore, the Modified Rankin Scale (mRS) will be administered, and walking ability will be assessed at 90 days.

Patient Population

Participants will be recruited from the hospital wards. The inclusion criteria for recruitment are as follows: (1) age: 18–80 years old; (2) patients with confirmed acute ischemic stroke (mRS $\leq$ 2 and NIHSS score: 6–16), including those who received intravenous thrombolysis or mechanical embolectomy; (3) randomized grouping $\leq$24 h of stroke onset or symptom exacerbation; and (4) written informed consent provided by the participant or legally authorized representative. The exclusion criteria for recruitment include the following: (1) contraindications for ischemic conditioning (e.g., severe soft tissue injury, fracture, and peripheral vascular disease in both upper limbs); (2) unstable vital signs (e.g., systolic blood pressure $<$120 or $>$220 mmHg, heart rate $<$40 beats/min or $>$100 beats/min, percutaneous oxygen saturation $\leq$92%, body temperature $\geq$38.5°C); (3) lower limb fracture(s) or other factors that would prevent exercise training completion; (4) history of poor compliance; (5) life expectancy $\leq$1 year; (6) severe hepatic, pulmonary, and/or renal dysfunction; (7) coagulation dysfunction or active bleeding; (8) combined acute coronary syndrome or severe arrhythmia; (9) pregnant or lactating patients; and/or (10) participation in another clinical trial currently or within 30 days before study inclusion.

Randomization

All enrolled patients will be randomly assigned to either the intervention group or the control group at a ratio of 1:1. Randomized sequence column orders will be made according to a predefined table generated by a computer program. The random sequence will be hidden in an enclosed opaque envelope. After the baseline patient data are collected by a specialized member of the research personnel, subjects will be randomly assigned to either the intervention group or the control group.

Interventions

RIC will be performed by placing an electronic tourniquet around both arms within 24 h of stroke symptom onset or symptom exacerbation. Participants in the intervention group will undergo five cycles of cuff inflation to 200 mmHg for 5 min, followed by deflation for 5 min. This will be repeated once daily for the subsequent 14 days. Patients in the sham RIC group will receive the same procedure as the treatment group, but the maximal inflation pressure will be set to only 60 mmHg.

All patients will receive daily out-of-bed exercise training twice a day for 30 min, starting from 4 days after symptom onset, for 11 days. Out-of-bed mobilization, as described previously by us (14), will include sitting, standing, and walking, which will be performed with or without assistance. While no special equipment will be used, mobilization will permit the use of standing bed and wheelchair when necessary. All mobilization protocols will be adjusted to each individual patient's tolerance, needs, and abilities and will be delivered by professional therapists or nurses. The frequency, dose, and content of mobilization will vary according to the individual patient's physical ability and will be recorded in detail by therapists or nurses. The dose of exercise will be monitored by a specially assigned staff to ensure good compliance for this study. Physicians will be asked to evaluate patients with deteriorating conditions during the exercise and to postpone mobilization when necessary (14). Patients in both groups will receive standard stroke treatment according to the guidelines, including thrombolysis, anti-platelet aggregation, and lipid reduction (**Figure 1**).

Early RIC combined with follow-up exercise training is a novel early rehabilitation model for acute stroke patients; therefore, we set the duration of RIC and exercise (RICE) rehabilitation to be 14 days according to the protocol of "A Very Early Rehabilitation Trial" (AVERT) (13), the well-known and evidence-based clinical study on early rehabilitation of stroke, and our previous study (14).

Outcomes

Primary Outcome

The primary outcome is safety, including any serious RIC-related and exercise-related adverse events. Other safety outcomes include clinical deterioration, recurrence of stroke, fall, angina, myocardial infarction, deep venous thrombosis, pulmonary embolism, pressure sore, chest infection, urinary tract infection, and depression during hospitalization. All adverse events will be determined independently by specially trained members of the

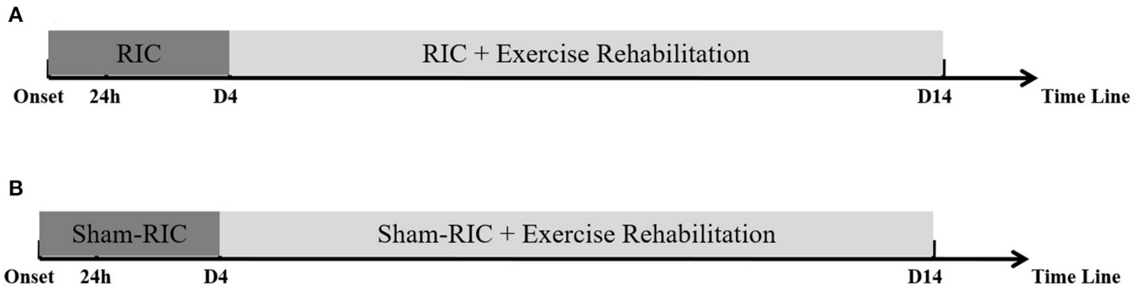

FIGURE 1 | Procedure timeline for experimental protocol. **(A)** RICE group (RIC with exercise); **(B)** Control group (Sham-RIC with exercise).

same research group who will be blinded to the randomization. Source data will be reviewed if necessary.

Secondary Outcomes

There will be two classes of secondary outcomes. (1) Clinical efficacy as determined by the mRS (mRS 0–2 was defined as a favorable prognosis and mRS 3–6 points as a poor prognosis), NIHSS score, Barthel scale, and the proportion of patients achieving independent walking after 90 days (Holden functional classification of walking). (2) Brain infarct volume as determined by MRI diffusion-weighted imaging technique, with the lesion profile plotted at each individual level by an image tool on the workstation to calculate the area. The levels will be multiplied by the thickness of each level and summed to calculate the infarct volume. The calculations will be performed by personnel blinded to clinical data and randomization at baseline and at day 12 ± 2.

Sample Size Estimation

This is a phase 1 safety and feasibility trial. There are no data available for reference because no clinical study of RIC and exercise therapy in patients with confirmed acute ischemic stroke (mRS ≤ 2, NIHSS score 6–16) has yet been completed. Hertzog (27) has suggested that 10–20 patients in each group are sufficient to assess the feasibility of a pilot study, while Dobkin (28) has shown that 15 patients in each group are usually enough to decide whether a larger multicenter trial should be conducted. A similar number of samples was selected in two other related protocols (29) (Lv et al., Frontiers in Neurology in press). We therefore set our recruitment goal to 20 patients per group in the present study. The results of this study will be used to determine the safety and feasibility of RICE and be used to estimate the sample size and perform power calculations necessary to plan the phase 2 trials.

Statistical Analysis

All statistical analyses will be performed using the statistical software SAS (version 9.1.3; SAS Institute, Cary, NC). Outcome event analyses will be based on the intention-to-treat (ITT) principle, including all randomly enrolled subjects. Subjects' baseline categorical variables will be recorded in percentages (%), and continuous variables will be recorded as means and standard deviations or medians and interquartile ranges. The comparison of baseline parameters of the study subjects will be performed with the Pearson chi-square test and either the *t*-test or the Wilcoxon rank sum test for the categorical and continuous variables, respectively.

The distribution difference of the 90-day mRS scores between the two groups will be evaluated using the common ratio. The public odds ratio of the mRS scores on the 90th day will be evaluated by the sequential logistic regression model. The ratios between the mRS categories (0–2 and 3–6) and adverse events will be estimated with the improved Poisson regression. Infarct volume and β coefficient of the NIHSS score will be estimated by multiple linear regressions. Efficacy assessment will be adjusted based on age, gender, NIHSS baseline score, baseline condition, stroke subtype, intravenous alteplase treatment, and mechanical thrombectomy. The homogeneous dominance ratio of each subgroup will be analyzed *via* the Breslow–Day test to analyze the functional independence of the subgroup for 90 days. The significance level will be set at 0.05 for all tests.

DISCUSSION

Exercise rehabilitation has been confirmed to be one of the most effective approaches to improving prognosis and preventing lasting complications after stroke (30). It is an indispensable component in the organizational management of cerebrovascular diseases (31). The latest domestic and international guidelines for stroke rehabilitation recommend early rehabilitation for patients with acute stroke (11). However, the optimal model of early rehabilitation is still controversial. Recent studies have confirmed that very early exercise rehabilitation exacerbates brain injury (12). The promotion of very early exercise rehabilitation is also limited in actual clinical practice for many reasons, such as unstable vital signs, low cardiorespiratory fitness, and poor muscle strength and muscle power in stroke patients (15).

Ischemic conditioning is an approach that provides neuroprotection (32) and has been observed to be efficacious in promoting rehabilitation for patients with global cerebral ischemia (33). The use of ischemic conditioning has been clinically demonstrated through hypobaric and normobaric hypoxia (34, 35). RIC has also been used widely in other contexts (36), including reduction of myocardial injury after ischemia in large animal models and human trials (37). In studies of cerebral pathologies, RIC has improved cognition in patients with subcortical ischemic vascular dementia (38) and conferred neuroprotective effects after acute ischemic stroke (39). It offered neuroprotection through enhanced cerebral perfusion, cerebral collateral formation, and tolerance of cerebral ischemia (40, 41). Furthermore, studies have shown that long-term RIC training can reduce nerve injury (42), promote nerve remodeling and angiogenesis (25), and promote the motor function of paralyzed limbs (43, 44). Chronic and repetitive RIC has been applied to clinical trials and is expected to exert its protective role against cerebral ischemia and repeated stroke in a long-term fashion (40). It has also been demonstrated to improve performance in sports medicine, akin to the physiological improvement that is appreciated in routine exercise training (24). Some underlying mechanisms of RIC and exercise have been evidenced to overlap—both therapies demonstrate increased expression of heat shock proteins, enhanced involvement of the nitric oxide (NO) pathway, modification of ATP-sensitive potassium (K_{ATP}) channels' functionality, enhanced antioxidant capacity, induction of autophagy, involvement of the opioid system, and regulation of the immune and inflammatory system (24). Together, these processes enhance neurogenesis, angiogenesis, and defense against oxidative stress in the brain after an ischemic event.

RIC and exercise have similar temporal windows in which they induce benefits in the rehabilitative stage of stroke recovery. They also have similar effects and mechanisms in performance improvement. These overlapping biochemical and clinical characteristics appoint RIC as a suitable candidate to fill the "gap" that is seen in very early rehabilitation, of which physical exercise is currently the sole therapy. Using RIC for the very early time frame would avoid the deleterious impact of exercise while potentially reaping RIC's unique benefits including ischemia and hypoxia tolerance. In other words, the combination of novel early RIC training followed by exercise rehabilitation, which is known to be effective, could form a new type of early stroke rehabilitation model. The model would enable the mechanisms of exercise therapy known to be beneficial to stroke patients, such as increased neurogenesis and angiogenesis in the brain, to be initiated earlier than is normally feasible. The subsequent application of traditional exercise therapy would reinforce these processes and lead to greater clinical progress and better prognosis after several months. This novel rehabilitation strategy will be applied for the investigation of functional recovery promotion, disability reduction, and prognosis improvement in patients with ischemic stroke.

The NIHSS score has been demonstrated to be a good prognostic indicator of stroke outcome (45). NIHSS scores of $\leq$6 indicate a high likelihood of good prognosis; scores of 7–10 and 11–15 indicate good prognosis rates of 46 and 23%, respectively (45); and scores of $\geq$16 suggests a poor prognosis and a high possibility of death or severe disability (46). Patients with disabilities after stroke mostly have NIHSS scores >6, which was set as the lower bound for our inclusion criteria in this study. Moreover, it has been reported by previous studies that it is difficult for patients with severe stroke-induced disability (NIHSS score $\geq$16) to perform early exercise rehabilitation due to various reasons, such as severe symptoms, unstable conditions, and intolerance of early out-of-bed rehabilitation treatment (15). Therefore, patients with NIHSS scores >16 will be excluded from this study. To summarize, moderate acute ischemic stroke patients with NIHSS scores of 6–16 will be included in this study, as these patients will likely be able to participate in the given tasks for rehabilitation and subsequently have a favorable prognosis.

RIC is a non-invasive, feasible, and promising rehabilitative method for patients recovering from ischemic stroke. It has been demonstrated that post-stroke RIC training can be carried out safely within 6–24 h of acute ischemic stroke attack and induce a significant neuroprotective and neurorehabilitative effect (39). Hence, RIC training will be initiated within 24 h after stroke onset in this study.

Very early exercise rehabilitation with physical exercise after stroke may aggravate brain injury and reduce the rate of good prognosis at 3 months post-cerebrovascular event (47). Previous expert consensus also recommends that exercise rehabilitation treatment be conducted within 48–72 h after stroke, after which patients have regained stable vital signs and no longer have acutely deteriorating neurological symptoms (12). Therefore, in this study, out-of-bed exercise rehabilitation will be carried out 72 h after stroke attack, that is, on the fourth day of stroke. Early RIC combined with follow-up exercise training is a novel early rehabilitation model for acute stroke patients; therefore, we set the duration of RIC and exercise rehabilitation to be 14 days according to the protocol of "A Very Early Rehabilitation Trial" (AVERT) (48), the most well-known and evidence-based clinical study on early rehabilitation of stroke.

In this way, our study will employ two treatments that are known to be effective in stroke rehabilitation at their respective temporal windows that are known to maximize benefits and reduce adverse events. This temporal optimization will enable stroke patients to benefit from the individual advantage of RIC and exercise rehabilitation and perhaps from a temporal and synergistic role of the two therapies.

There are some limitations to this study. First, as previous research is lacking, the sample size was calculated based on previous relevant literature (27, 28). Additionally, the patient population is highly targeted in this study: we have limited the inclusion criteria to patients with moderate acute cerebral infarction and moderate-to-high disability rate (NIHSS scores 6–16). Therefore, the results may not be accurately generalizable to all patients with acute cerebral infarction. Future directions should seek to apply this modem of post-stroke therapy to patients with infarcts varying in size and severity as well as diverse degrees of post-stroke disability as determined by the NIHSS score.

PERSPECTIVE AND PROSPECTIVE

The aim of this study is to clarify the safety and efficacy of early RIC combined with follow-up exercise training as rehabilitation for patients with moderate acute cerebral infarction. The experimental results will reflect a new strategy for stroke rehabilitation that can improve the clinical prognosis of patients with acute cerebral infarction.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee of Beijing Luhe Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZH, YT, WZ, HL, MW, and XL prepared the manuscript. ZH, ZC, QD, QW, XJ, YD, and XG designed the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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