LONG TERM DISABILITY IN NEUROLOGICAL DISEASE: A REHABILITATION PERSPECTIVE

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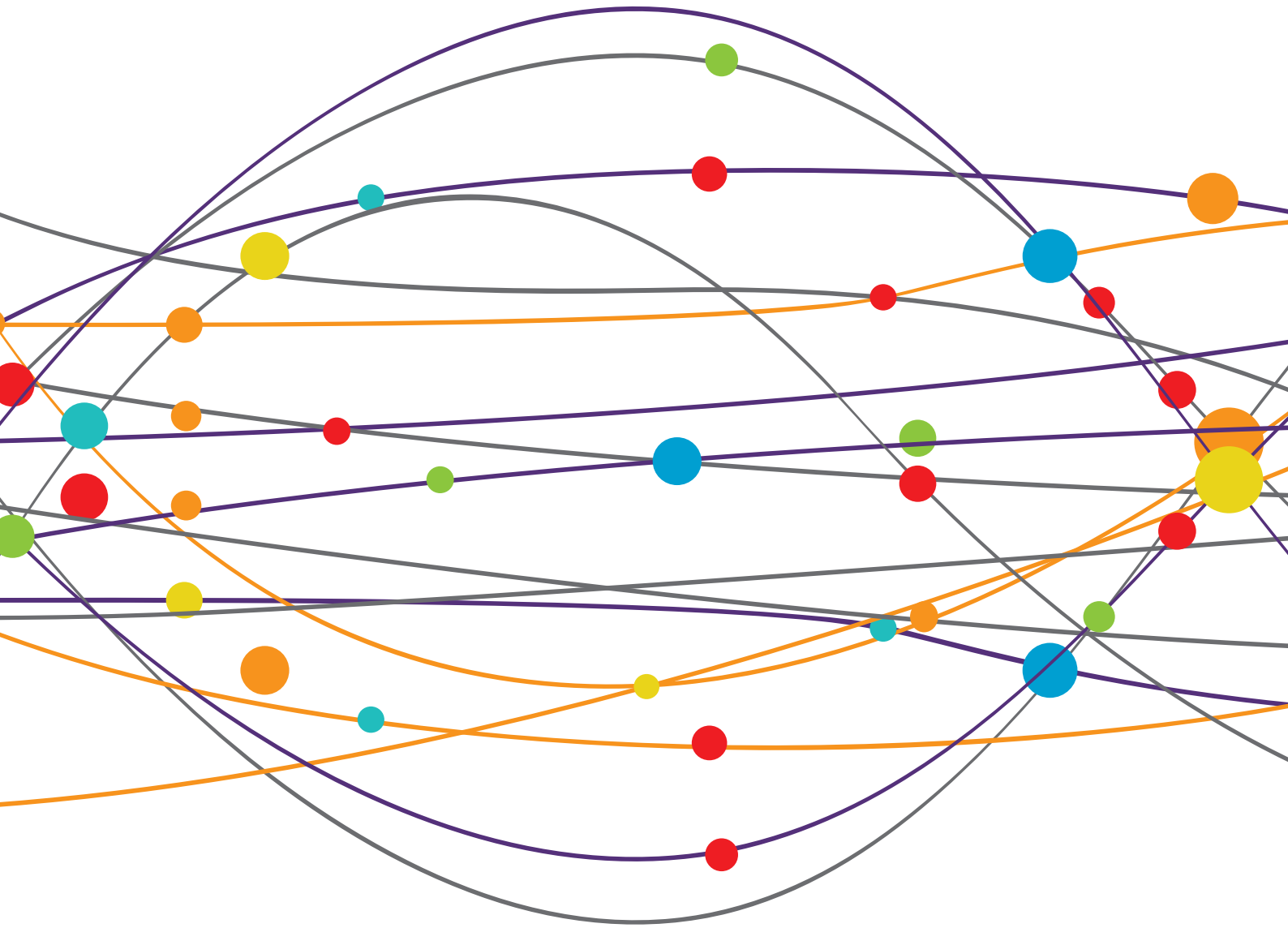

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LONG TERM DISABILITY IN NEUROLOGICAL DISEASE: A REHABILITATION PERSPECTIVE

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Table of Contents

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Editorial: Long term disability in neurological disease: A rehabilitation perspective

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Editorial on the Research Topic
Long term disability in neurological disease: A rehabilitation perspective

Neurological diseases are often associated with a significant burden of disability, which can severely affect different aspects of patients' autonomy, notably motor and cognitive impairments. These impairments can arise in a progressive and long-term manner, as expected in neurodegenerative diseases and after acute conditions such as strokes, traumatic brain injuries, or spinal cord injuries. The clinical and social impact of these conditions is critical.

As outlined in the recent guidelines, stroke represents the second cause of mortality worldwide, drawing attention to improving the acute care of disease successfully, leading to a significant reduction in mortality (1).

However, due to this central focus, the long-term effects have been under-explored, leaving strokes a significant cause of disability. Even if strokes are generally considered and managed as a transient condition, most stroke survivors suffer from persistent critical limitations in the activities of daily living. 50% of stroke survivors report unmet needs such as incontinence, emotional problems, mobility, pain, and speaking problems. However, most of them do not receive a rehabilitative follow-up or other therapeutic approaches (2).

It is known that recovery is a complex process, which probably implies a combination of spontaneous and learning-dependent processes and adaptive behavior. Current evidence suggests that several mechanisms are involved, including restoring the functionality of damaged neural tissue (e.g., restitution), reorganization of spared neural pathways (e.g., substitution), improvement of impaired skills in the activities of daily living (e.g., compensation) (3) and last but not least, the recovery of cognitive skills.

Considering these aspects, there is cumulative evidence that interdisciplinary rehabilitation treatment improves the outcomes of stroke survivors when applied in acute and subacute phases after the event (4, 5). Indeed, the "formal" post-stroke motor rehabilitation usually ends 3–4 months after the event, based on the fact that motor and functional recovery reaches a debated plateau 3–6 months after stroke (6). However, current evidence supports the hypothesis that cognitive (Wang et al.; Rohrbach et al.) and motor skills may improve at any time after stroke, as well as in other pathologies such as other conditions that might critically affect the central nervous system (Cammisuli et al.; Elena et al.; Calafiore et al.) or muscular inherited muscular diseases (Alvarez et al.).

Brain plasticity phenomena are also widely involved in the chronic phase, albeit to a lesser extent than in the subacute phase. They lead to a modification of the cortical network, which can, in some cases, lead to clinically significant functional improvements. We know that rehabilitation may promote favorable neural plasticity (7, 8); notably, these processes may be reinforced by the use of innovative techniques and devices (Bressi et al.; Li et al.; Caimmi et al.; Peng et al.). In addition, the use of innovative orthoses and prostheses can reduce the impact that loss of function or organ damage has on the patient's abilities, improving their emotional state and consequently increasing social engagement (Pundik et al.).

However, future studies should focus on the development of a theoretical model to better understand the neurophysiological aspects of CNS recovery, as suggested by an interesting study protocol proposed by Simis et al.

In chronic stroke, modifications and possible modulations are linked not only to the brain and brain plasticity but also to the peripheral skeletal muscle in an interdependent way. Azzollini et al. discuss this topic in their review.

In addition, long-term unmet needs are observed in many domains, including social reintegration, health-related quality of life, maintenance of activity, and self-efficacy. From this point of view, stroke should be considered a chronic disease, and rehabilitation processes should be designed considering also these aspects. In this regard, rehabilitation services must have proper patient management in the form of a dedicated clinical pathway considering each individual's many different factors, including clinical, social, and economic aspects. In this line, identifying the target patient subgroup is the new challenge of translational medicine and, in particular, the rehabilitation that has high costs and is resource consuming. Studies that aim to identify prognostic factors, not only for conventional therapy but even for technologically assisted training, are essential to plan future effective rehabilitation plans (Wu et al.; Lee and Shin) or to identify subjects unable to return to work after a CNS lesion (Iosa et al.).

Additionally, some recent technology innovations may help patients' follow-up adherence. These aspects should be considered where the patient is unable to reach rehabilitation facilities or in low-income countries where outcomes are less favorable, as suggested by Contrada et al..

Technology is not the only answer to meeting patients' needs in a long-term perspective.

Current literature suggests the positive impact of peer support programs (9), and Baumgartner-Dupuits et al. proposed a study protocol to clarify these aspects.

In another intriguing study, Grimm et al. explored the potential impact of biographical music and biographical language on physiological responses and the endocrine system of people with disorders of consciousness.

From what has been briefly set out, a picture emerges in which an initial acute phase must necessarily be followed by a phase involving long-term interventions. In this phase, patient care must include an intervention in which the various professional figures together with territorial medical services must tune in and integrate to allow the patient the best possible quality of life.

Author contributions

AB: conception and design of the paper and first draft of the manuscript. GM and GS: conception and design of the paper and manuscript and revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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BRIEF RESEARCH REPORT
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Artificial Neural Network Analyzing Wearable Device Gait Data for Identifying Patients With Stroke Unable to Return to Work

Marco Iosa[1,2]*, *Edda Capodaglio*[3], *Silvia Pelà*[3], *Benedetta Persechino*[4], *Giovanni Morone*[2], *Gabriella Antonucci*[1,2], *Stefano Paolucci*[2] and *Monica Panigazzi*[3,5]

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A potential dramatic effect of long-term disability due to stroke is the inability to return to work. An accurate prognosis and the identification of the parameters inflating the possibility of return to work after neurorehabilitation are crucial. Many factors may influence it, such as mobility and, in particular, walking ability. In this pilot study, two emerging technologies have been combined with the aim of developing a prognostic tool for identifying patients able to return to work: a wearable inertial measurement unit for gait analysis and an artificial neural network (ANN). Compared with more conventional statistics, the ANN showed a higher accuracy in identifying patients with respect to healthy subjects (90.9 vs. 75.8%) and also in identifying the subjects unable to return to work (93.9 vs. 81.8%). In this last analysis, the duration of double support phase resulted the most important input of the ANN. The potentiality of the ANN, developed also in other fields such as marketing on social networks, could allow a powerful support for clinicians that today should manage a large amount of instrumentally recorded parameters in patients with stroke.

Keywords: neurorehabiliation, long-term disability, occupational medicine, psychometrics, walking, artificial intelligence, machine learning

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INTRODUCTION

In a complex and fast-changing environment in which a growing amount of data is everyday collected, there is a need to find patterns and connections to make better decisions at every turn. Artificial neural networks (ANNs) are increasingly being used with these purposes. An artificial neural network is a machine learning algorithm inspired on the brain biological neural networks, with an artificial intelligence inspired by the human one (1). Among all the artificial intelligences, ANNs are a type of model for machine learning widely used, for example, in social networks to define customer profiles and discover their preferences, hence optimizing marketing campaigns.

In the scientific healthcare field, there is a growing amount of electronic data, deriving from sensors and electronic clinical sheets, that may favor a medical outcome analysis, for example, for predicting the length of a hospital stay or the risk of fall associated to a walking patient. However, given the wide amount of data, there is a need for automatic analysis that could have the

ability to discover complex relationships in the data and generate accurate performing predictive models. In this field, ANNs are becoming relatively competitive to prognostic regressions and other conventional statistical models (2).

An artificial neural network is a non-linear data computational model consisting of input and output layers plus one or more hidden layers. The connections between neurons in each layer have associated weights, which are iteratively adjusted by the training algorithm to minimize error and provide accurate predictions (3).

For patients with stroke, artificial neural networks have been used as models for screening (4), risk identification (5), or as a prognostic tool (6). Lee and colleagues were pioneers in using an ANN with an accuracy of about 80% in identifying movement disorders from spatial parameters obtained by video analysis of gait (7). Scheffer and Cloete had the intuition of the potentialities of combining two emerging technologies: an artificial neural network and inertial motion capture (8). In their study, the ANN was able to correctly classify patients with stroke in 99.4% of cases with respect to healthy subjects starting from the data of an inertial measurement unit (IMU). So, they suggested the usability of the ANN and IMU for planning gait rehabilitation therapy and monitoring its outcomes in stroke. For years, gait analysis was performed using complex stereophotogrammetric systems requiring large economic and temporal resources, whereas now there is a wide diffusion of more simply (despite less informative) wireless inertial sensors that allow to compute the spatiotemporal parameters of gait and trunk kinematics during walking (9–11). Among the information provided by IMUs, the upright gait stability has been associated to the risk of fall (12), and walking speed resulted an important prognostic factor of functional recovery (13), community mobility, and quality of life in patients with stroke (14).

We have recently highlighted that in subjects in which stroke occurred in their working age, the long-term disability affects the possibility to return to work (RTW) and, in turn, the quality of life after discharge from a rehabilitation hospital (15). In fact, psychological and economic problems can be related to the impossibility to return to work after stroke, as it occurs in about 80% of workers suddenly impaired by stroke (16). This is a dramatic percentage, especially considering that the mean age of stroke onset is decreasing, and, in Western countries, the retirement age is increasing, leading to an increment of the incidence of stroke during the working age (17). The return to work may depend on many several cognitive and motor factors, strictly intertwined with each other; among these is the independence in daily living activities including walking (15).

The aim of this pilot study was to use an ANN for analyzing the data of a wireless inertial system for gait assessment to evaluate the possibility to return to work after stroke.

MATERIALS AND METHODS

Participants

Thirty-three subjects were enrolled in this study, all of them in working age (between 18 and 66 years), 17 healthy subjects and 16 patients with a diagnosis of stroke in chronic phase (7 with left hemiparesis and 9 with right hemiparesis). Exclusion criteria included cognitive impairments with Mini-Mental State Examination < 24, severe unilateral spatial neglect, and severe comorbidities. The age of patients ranged between 21 and 66 years old (mean age: 54.6 ± 13.7 years), whereas that of healthy subjects ranged between 22 and 63 years old (mean age: 45.7 ± 13.4 years, not significantly different from that of patients, $p > 0.05$). Ten patients did not return to work at the moment of the evaluation. Independent Local Ethical Committee approved the study, and all the participants signed the informed consent.

Gait Analysis

Gait data were acquired by means of a wearable inertial measurement unit endowed with a triaxial accelerometer, a triaxial gyroscope, and a magnetometer (G-Walk, BTS, Padua). The device was placed at the level of the sacral vertebras S1–S2 embedded into an ergonomic waist belt. This wearable IMU was connected to a portable computer via Bluetooth. The sample frequency of recording was 100 Hz. Subjects were asked to walk along a linear pathway of 10 m from a starting to a stop line. During walking, the IMU recorded lower trunk accelerations and angular velocities (respectively, along and around the anterior–posterior, laterolateral, and craniocaudal body axis), estimating from these signals the gait temporal and angular parameters. Given the information about the path length, the IMU software also computed the walking speed and step lengths (18). The temporal variables extracted by the IMU and acquired by the ANN were as follows: the cadence of steps, the stance, the swing, the single support, and the first and second double support gait phases. The trunk kinematics variables extracted by the IMU and acquired by the ANN were as follows: the range of motion (ROM) of the trunk tilt, obliquity, and rotation (also definable as trunk rotations around the latero-lateral, antero-posterior, and cranio-caudal axes, respectively, or as pitch, roll, and yaw). Despite from a theoretical point of view right and left strides are equal in a reliable walk, the measured parameters often do not, so for all the above parameters, but cadence, we computed the absolute mean value between left and right strides and their differences.

Artificial Neural Network

We designed an artificial neural network working on the basis of a multilayer perceptron procedure. The ANN was formed by four layers: the input layer from which the above listed 17 variables extracted by the IMU software were entered, 2 hidden layers of 5 elements each, and a final output layer (**Figure 1**). The architecture of our ANN was that of a feedforward neural network (FFNN), with data moving in only one direction, from the input nodes through the two hidden layers to the output nodes (3). The activation functions for all units in the hidden layers and that for the output layer were both a hyperbolic tangent. The chosen computational procedure was based on an online training (details: initial learning = 1.2; lower learning = 0.001, learning epochs = 10, momentum = 0.9 interval center = 0, interval offset = ± 0.5, memsize = 1,000, steps without error = 1, error change = 0.0001, error ratio = 0.001). The ANN was

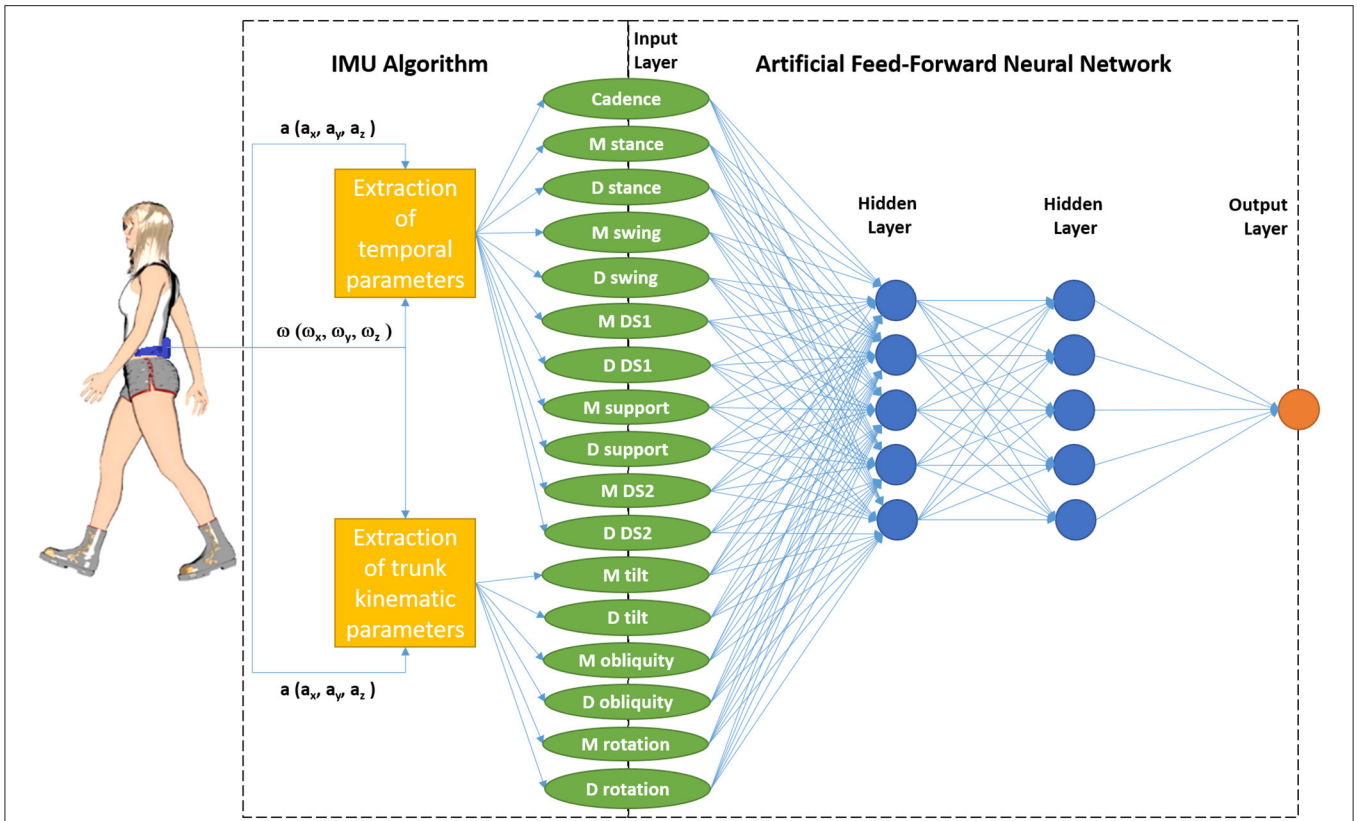

FIGURE 1 | Schematic representation of the combination of Inertial Measurement Unit (IMU, measuring triaxial acceleration a, and triaxial angular speed ω) and its software with the feedforward neural network formed by an input layer (M stands for mean values between right and left strides, and D for their difference, DS 1 and 2 for first and second double support phases; support is the phase with only one foot on the ground), two hidden layers, and an output layer (which represents the identification of patients in the first analysis and the identification of patients who did not return to work in the second analysis).

developed using the IBM SPSS Neural Networks module of IBM SPSS Statistic, version 23.

Firstly, we tested this ANN on its capacity to identify patients with respect to age-matched healthy subjects. Then, we tested the ANN on the identification of patients who did not return to work on the entire sample (patients and healthy subjects) and finally on their identification only among patients. It means that the dependent variable was categorical, and the ANN worked to classify cases into the best category based on the input predictors. We choose to test an ANN standing alone, without the need of demographical or clinical conditions of subjects used as covariates; so our ANN worked without covariates, and all the inputs were possible predictor factors. Because the computation of speed and step lengths by the IMU software needed the manual input about the definition of the walked distance, these parameters were not taken into account, since we were basing our ANN only on parameters automatically estimated by the wearable device.

Statistical Analysis

Data were reported in terms of means and standard deviations for the three groups of subjects (healthy subjects, patients who returned, and those who did not return to work). A preliminary analysis of variance was performed, followed by Tukey's *post-hoc* analysis, to highlight gait parameters significantly different among the three groups.

The performances of our feedforward neural network (FFNN) were compared with those of a forward stepwise logistic regression (FSLR), typically used for identifying the prognostic factors of patients with stroke. The normalized importance of input factors evaluated by the FFNN (with 100% as the most possible value) was compared with the *p*-value of those input factors evaluated by logistic regression (with $p < 0.05$ for a statistically significant result: some variables could enter into the model of logistic regression despite a value of $p > 0.05$ because, if removed, the effect was <0.05).

The performances were tested in terms of accuracy (the percentages of correct identifications, given by the sum of true positive and true negative divided by the sample size), sensitivity (the percentages of correct identifications of positive cases: subjects correctly identified as cases on the total number of cases), and specificity (the percentage of correct identification of true negatives: subjects correctly identified as non-case on the total number of non-cases). In the first analysis (identification of patients), we defined the patients as cases and the healthy subjects as non-cases. In the second analysis (identification of not

working subjects), all healthy subjects and patients who returned to work were non-cases, whereas patients who did not return to work were cases. Then, in the third analysis (identification of not working patients), only patients' data were analyzed with those who did not return to work classified as cases and those who returned to work as non-cases. The odds ratio and relevant 95% confidence interval ($CI_{95\%}$) were computed for the FSLR, whereas the receiver operating characteristic (ROC) curve was computed for the FFNN and the relevant area under the curve was evaluated. For all the statistics, the IBM SPSS Statistic, version 23, was used.

RESULTS

The gait parameters estimated by the IMU are reported in **Table 1**. Significant differences were found for cadence and the mean percentage values of gait phases among the three groups of subjects. *Post-hoc* analyses showed that these parameters were significantly different in the group of patients who did not return to work, but not in those who returned to work, with respect to healthy subjects. The trunk obliquity ROM resulted significantly lower in patients who did not return to work and more asymmetric in patients who returned to work.

The first analysis tested the capacity of the FFNN to identify the patients with stroke gait with respect to the healthy subjects. The FFNN showed an accuracy of 90.9%, a sensitivity of 93.8%, and a specificity of 88.2% in the identification of patients with stroke. The area under the ROC curve was 0.930. The most important parameters for the FFNN resulted the trunk obliquity ROM (100%) followed by the percentage duration of stance phase (99.6%). When the same investigation was performed using the FSLR, the accuracy in patient identification was 75.8% with a sensitivity of 68.8% and a specificity of 82.4%. The variables entered into the model of the FSLR were the same as those of the FFNN: the trunk obliquity ROM (OR = 0.717, $p = 0.010$, $CI_{95\%} = 0.56–0.92$) and the percentage duration of the stance phase (OR = 1.547, $p = 0.088$, $CI_{95\%} = 0.94–2.55$). The latter one had a not statistically significant effect ($p = 0.088$), but if removed by the model, this effect was significant ($p = 0.016$). These results and those of the further analyses are reported in **Table 2**.

The second analysis was focused on the capacity of the FFNN to identify the patients who did not return to work with respect to the entire sample. The accuracy of the FFNN in this identification was 90.9%, resulting from a specificity of 91.3% and a sensitivity of 90%. In fact, the FFNN had only two false positive cases and one false negative case. The area under the ROC curve was 0.978. The variables that mostly contributed to the FFNN were the percentage duration of the first double support phase (100%) and trunk rotation ROM (88.6%). The logistic regression showed an accuracy of 81.8% in this investigation. The variables entered into the model were the cadence (at the first step of regression) and the percentage duration of the swing phase (at the second step). The former entered into the model in the first step and showed a significant effect ($p = 0.017$, OR = 0.87, $CI_{95\%} = 0.78–0.98$), whereas the latter entered into the model in the second step, but with a not significant effect ($p = 0.054$, OR = 0.449, $CI_{95\%} = 0.20–1.01$). It should be specified that despite the effect of percentage duration of the swing phase being

TABLE 1 | Means ± standard deviations of gait parameters estimated by the inertial measurement unit for healthy subjects, patients who returned to work and patients unable to return to work.

Type of variable	Gait parameter	Healthy subjects	Patients returned to work	Patients not returned to work	*p*-value
Mean values of gait parameters	Cadence (steps/min)	114 ± 9	109 ± 10	**97 ± 12**	**<0.001**
	Stance phase (%)	60.7 ± 1.7	60.6 ± 2.5	**64.2 ± 3.8**	**0.005**
	Swing phase (%)	39.9 ± 1.7	39.4 ± 2.5	**36.8 ± 2.2**	**0.009**
	1st double support (%)	10.7 ± 1.7	10.6 ± 2.3	**13.1 ± 2.3**	**0.015**
	2nd double support (%)	10.8 ± 1.7	10.6 ± 2.6	**13.2 ± 2.2**	**0.013**
	Single support phase (%)	39.2 ± 1.7	39.5 ± 2.6	**37.0 ± 2.3**	**0.022**
	Tilt ROM (degrees)	6.3 ± 2.1	6.0 ± 1.6	5.6 ± 2.1	0.728
	Obliquity ROM (degrees)	14.5 ± 4.5	9.9 ± 5.4	**7.9 ± 4.5**	**0.004**
	Rotation ROM (degrees)	18.0 ± 6.3	14.0 ± 5.8	12.5 ± 6.9	0.100
Asymmetry in gait parameters (side-to-side differences)	Stance phase (%)	1.5 ± 2.4	3.0 ± 1.8	5.4 ± 6.3	0.058
	Swing phase (%)	1.5 ± 2.4	3.0 ± 1.8	3.4 ± 3.8	0.205
	1st double support (%)	1.4 ± 1.1	2.0 ± 1.5	1.4 ± 1.5	0.645
	2nd double support (%)	1.5 ± 1.2	2.1 ± 1.3	1.3 ± 1.2	0.453
	Single support phase (%)	1.4 ± 2.3	3.2 ± 1.7	3.3 ± 3.5	0.173
	Tilt ROM (degrees)	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.717
	Obliquity ROM (degrees)	0.2 ± 0.3	**0.6 ± 0.5**	0.4 ± 0.2	**0.013**
	Rotation ROM (degrees)	0.4 ± 0.3	1.0 ± 0.7	0.8 ± 0.6	0.069

The last column report the p-values of the analysis of variance performed among the three groups (p-values are reported in bold if statistically significant, whereas data are in bold if post-hoc analysis revealed that they are significantly different from those of healthy subjects).

TABLE 2 | Comparisons of the performances (accuracy, sensitivity, and specificity) of feedforward neural network (FFNN) and forward stepwise logistic regression (FSLR) for identification of patients and patients unable to return to work (No-RTW).

FFNN vs. FSLR	**Group**	**Healthy subjects and patients**		**Healthy subjects and patients**		**Only patients**	
	Parameter	**Patient identification**		**No-RTW identification**		**No-RTW identification**	
	Model	**FFNN**	**FSLR**	**FFNN**	**FSLR**	**FFNN**	**FSLR**
Model results	Accuracy	90.9%	75.8%	90.9%	81.8%	93.8%	81.3%
	Sensitivity	93.8%	82.4%	90.0%	87.0%	90.0%	90.0%
	Specificity	88.2%	68.8%	91.3%	70.0%	100.0%	66.7%
Input	Cadence	66.3%	0.768	76.2%	**0.017**	61.0%	0.128
Mean values of Input parameters	Stance phase	**99.6%**	**0.088**	83.0%	0.452	73.1%	0.564
	Swing phase	93.4%	0.877	81.5%	**0.054**	71.1%	**0.026**
	1st double support	84.1%	0.875	**100%**	0.678	65.9%	0.732
	2nd double support	89.7%	0.809	64.8%	0.816	67.1%	0.497
	Single support phase	94.5%	0.789	72.5%	0.902	81.2%	0.497
	Tilt	95.6%	0.312	78.8%	0.223	70.8%	0.985
	Obliquity	**100%**	**0.010**	79.5%	0.561	77.5%	0.454
	Rotation	83.6%	0.892	**88.6%**	0.549	95.0%	0.658
Asymmetry of Input (differences of values)	Stance phase	83.6%	0.757	81.6%	0.166	67.1%	0.280
	Swing phase	90.4%	0.795	80.2%	0.283	62.4%	0.408
	1st double support	91.1%	0.467	84.0%	0.833	**98.8%**	0.805
	2nd double support	91.6%	0.532	76.7%	0.378	**100%**	0.409
	Single support phase	81.2%	0.712	76.0%	0.340	62.9%	0.570
	Tilt	59.7%	0.499	68.4%	0.854	52.8%	0.388
	Obliquity	91.0%	0.083	63.7%	0.649	72.9%	0.354
	Rotation	85.1%	0.080	82.8%	0.711	71.4%	0.894

Below, the normalized importance of input for FFNN (maximum = 100%, in bold the two highest values) and the p-values of the effect of input for FSLR (in bold if entered into the model because their effect was statistically significant, or if the effect of their removal from the model was significant).

not significant, if removed by the model, it had a significant effect ($p = 0.007$).

The third analysis was performed only on the patients. The accuracy of the FFNN was 93.8%, with the same sensitivity as the second analysis (90%) but with a specificity that is even higher (100%). In this analysis, the most important parameter resulted the asymmetry in both the double support phases, followed by the trunk rotation ROM, which was already found as playing a key role for the identification of subjects who did not return to work also in the second analysis. Also, accuracy, sensitivity, and specificity of the FSLR were similar to those found in the second analysis, with the swing phase again found as a variable entered into the model, the only one in this case.

DISCUSSION

The FFNN showed good performances both in identifying patients with respect to healthy subjects as well as in identifying those patients unable to return to work among all the enrolled subjects. Its performances were higher than those of a classical statistical analysis such as the FSLR. It is noteworthy that both the analyses (FFNN and FSLR) had some analogies in the identification of the parameters that mostly contributed to the outputs (as well as with the results of the preliminary analysis of variance). In both, the identification of patients was based on the percentage duration of the stance phase and on the range of motion of trunk obliquity. The gait phases, and in particular the ratio between stance and swing phases, have been highlighted as fundamental for a harmonic walking because they formed, together with the double support phases, a fractal autosimilar structure of walking (19). The autosimilarity of the ratios between consecutive gait phases is altered in pathological conditions (20, 21), but in physiological conditions, walking allows for an optimization of energy expenditure (21) and an optimal equilibrium between balance and speed (22). In our study, the FSLR showed that a longer stance phase was associated to the identification of patients (OR = 1.547). The trunk kinematics was also reported as fundamental for the upright balance during walking in patients with stroke, being exposed to the risk of fall (23, 24). The inertial measurement of trunk kinematics during walking is probably the most important factor associated to this dynamic balance (11, 12). An excessive obliquity of trunk could be used as a compensation strategy for lower limb deficits in neurological and also neuromuscular diseases (12, 25). It is conceivable that patients who returned to work adopted this strategy to compensate for the affected side, resulting in an asymmetric lateral trunk bending during walking. Conversely, patients unable to return to work showed a lower trunk obliquity

range of motion than healthy subjects (OR = 0.717). It was probably due to the reduced walking speed, which reduces the trunk oscillations (10, 11), and to the incapacity to put in action the above-described effective compensation strategy.

The inability to return to work was found associated by the ANN to the first double support phase and to the trunk rotation ROM. In this case, these parameters were different from those identified by analysis of variance as significantly different among groups and by logistic regression, for which cadence and swing phase entered into the model. In this latter case, reduced cadence and reduced limb oscillation phases were found to be associated to patients who did not return to work. This is conceivable with a reduced speed and hence a reduced mobility. For the ANN, the most important parameters associated to not returning to work were those related to the double support phase. This result was in accordance with that of logistic regression: the longer the double support phase, the longer the stance, and the shorter the swing phase (19). But also trunk rotation ROM highly contributed for the ANN, being reduced in patients who are unable to return to work. As well as for trunk obliquity, also rotation could be related to a reduced speed, but its reduction can also be associated with a lack of upper limb oscillations during walking. The contralateral oscillations of the upper limb with respect to the lower limbs are a strategy to stabilize the trunk and the head during walking, counteracting the momentum produced by the lower limbs during their swing phases (12).

The identification of inability to return to work performed only on patients (the third analysis of this study) also confirmed that the FFNN had higher accuracy and specificity than the FSLR, with similar sensitivity. However, caution is needed in the interpretation of these last results given the small sample size of this specific analysis ($n = 16$) with respect to the high number of computed parameters ($n = 17$). In spite of this, this analysis also confirmed a key role of double support phases and trunk kinematics for correct identification performed by the FFNN, whereas the swing phase was confirmed as a variable that should enter into the model of the FSLR.

With respect to logistic regression and general linear models, an artificial neural network has two main advantages. The first one is that the ANN exploits the contribution of each variable that concurs in the identification, whereas in the logistic regression, only those entering into the model do it. On one hand, it could be a complication because the model includes all the inputs, but on the other hand, the accuracy of the output is higher. The second advantage is that each variable can contribute only in a linear manner in the logistic regression and analyses of variance, whereas more complex relationships, also including linear or non-linear interactions, can be taken into account by an ANN. This aspect could be very important: the physiological stance to swing ratio is about 1.618 (19); both a reduction as well as an increment of this ratio could be associated to a pathological walking with a consequent increment of energy expenditure (21). The ANN could intercept this non-linear alteration more than the logistic regression, although the interpretation of the importance of each variable into the ANN is more hidden than as it is in the logistic regression. Other potential disadvantages of the ANN are its sensitivity to the setup of the parameters in its architecture, which may also reduce the repeatability of its optimization process.

This study had some limits; first of all, it should be considered as a pilot study because of the reduced sample size that also led to a reduced number of patients with stroke who returned to work. Another limit is its focus on gait; further analysis may include also upper limb kinematic analysis, cognitive factors, and potential social and environmental barriers into the input of the ANN. At the same time, this study has some strengths such as the innovative approach of combining an IMU and an ANN for determining the possibility to return to work of patients with stroke. The second one is its intrinsic simplicity despite the technologies used. We chose to use only one IMU without any external input (such as spatial distance helpful to compute walking speed or step lengths) and also without any covariate (age or other demographical features, clinical scale scores, and other clinical information were not used). Then, the architecture chosen for the FFNN was relatively simple. The resulting system was standalone.

In conclusion, the wide amount of clinical data today that is easily measurable with wearable technologies needs a powerful computational analysis, such as those provided by artificial neural networks. The hidden layers of artificial intelligences should not scare clinicians, but it is fundamental to provide meaningful information that is helpful for them and especially for patients (26). The integration of machine learning with instrumental movement analysis not only may simplify the assessment of several interdependent parameters (27) but also may provide an evolution of gait analysis allowing for the identification of parameters related to poorly explored fields, such as the return to work and the related quality of life of people affected by long-term disability due to stroke.

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 Independent Ethical Committee of Santa Lucia Foundation. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MI and MP: conceptualization. EC, SPe, and MP: data collection. MI: data analysis and original draft preparation. GM, GA, and SPa: review and editing of the draft. MI, MP, SPa, and GA: supervision. MP, MI, and BP: project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Analysis of Prognostic Risk Factors Determining Poor Functional Recovery After Comprehensive Rehabilitation Including Motor-Imagery Brain-Computer Interface Training in Stroke Patients: A Prospective Study

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Objective: Upper limb (UL) motor function recovery, especially distal function, is one of the main goals of stroke rehabilitation as this function is important to perform activities of daily living (ADL). The efficacy of the motor-imagery brain-computer interface (MI-BCI) has been demonstrated in patients with stroke. Most patients with stroke receive comprehensive rehabilitation, including MI-BCI and routine training. However, most aspects of MI-BCI training for patients with subacute stroke are based on routine training. Risk factors for inadequate distal UL functional recovery in these patients remain unclear; therefore, it is more realistic to explore the prognostic factors of this comprehensive treatment based on clinical practice. The present study aims to investigate the independent risk factors that might lead to inadequate distal UL functional recovery in patients with stroke after comprehensive rehabilitation including MI-BCI (CRIMI-BCI).

Methods: This prospective study recruited 82 patients with stroke who underwent CRIMI-BCI. Motor-imagery brain-computer interface training was performed for 60 min per day, 5 days per week for 4 weeks. The primary outcome was improvement of the wrist and hand dimensionality of Fugl-Meyer Assessment (δFMA-WH). According to the improvement score, the patients were classified into the efficient group (EG, δFMA-WH $>$ 2) and the inefficient group (IG, δFMA-WH $\leq$ 2). Binary logistic regression was used to analyze clinical and demographic data, including aphasia, spasticity of the affected hand [assessed by Modified Ashworth Scale (MAS-H)], initial UL function, age, gender, time since stroke (TSS), lesion hemisphere, and lesion location.

Results: Seventy-three patients completed the study. After training, all patients showed significant improvement in FMA-UL ($Z = 7.381$, $p = 0.000$**), FMA-SE ($Z = 7.336$, $p = 0.000$**), and FMA-WH ($Z = 6.568$, $p = 0.000$**). There were 35 patients (47.9%) in the IG group and 38 patients (52.1%) in the EG group. Multivariate analysis revealed that presence of aphasia [odds ratio (OR) 4.617, 95% confidence interval (CI) 1.435–14.860; $p < 0.05$], initial FMA-UL score ≤ 30 (OR 5.158, 95% CI 1.150–23.132; $p < 0.05$), and MAS-H $\geq$ level I+ (OR 3.810, 95% CI 1.231–11.790; $p < 0.05$) were the risk factors for inadequate distal UL functional recovery in patients with stroke after CRIMI-BCI.

Conclusion: We concluded that CRIMI-BCI improved UL function in stroke patients with varying effectiveness. Inferior initial UL function, significant hand spasticity, and presence of aphasia were identified as independent risk factors for inadequate distal UL functional recovery in stroke patients after CRIMI-BCI.

Keywords: motor-imagery brain-computer interface, regression analysis, stroke, upper limb, rehabilitation

INTRODUCTION

Previous studies have reported that 85% of stroke survivors suffer from upper limb (UL) dysfunction, which has significant long-term effects on activities of daily living (ADL), leisure activities, and work (1). Upper limb motor function recovery, especially distal function, is one of the main goals of stroke rehabilitation. Only 12% of patients with stroke regain full UL function, while other patients require long-term care (2). Brain-computer interface (BCI) is an interactive system for internal and external environment that directly reflects brain activity (3). Motor-imagery brain-computer interface (MI-BCI) can quantify and reinforce feedback from motor imagery tasks and affect changes in neural network plasticity. For patients with stroke, MI-BCI training significantly improves UL motor function (4), electromyography signals (EEG) (5), joint mobility, daily living skills (6), mood (7), and brain network connectivity (8).

The effect of BCI is multidimensional, including the improvement of the clinical score and some subclinical indicators. Previous studies have shown significant improvement in UL function after MI-BCI training in patients with stroke (9, 10). Subclinical effects with improvement in the neuroelectrophysiological index have also been observed (11, 12). The mechanism of motor function recovery in the distal UL differs from that in the proximal UL. Most patients with stroke with inadequate overall UL functional recovery show predominantly improved proximal UL function, for instance, shoulder and elbow function, which results from non-decussated corticospinal fibers stemming from the unaffected hemisphere (13, 14). However, the distal UL function is markedly affected by the integrity of the corticospinal tract (CST) (12), which lacks a compensatory mechanism and therefore recovers inadequately. Motor function in the distal UL has a substantive effect on ADL (10, 15).

Most stroke patients receive comprehensive treatment that not only includes MI-BCI but also routine training. Multiple factors affect the prognosis of UL functional recovery. First, there is a large variation in user performance between healthy individuals, and the possible factors include cognitive function, sensory, motor imagery ability (16), psychological factors (17), age (18), gender (19), dominant hand (20), sensorimotor rhythm bias (21), cortical gray matter volume, and medical treatment. Second, studies on the prognosis prediction of UL motor recovery in patients with stroke have incorporated age, gender, dominant hand, lesion of hemisphere and location, initial UL function, and presence of comorbidities into models that can predict UL recovery type up to 6 months after onset (22).

In studies on MI-BCI fitness, gender, age, event-related potential, classification accuracy, neuropsychological score (23), EEG laterality index, and cortical activation intensity (24) were found to be useful to predict the performance of stroke patients who could manipulate MI-BCI devices, and the symmetry of the EEG signal could be used as a predictor of the degree of UL improvement (25, 26). Subacute phase is an essential rehabilitation period for patients with stroke, and an increasing number of studies have included subacute stroke patients in BCI studies. However, the effect of these factors on the effectiveness of comprehensive treatment including MI-BCI in patients with stroke is unclear. The elucidation of this aspect will enable us to better define the indications for MI-BCI, guide the development of individualized rehabilitation programs, and improve treatment effectiveness in patients with stroke.

Therefore, the present study aimed to investigate the independent risk factors that might lead to inadequate distal UL recovery of patients with stroke after comprehensive rehabilitation including MI-BCI (CRIMI-BCI).

SUBJECTS AND METHODS

General Information

Eighty-two patients with ischemic stroke hospitalized at Tsinghua Changgung Hospital, Beijing, between January 2018 and December 2019 were recruited for the study. The diagnostic criteria were based on the "Consensus on Clinical Research Specifications for Acute Stroke in China 2018," along with

differential diagnosis by magnetic resonance imaging (MRI) or computerized tomography (CT) (27). The inclusion and exclusion criteria were chosen according to a previous study (8).

Inclusion Criteria

The following inclusion criteria were used: (1) age 18–75 years; (2) sufficient cognition [Montreal Cognitive Scale (MOCA) score >20]; (3) a history of first-ever unilateral brain lesion confirmed by MRI; (4) stroke occurrence [time since stroke (TSS)] 1–6 months prior to inclusion; (5) moderate to severe UL paralysis (Brunnstrom stages ≤IV); and (6) right-handedness (Edinburgh Handedness Inventory score ≥40).

Exclusion Criteria

The following exclusion criteria were used: (1) severe spasticity of the affected hand [Modified Ashworth Scale (MAS) score ≥3]; (2) open wound or deformity of the affected UL; (3) visual field deficit or unilateral spatial neglect; (4) severe aphasia [Boston Diagnostic Aphasia Examination (BDAE) score <3]; (5) currently undergoing antipsychotic treatment; (6) severe dystonia and/or involuntary movements; (7) other severe neurological disorders such as epilepsy; and (8) currently undergoing neuromodulation treatment.

Nine patients were excluded at follow-ups conducted during the study due to changes in their conditions. Complete data were collected from 73 patients. The experimental flow chart is shown in **Figure 1**.

The study was approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (No. 18172-0-02) and registered at http://www.chictr.org.cn (No. ChiCTR1900022128). All patients signed an informed consent form prior to the trial. The following data were obtained from patients with stroke: gender, age, TSS, lesion hemisphere and location, and presence of concomitant aphasia. The lesion location was staged according to the Oxfordshire Community Stroke Study (OCPS) (28, 29). Aphasia diagnostic criteria were determined by the Aphasia Battery of Chinese (ABC), aphasia diagnostic criteria set as total score <25 (30).

General information of the 73 included patients is shown in **Table 1**.

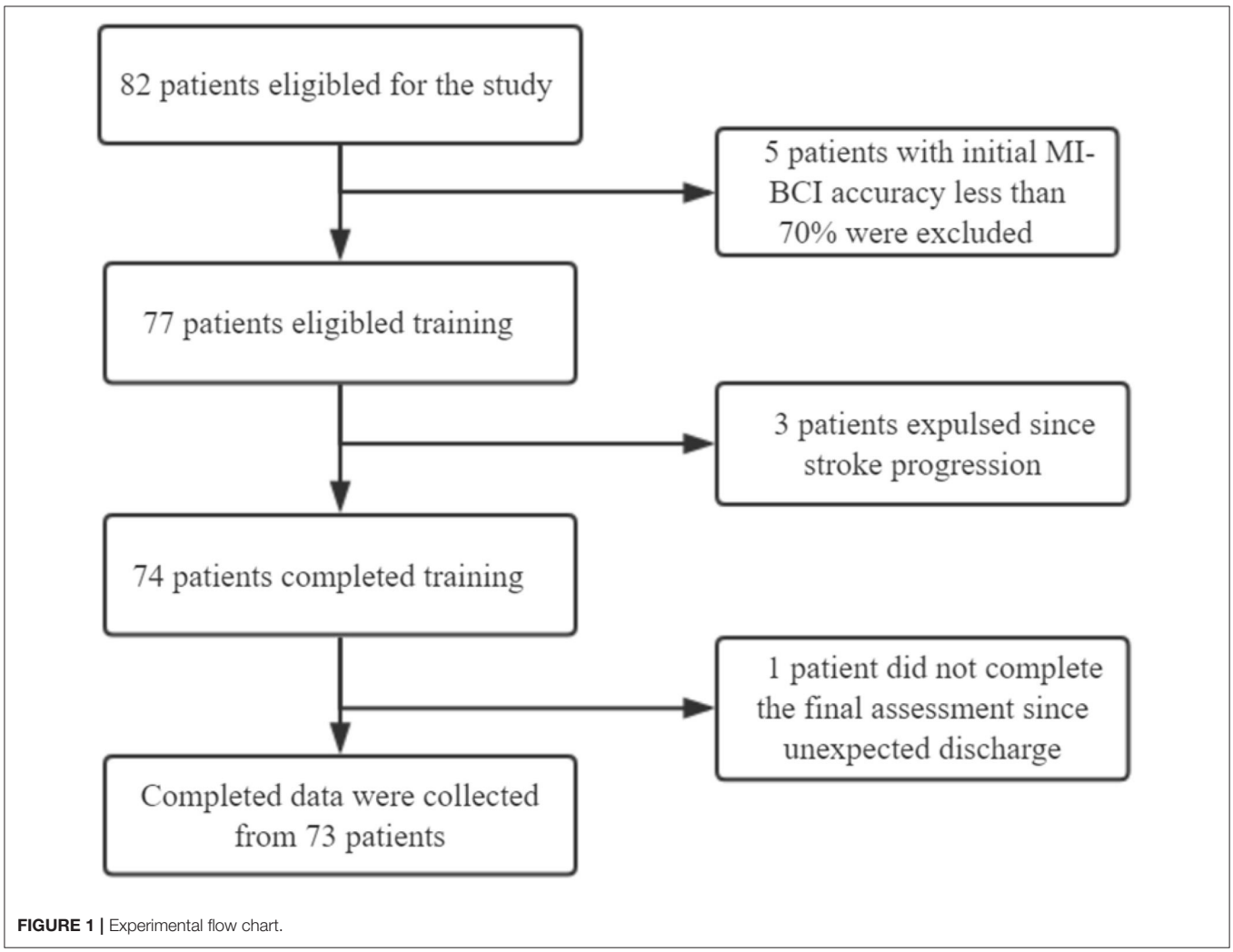

FIGURE 1 | Experimental flow chart.

TABLE 1 | General information of 73 patients.

	Mean/Median	Classification	Number	*n* (%)
Age (year)	61.00 (46.00, 67.00)	<65	50	68.49
		≥65	23	31.51
TSS (month)	3.00 (2.00, 5.00)	≤6	60	82.19
		>6	13	17.81
Lesion		TACI	29	39.73
		PACI	44	60.27
Gender		Female	25	34.25
		Male	48	65.75
Aphasia		With	49	67.12
		Without	24	32.88
Affected hemisphere		Right	31	42.47
		Left	42	57.53

PACI, Partial anterior circulation infarct; TACI, Total anterior circulation infarct.

EEG Acquisition

Scalp EEG potentials were collected from eight dry electrodes (according to 10–20 International System), band-passed by 2–60 Hz filter and a notch filter (48–52 Hz) to remove artifacts and power line interference, respectively; digitized at 256 Hz, and amplified by a commercial EEG system (g. LADYbird, g. Tec Medical Engineering GmbH, Schiedlberg, Austria) and then processed by a computer.

EEG signals were grounded to a unilateral earlobe and referenced at the other one. Electrodes were positioned over FC3, FC4, C3, C4, CP3, CP4, C1, and C2. Signals from the C3 and C4 were used for device control. Motor function related electrodes were used for offline analyses (left hemisphere: FC3, C3, and CP3; right hemisphere: FC4, C4, and CP4). Mu suppression, which reflects Event-Related Desynchronization (ERD), was due to increased neural activity. The mu suppression score provides information about motor innervation, and was posted on the screen, encouraged patients to get higher scores. For mu suppression score computation, EEG data from C3 to C4 were transformed into the frequency domain by a Fourier transform algorithm with a Hanning window covering the EEG data during the video period of the paradigm. The equation of mu suppression scored are as follows (8):

$$\text{Musupp} = -\frac{\text{Mup}_{\text{task}} - \text{Mup}_{\text{rest}}}{\text{Mup}_{\text{rest}}} \times 100$$

Musupp: Mu suppression score, Mup_{test}: EEG power during MI; Mup_{rest}: EEG power during the resting state.

Comprehensive Rehabilitation Training Program

All patients received standard treatment for stroke in terms of medical care and rehabilitation, which consisted of conventional treatment, including an intensive occupational therapy focused on activities of daily live, such as grasping a toothpaste tube, eating, and reaching. A conventional treatment session lasted for 1 h per day, 5 days per week, for 4 weeks. MI-BCI training was applied based on conventional treatment. The detailed protocol refers to previous studies (8).

MI-BCI Training Paradigms

To facilitate MI performance, patients were given the opportunity to execute tasks with the affected and unaffected hand several times before MI-BCI training. Meanwhile they were instructed to perform only MI tasks and to avoid movement attempts of the affected UL.

MI-BCI training consisted of 20 sessions, five sessions per week, for 4 weeks. During each session, the patient was comfortably seated in a soundproofed room, with their affected hand resting in an exoskeleton hand. A video of the unaffected hand grasping/opening was presented on a screen in front of the patient to guide the MI task. The exoskeleton hand provided mechanical support and assistance to the affected hand based on the mu suppression algorithm calculated during the follow up trial.

(1) Movement observation: a dark screen was first displayed for 2 s, followed by a white cross for 2 s. A vocal cue of "hand grasp" or "hand open" was displayed for 2 s. Then a video clip was displayed for a duration of 6 s. Patients were requested to observe the video and avoid blinking, coughing, chewing, and performing head movements.
(2) Exoskeleton hand assistance: If the mu suppression score was above 20, the exoskeleton hand would assist the hand grasping/opening task during the following 3 s.
(3) End of process: the mu suppression score was then shown for 2 s. The trial ended with the display of a dark screen for 2 s. During each session, the trial was repeated 100 times for one session, and video clips of the grasping and opening hand were shown randomly. Patients were permitted to rest for 1 min after 10 trials.

Functional Evaluation

Before and after 20 training sessions, the motor function of the affected UL and muscle tone of the affected finger flexor were

evaluated. A simplified version of the Fugl-Meyer Assessment UL (FMA-UL), which was without sensory, passive joint mobility, and pain and reflex sections, was used to assess the motor function of the affected UL (31). The total FMA-UL score was 60, which was obtained by summing the five items on the FMA-UL scale: shoulder, elbow, wrist, hand, and coordination/speed. The sum of the wrist and hand score (FMA-WH) was 24. The sum of the shoulder and elbow score (FMA-SE) was 30. A higher score for each dimension implied that the patient was more functional. The simplified FMA-UL score was categorized as severe (0–12), severe-moderate (13–30), moderate-mild (31–47), and mild (48–60) (2). Because the initial FMA-UL scores of most patients were between severe-moderate to moderate-mild, a score of 30 was selected as the watershed in the following regression analysis.

The MAS was used to measure the muscle tone of the affected finger flexors and recorded as MAS-H (32, 33). For statistical convenience, the scores were recorded as follows: level 0 was set as 1, level I–I+ as 2, level II as 3, and level III–IV as 4. Because the initial MAS-H scores of most patients were between 2 and 3, level I+ was selected as the watershed.

All assessments were performed by one trained therapist, and the assessor was unaware of the therapeutic condition of the patients. Functional evaluation of the 73 patients is shown in **Table 2**.

Comparison of Group Characteristics

The 73 patients who completed all training and testing procedures were divided into two groups according to whether the increase in the FMA-WH score (δFMA-WH) was higher than two points before and after treatment. The differences between the two groups were compared in terms of gender, age, TSS, lesion hemisphere and location, presence of aphasia, MAS-H, and FMA-UL and its component score.

Statistical Analysis

Data were analyzed using SPSS 22.0 statistical software, and measured values were expressed as mean and standard deviation ($x \pm s$) or median and interquartile range (25th percentile, 75th percentile). Data were verified for normality of distributions with the Kolmogorov-Smirnov test ($n > 50$) or Shapiro-Wilk test ($n < 50$). Because of the ordinal nature of the data, the study data were compared between groups using independent sample *t*-test and Mann-Whitney U test. Data were compared within the group using an independent *t*-test and a paired-sample Wilcoxon test. Categorical variables were expressed as percentages and analyzed with the chi-square test or Fisher's exact test, and significance was set at $p < 0.05$. For regression analysis, the δFMA-WH score was used as the criterion for grouping. Binary logistic regression was performed on the basis of the results of univariate analysis for $p < 0.10$ and by incorporating the parameters into the model through the Forward LR method. The results of multivariate analysis were expressed as odds ratio (OR) and 95% confidence interval (CI). A two-sided $p < 0.05$ was considered to be statistically significant.

TABLE 2 | UL function in 73 patients before and after training.

	Pre	Post	Z	*p*
FMA-UL	18 (8, 27.5)	30 (16, 45.5)	7.381	0.000**
FMA-SE	13 (8–19)	20 (12, 28.5)	7.336	0.000**
FMA-WH	3 (0, 8)	9 (4–16)	6.568	0.000**

$^{**}p < 0.01$.

RESULTS

Overall Efficacy of Comprehensive Rehabilitation

After comprehensive rehabilitation, 73 patients showed significant improvement in FMA-UL, FMA-SE, and FMA-WH (Wilcoxon signed-rank test, $p < 0.000$), as shown in **Table 2** and **Figure 2**.

Differences in Functional Recovery

It was difficult to perceive changes in hand function when δFMA-WH $\leq$ 2 points (33) and by referring to the definition of minimum clinically important difference (MCID). Hence, δFMA-WH $\leq$ 2 points before and after training was selected as the criterion for judging the efficacy (34, 35). The 73 patients were divided into the efficacy group (EG, with δFMA-WH > 2 points, $n = 38$, 52.1%) and the inefficacy group (IG, δFMA-WH $\leq$ 2 points, $n = 35$, 47.9%).

The difference in UL motor function status was compared between the two groups. The results showed no significant differences in the FMA-UL pre (Mann-Whitney U test, $p = 0.584$), FMA-SE pre (Mann-Whitney U test, $p = 0.615$), and FMA-WH pre (Mann-Whitney U test, $p = 0.950$) between the groups before training.

After training, the total score and the WH score in both EG and IG groups were significantly higher than those before the training [FMA-UL post (Mann-Whitney U test, $p = 0.026$) and FMA-WH post (Mann-Whitney U test, $p = 0.001$)]. The improvement in the total, SE, and WH scores of FMA-UL in the EG group was also significantly higher than that in the IG group [δFMA-UL (Mann-Whitney U test, $p = 0.000$), δFMA-WH (Mann-Whitney U test, $p = 0.000$), and δFMA-SE (independent samples *t*-test, $p = 0.000$)], as listed in **Table 3** and **Figure 3**.

Risk Factor of Unfavorable Recovery

The univariate analysis revealed that TSS (chi-square test, $p = 0.040$), MAS-H (chi-square test, $p = 0.007$), presence of aphasia (chi-square test, $p = 0.025$), and FMA-UL pre (chi-square test, $p = 0.05$) might be associated with unfavorable hand function recovery after BCI training in patients with stroke. Age (chi-square test, $p = 0.989$), lesion (chi-square test, $p = 0.205$), gender (chi-square test, $p = 0.626$), and affected hemiplegia (chi-square test, $p = 0.377$) were not found to be relevant for the functional

change of the distal UL after training in patients, as listed in **Table 4** and **Figure 4**.

Binary logistic regression analysis was performed based on the results of univariate analysis for $p < 0.10$. Presence of aphasia [odds ratio (OR) 4.617, 95% confidence interval (CI) 1.435–14.860; $p = 0.010$], FMA-UL pre $\leq$ 30 (OR 5.158, 95% CI 1.150–23.132; $p < 0.032$), and MAS-H $\geq$ level I+ (OR 3.810, 95% CI 1.231–11.790; $p = 0.020$) were found to be risk factors for inadequate distal UL recovery in patients with stroke after CRIMI-BCI training, as shown in **Table 5**.

DISCUSSION

The results of the present study showed that for the target population, CRIMI-BCI significantly improved the overall and distal motor function of the UL in stroke patients, but the degree of improvement varied. Classification according to distal functional improvement showed that although no significant differences were observed in UL motor function before training, the proportion of patients with aphasia, TSS > 6 months, and finger flexor tone >1+ grade on the affected hand was significantly higher in the IG group. Regression analysis showed that significant hand spasticity, poor initial function, and concomitant aphasia were the important factors that influenced the inadequate distal UL motor function after CRIMI-BCI in this study.

The results of the present study showed that CRIMI-BCI improved UL function, including distal motor function, in patients with stroke. This result is consistent with many studies (6, 25, 35). Bundy DT found significant improvements in grip

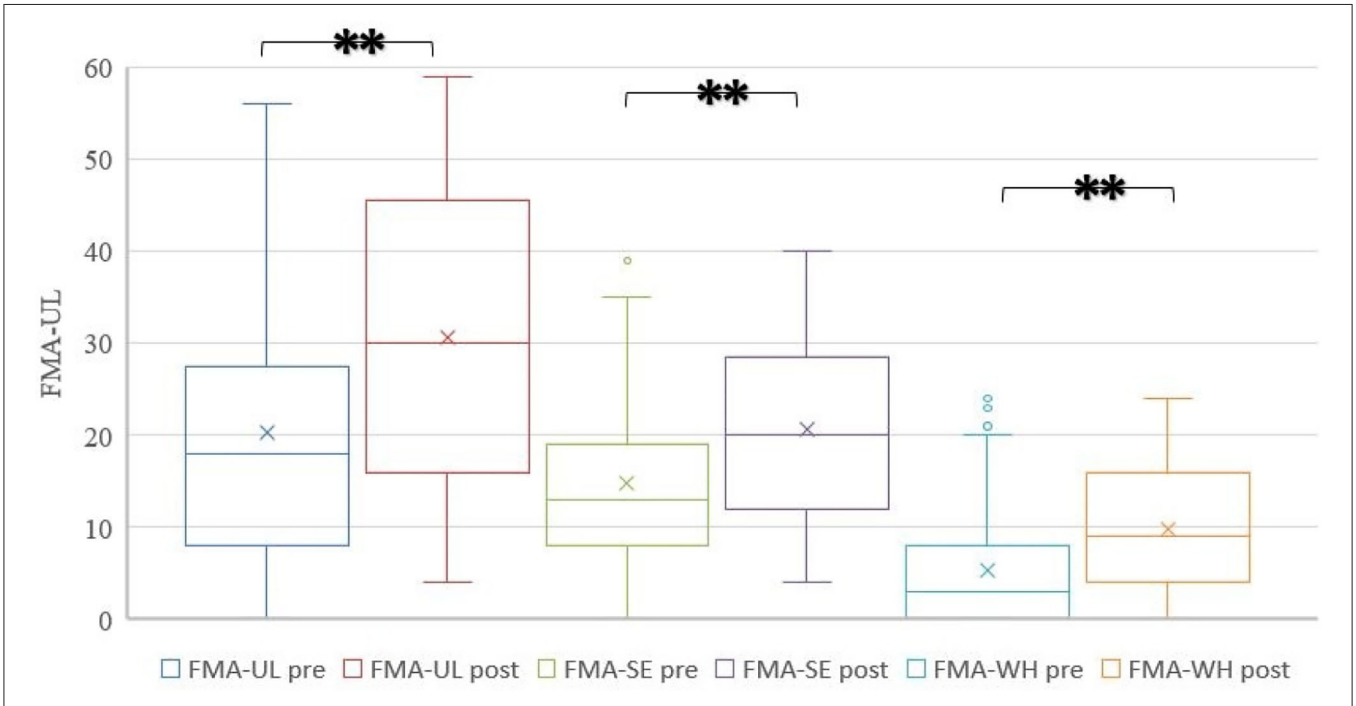

FIGURE 2 | Improvement of 73 patients after treatment.

TABLE 3 | Comparison of changes before and after training between groups.

	EG ($n = 38$)	IG ($n = 35$)	t/Z	p
FMA-UL pre	18,000 (12.0, 24.0)	12,000 (6.0, 40.0)	−0.548	0.584
FMA-SE pre	13,000 (10.0, 18.0)	10,000 (6.0, 24.0)	−0.503	0.615
FMA-WH pre	4,000 (0.0, 7.0)	2,000 (0.0, 13.0)	−0.063	0.950
FMA-UL post	32,000 (23.0, 47.3)	18,000 (8.0, 44.0)	−2.226	0.026*
FMA-SE post	21,000 (16.0, 28.3)	17,000 (8.0, 29.0)	−1.261	0.207
FMA-WH post	12,000 (7.8, 16.3)	4,000 (0.0, 13.0)	−3.406	0.001**
δFMA-UL	14,000 (9.8, 18.3)	4,000 (3.0, 5.0)	−6.264	0.000**
δFMA-SE	17.42 ± 7.06	13.09 ± 6.24	2.770#	0.007**
δFMA-WH	7,000 (4.0, 11.0)	1,000 (0.0, 2.0)	−7.388	0.000**

*$p < 0.05$, **$p < 0.01$, #Mann-Whitney U test.

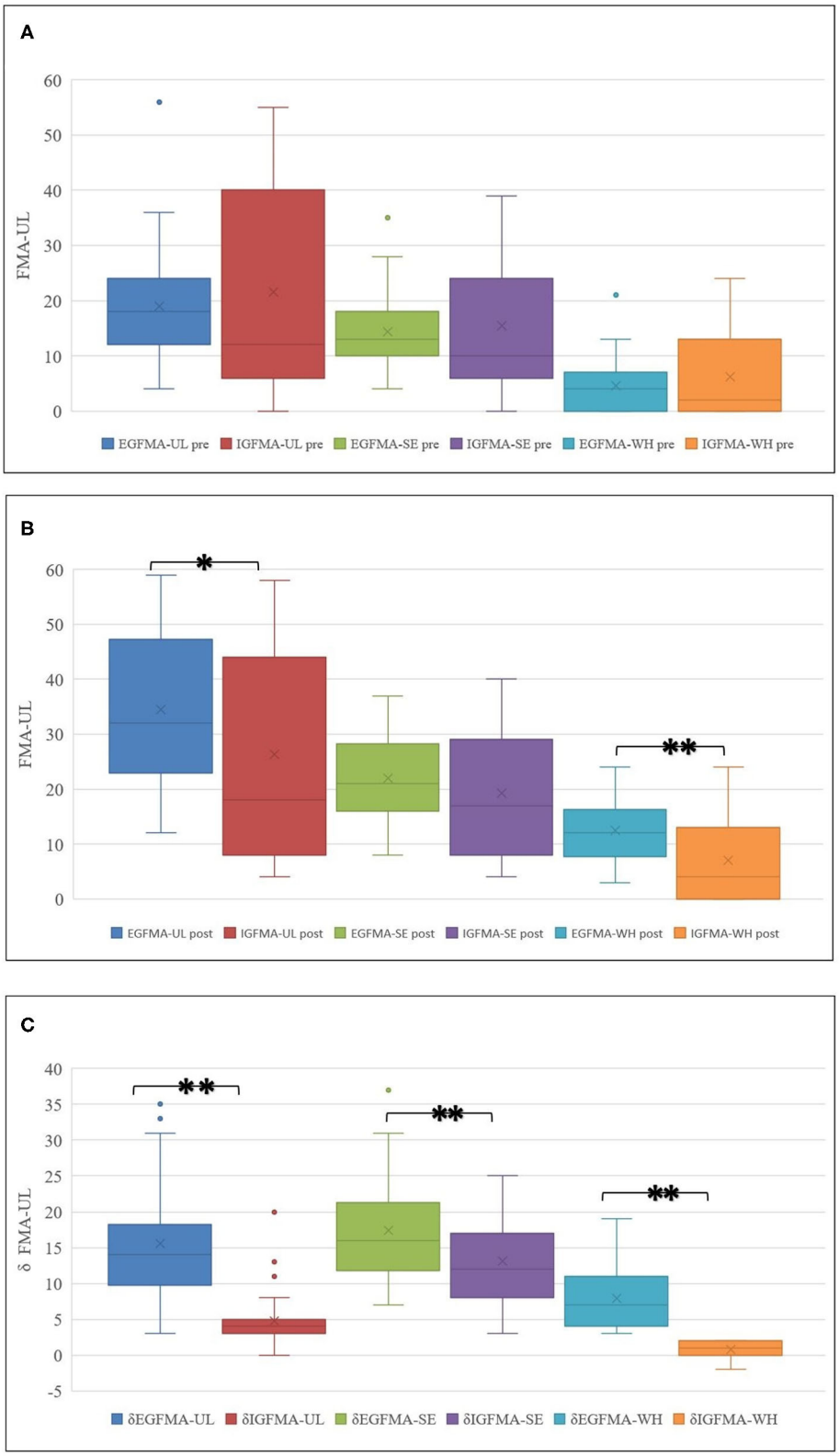

FIGURE 3 | (A–C) UL function improvement in groups. Although the overall FMA-UL score improved, the FMA-WH scores in two patients regressed after training in IG. *$p < 0.05$, **$p < 0.01$.

TABLE 4 | Comparison of the characteristics between groups.

	Classification	EG (%)	IG (*n* %)	Subtotal (*n* %)	χ^2	*p*
Age (year)	≤65	26 (68.42)	24 (68.57)	50 (68.49)	0	0.989
	>65	12 (31.58)	11 (31.43)	23 (31.51)		
TSS (month)	≤6	35 (92.11)	26 (74.29)	61 (83.56)	4.212	0.040*
	>6	3 (7.89)	9 (25.71)	12 (16.44)		
MAS-H	≤1+	28 (73.68)	15 (42.86)	43 (58.90)	7.152	0.007**
	>1+	10 (26.32)	20 (57.14)	30 (41.10)		
Lesion	TACI	15 (39.47)	19 (54.29)	34 (46.58)	1.606	0.205
	PACI	23 (60.53)	16 (45.71)	39 (53.42)		
Gender	Female	14 (36.84)	11 (31.43)	25 (34.25)	0.237	0.626
	Male	24 (63.16)	24 (68.57)	48 (65.75)		
Aphasia	Without	30 (78.95)	19 (54.29)	49 (67.12)	5.021	0.025*
	With	8 (21.05)	16 (45.71)	24 (32.88)		
Affected hemisphere	Left	18 (47.37)	13 (37.14)	31 (42.47)	0.780	0.377
	Right	20 (52.63)	22 (62.86)	42 (57.53)		
FMA-UL pre	≤30	34 (89.47)	25 (71.43)	59 (80.82)	3.827	0.050
	>30	4 (10.53)	10 (28.57)	14 (19.18)		

*$p < 0.05$, **$p < 0.01$.

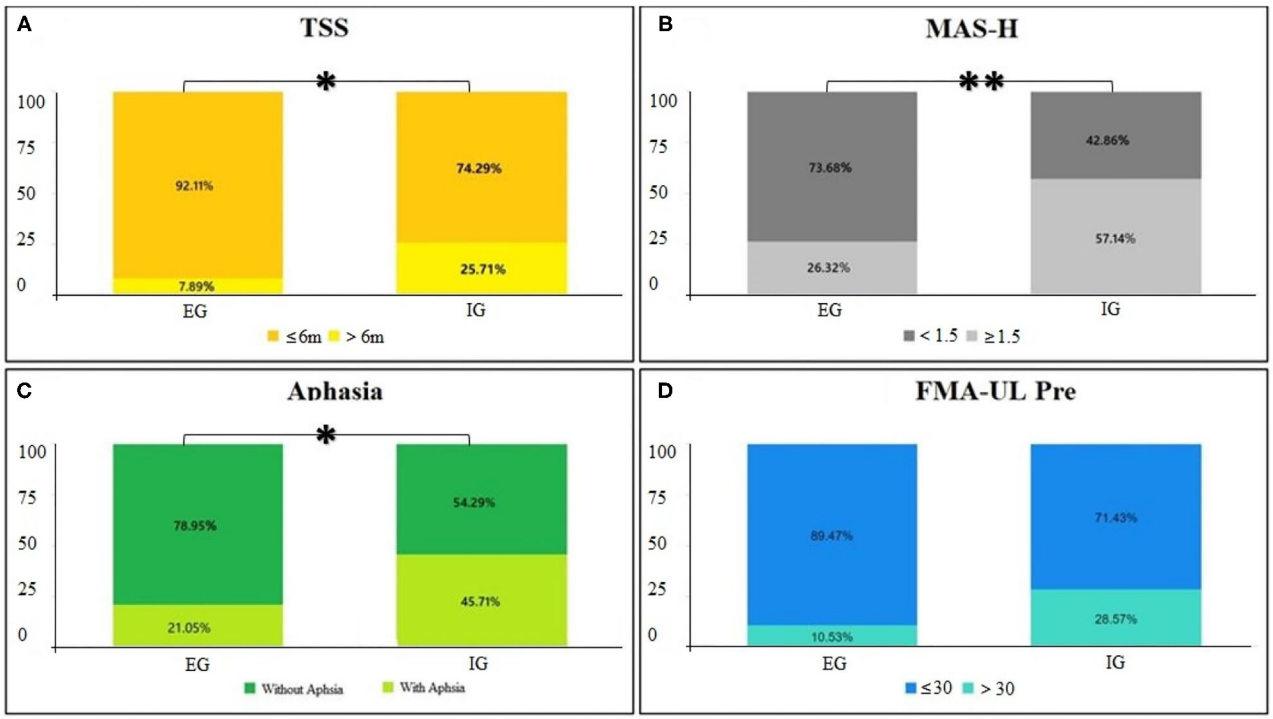

FIGURE 4 | (A–D) Univariate analysis of characteristics. Cross graph of groups and classification for $p < 0.05$, **$p < 0.01$.

strength, grasp, and pinch function in stroke patients with chronic moderate to severe UL paresis, after using BCI combined with exoskeleton training in the unaffected hemisphere (35). Frolov et al. showed that in patients with stroke, BCI combined with exoskeleton training showed a significant advantage in the grip and pinch function of the affected finger as compared to exoskeleton training alone (25).

Previous studies on factors influencing the clinical outcome of MI-BCI have shown no correlation between spasticity and training outcome in patients with stroke. However, the effect

TABLE 5 | Binary logistic regression of risk factors.

	B	*SE*	*Z*-value	Wald χ^2	*P*	OR	OR (95%CI)
MAS-H	1.338	0.576	2.321	5.386	0.020*	3.810	1.231–11.790
FMA-UL	1.641	0.766	2.143	4.591	0.032*	5.158	1.150–23.132
TSS	0.515	0.812	0.635	0.403	0.526	1.674	0.341–8.222
Aphasia	1.530	0.596	2.565	6.579	0.010*	4.617	1.435–14.860

*B, estimate coefficient; SE, standard error; OR, odds ratio; CI, confidence interval. *$p < 0.05$.*

of spasticity on UL motor function was demonstrated by numerous studies on the prediction of motor function in stroke patients. The present study showed that the MAS-H score was an independent factor that influenced inadequate functional improvement of the distal UL in patients after CRIMI-BCI. Finger and wrist flexor spasticity is very common in patients with stroke, and the recovery of wrist and hand movements vary greatly among patients with different degrees of spasticity. Patients with severe spasticity have minimal improvement in the FMA of the hand (34, 36). In contrast, patients with moderate and mild spasticity exhibit greater hand motion recovery. Hand spasticity affects the recovery of random finger movements as well as grasp and release functions. Spasticity can also impede motor learning ability after stroke (37). The severity of distal spasticity directly reflects the severity of the CST injury, as there is no compensation of the ipsilateral motor conduction. Spasticity of the hand is an extremely critical influencing factor in the recovery of motor function after stroke (36). The understanding of the relationship between hand spasticity and the effect of MI-BCI training in patients with stroke can be helpful in designing individualized rehabilitation programs.

Previous studies have suggested that complications such as depression, cognitive impairment, aphasia, hemianopia, and unilateral neglect after stroke also affect the recovery of motor function (38). The presence of spontaneous speech is a favorable factor for the recovery of motor function (39, 40). The present study showed that concomitant aphasia was an independent influencing factor of modest functional improvement of the distal UL in the patients. A possible reason for this was that although patients with concomitant aphasia in this study had mild speech impairment, the training process involved more complex instructions such as hearing vocal signals—watching videos—closing eyes—completing motor imagery—opening eyes to prepare for the next cycle; hence, speech dysfunction not only affected the reception and expression of information by the patients, but it may also have involved factors such as attention and working memory, resulting in inefficiency training and inadequate rehabilitation. Further research is necessary to understand the effect of aphasia on the effectiveness of MI-BCI in terms of the type, severity, and mechanism of the disorder.

Many studies have confirmed that the performance of MI-BCI manipulation does not correlate with motor function. However, in most stroke prediction models, the initial UL function score significantly affects prognosis. The patients in the present study had no significant differences in FMA-UL pre as observed in Mann-Whitney U test; all of these patients had moderate or severe impairment. However, the difference in data dispersion between the groups can be observed from the box plot. There was an inter group difference in the trend of the initial FMA-UL degree (classified by 30 points), and a further increase in sample size might have cleared the difference. We incorporated the FMA-UL pre-score into the regression analysis based on clinical experience and prognostic studies. However, the initial motor function still showed a significant effect on treatment outcome in the regression analysis; this finding is consistent with the general pattern of UL functional recovery in patients with stroke. The result may be related to the initial FMA-UL score distribution or the interaction between the variables.

It is worth noting that, unlike previous studies, the present study did not show any influence of TSS, age, gender, and lesion on the effect of CRIMI-BCI. This may be explained by the distinctive population scope of the study. For example, in the intragroup comparison, the number of cases with TSS $>$ 6 months was significantly greater in the IG group than in the EG group. However, in the multivariate analysis, TSS did not constitute an independent risk factor affecting the unfavorable functional recovery of the distal UL in stroke patients. Age has been reported to influence the performance of MI-BCI in healthy individuals, with older patients showing reduced EEG power, laterality, and significantly lower discrimination accuracy than younger patients (40, 41). Advanced age is also an influential factor in the inadequate prognosis of UL function after stroke (22, 42, 43). Regarding the effect of gender on outcome, many studies on the prognosis of stroke have shown that male patients have a better prognosis than female patients. However, Randolph reported that male patients had poorer ability to regulate μ-rhythms in the EEG and poorer control of the MI-BCI system than female patients (19). In terms of the location of lesions, the anterior putamen, internal capsule, thalamus, periventricular white matter, and premotor cortex were associated with inadequate UL recovery in patients with hemorrhagic stroke (44). Studies on chronic ischemic stroke have shown poorer recovery in patients with internal capsule injury (45). The prognosis of the TACI was worse than that of the other types (46, 47). In the present study, most patients with complete anterior circulation and severe posterior circulation could not complete MI-BCI training because of other comorbidities. In contrast, there is a POCI type in OCPS, but no patient with this type was not recruited in this study. This might be because such types of patients generally face less

obstacles and therefore hardly meet the test conditions. This may be related to the generally mild motor dysfunction of these patients. Therefore, the results of the present study were limited to the current population for whom MI-BCI is indicated, and the duration of the disease was restricted to the subacute phase. Additionally, cognitive impairment, severe aphasia, severe spasticity, depression, hemianopia, unilateral neglect, and other comorbidities were excluded, and the effect of the dominant hand was limited. The patient population in the present study was more homogeneous than that observed in actual clinical patients, and no remarkable differences were observed in TSS, age, gender, and lesion. Hence, the effect of the training might not be evident. This suggested that the study of factors influencing the effect of CRIMI-BCI on patients with stroke was very complicated, and the findings need to be tailored to its scope of application. Moreover, there is an urgent need to combine neuroimaging and neurophysiological investigations in the next step of this study.

The results of the present study answered the initial queries and showed the following findings: (1) CRIMI-BCI can improve UL motor function, especially the distal function, in patients with stroke in the subacute stage; (2) a heterogeneity was observed in the effect of CRIMI-BCI on distal UL function, with significantly better overall and distal UL function improvement in EG patients than in IG patients; and (3) in stroke patients with subacute phase UL paralysis who underwent CRIMI-BCI, poor initial UL function, severe hand spasticity, and concomitant aphasia were the influencing factors of inadequate distal function recovery.

LIMITATIONS

The generalization of these results is subject to certain limitations. First, although previous studies have compared the effects of conventional therapy with BCI training on patients with subacute stroke, the present study did not include a control group, and therefore, it cannot be determined whether the abovementioned findings differ from those of patients with conventional stroke. Second, the sample size was insufficient and limited by the strict screening requirement of the patients and the long-term training duration. Moreover, there was inadequate inclusion of factors influencing clinical outcomes, including NIHSS score and some early clinical predictors such as the presence of shoulder shrugging, active finger extension, and grip strength of the affected hand. Third, indicators reflecting the ability to manipulate MI-BCI, including classification rate and EEG activity, were lacking. Fourth, neuroimaging-related evidence was lacking. In addition, long-term and interaction effects were not analyzed. Therefore, controlled, long-term studies with larger sample siues, more factors, and neuroimaging and neurophysiological evidence are needed to further validate the results of the present study.

CONCLUSION

The present study aimed to investigate the factors influencing the effect of CRIMI-BCI on the functional recovery of the distal UL in patients with stroke. The main results suggest that CRIMI-BCI improved overall and distal UL function in patients with subacute stroke, but that the outcomes were varied. Poor initial UL function, severe hand spasticity, and concomitant aphasia were independent risk factors for inadequate MI-BCI training outcomes. This study was restricted to a specific population with subacute stroke who underwent CRIMI-BCI. It clarified the effect of BCI on distal UL function and explored further indications, prognosis, and protocols for rehabilitation. The study findings can be applied to design individualized rehabilitation programs for patients with stroke.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository and accession number can be found below: Chinese Clinical Trial Registry (ChiCTR), http://www.chictr.org.cn, No. ChiCTR1900022128.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Beijing Tsinghua Changgung Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QW, YP, WD, and TZ designed the study. DM, XP, and YC performed experiments. QW and YG wrote the paper. All authors contributed to the article and approved the submitted version.

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Predicting Clinically Significant Improvement After Robot-Assisted Upper Limb Rehabilitation in Subacute and Chronic Stroke

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Prior studies examining predictors of favorable clinical outcomes after upper limb robot-assisted therapy (RT) have many shortcomings. Therefore, the aim of this study was to identify meaningful predictors and a prediction model for clinically significant motor improvement in upper limb impairment after RT for each stroke phase. This retrospective, single-center study enrolled patients with stroke who received RT using InMotion2 along with conventional therapy (CT) from January 2015 to September 2019. Demographic characteristics, clinical measures, and robotic kinematic measures were evaluated. The primary outcome measure was the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) and we classified patients with improvement more than the minimal clinically important difference as responders for each stroke phase. Univariable and multivariable logistic regression analyses were performed to assess the relationship between potential predictors and RT responders and determine meaningful predictors. Subsequently, meaningful predictors were included in the final prediction model. One hundred forty-four patients were enrolled. The Hand Movement Scale and time since onset were significant predictors of clinically significant improvement in upper limb impairment ($P = 0.045$ and 0.043, respectively), as represented by the FMA-UE score after RT along with CT, in patients with subacute stroke. These variables were also meaningful predictors with borderline statistical significance in patients with chronic stroke ($P = 0.076$ and 0.066, respectively). Better hand movement and a shorter time since onset can be used as realistic predictors of clinically significant motor improvement in upper limb impairment after RT with InMotion2 alongside CT in patients with subacute and chronic stroke. This information may help healthcare professionals discern optimal patients for RT and accurately inform patients and caregivers about outcomes of RT.

Keywords: robotics, upper extremity, minimal clinically important difference, prognosis, rehabilitation, stroke

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INTRODUCTION

Upper extremity dysfunction commonly occurs after a stroke, affecting ∼80% of people with acute stroke and 50% of people with chronic stroke. It negatively affects activities of daily living as well as social activities (1, 2). Therefore, improving upper extremity function is a primary therapeutic goal in stroke rehabilitation (3). Several systematic reviews

suggest that repetitive, task-specific, and intensive therapy may result in motor improvement after stroke (4, 5). Robotic systems can provide more consistent, intensive, and repetitive training without fatigue, along with task-specific training by easily applying new constraints to optimize the required movement pattern, as compared to conventional therapy (CT) (6). Recent systematic reviews on robot-assisted therapy (RT) of the upper limb after stroke have reported that a more meaningful clinical outcome is obtained with RT than with CT (7, 8).

Identifying the predictors of a favorable clinical outcome after RT is imperative. It could help healthcare professionals to identify those patients who are best suited for RT and to accurately guide patients and caregivers about the outcomes of RT. It would also improve the cost efficiency of RT, which is currently steep.

Several studies have been conducted to identify predictors so that favorable outcomes with upper limb RT can be ensured among patients with stroke. Hsieh et al. (9) enrolled 55 patients with stroke who had undergone RT using the Bi-Manu-Track (Reha-Stim, Berlin, Germany) and found that the Box and Block Test score and female sex could predict favorable outcomes in the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) and Motor Activity Log scores. The same researchers conducted a secondary analysis by enrolling 66 patients with stroke using the cohort data generated in the aforementioned study (10). Spasticity of the upper extremity and kinematic measures were added to the potential predictors analyzed in the previous study, and lessened flexor synergy and spasticity were found to be predictors of a favorable Wolf Motor Function Test result. Franceschini et al. (11) demonstrated that the Box and Block Test score, FMA-UE score, and Motricity Index (MI) upper limb could predict a favorable post-RT Modified Barthel Index using data from 60 patients with stroke who had undergone RT using InMotion2 (Interactive Motion Technologies, Watertown, MA, USA). Duret et al. (12) enrolled 46 patients with stroke who had undergone RT using InMotion2 and demonstrated that the time since onset and Fugl-Meyer Assessment (FMA) shoulder/elbow score were predictors of a favorable post-RT FMA shoulder/elbow score. Although these two variables could predict improvement after RT, they could not predict improvement more than the minimal clinically important difference (MCID), which is the minimal effect that has clinical relevance in patient management (13).

Many studies have been conducted to identify predictors; however, they had several limitations, such as inconsistently identified predictors, inadequate number of subjects, limited numbers of analyzed potential predictors, and unclearly distinguished stroke phases, despite the difference in recovery depending on the stroke phase. No predictor identified thus far can predict an improvement more than the MCID in the FMA-UE, the main tool used to assess impairment. We hypothesized that some predictors may have the potential to predict improvement more than the MCID of FMA-UE after RT, and these predictors may vary depending on the phase of the stroke. Therefore, the aim of the present study was to identify meaningful predictors and a prediction model for clinically significant motor improvement in cases of upper limb impairment after RT for each stroke phase.

METHODS

Study Design and Setting

This retrospective, single-center study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (14). The Ethics Committee of the Institutional Review Board of the National Rehabilitation Center in South Korea approved this study (approval number, NRC-2019-04-030) and waived the requirement for informed consent because of the retrospective design.

From January 2015 to September 2019, patients with stroke who were admitted to the National Rehabilitation Center in South Korea, and who received RT using InMotion2, were enrolled in this study. The inclusion criteria were a definite diagnosis of unilateral stroke, as evidenced by computed tomography, magnetic resonance imaging, or medical records; a time since onset of $\geq$7 days for a first-ever stroke; and age $\geq$19 years. The exclusion criteria were as follows: neurological disorders other than stroke that can cause motor deficits, e.g., Parkinson disease, spinal cord injury, Guillain-Barré syndrome, traumatic brain injury, brain tumor, hypoxic brain injury, cerebral palsy, and peripheral neuropathy; spasticity in the elbow joint with a Modified Ashworth Scale (MAS) grade $>$3; severe upper extremity pain that could interfere with RT (Numeric Rating Scale score $\geq$5); upper extremity fracture within 3 months; uncontrolled severe medical conditions; a history of non-invasive brain stimulation; RT for $<$20 sessions; and incomplete medical records.

The patients' data were sourced from the electronic medical records in the database of our health care institute. The demographic, clinical, and robotic records were extracted. The patients' records were de-identified before analysis. The principal investigator (JH) conceived and designed the study, and an occupational therapist (SY) collected the data. Investigators (JJ and JH) performed data curation and statistical analysis and wrote and edited the paper.

We analyzed patients with stroke according to time since onset, which was classified as subacute phase (time since onset of $\geq$7 and $<$180 days) and chronic phase (time since onset of $\geq$180 days) (15).

Intervention and Apparatus

Each patient participated in a total of 20 sessions of RT using InMotion2; patients underwent one 30-min RT session per day, 5 days a week for 4 weeks. InMotion2, which has been proven efficient and safe for patients with subacute and chronic stroke (16, 17), is a two-degrees-of-freedom end-effector type robotic device that provides shoulder-elbow flexion/extension training in the horizontal plane. In the seated position with the trunk restrained by a five-point seatbelt to minimize compensatory movement and with the forearm supported by a forearm cradle, each patient performed goal-directed reaching movements in the gravity-compensated horizontal plane. The patients were instructed to move the handle from the center target to each of eight peripheral targets positioned 45 degrees apart in circular arrangements, and the position of the handle was marked on the screen for real-time visual feedback. All the patients

also received CT, according to the standardized rehabilitative protocol, involving range of motion exercises, strengthening exercises for the affected upper extremity, and activities of daily living training.

Potential Predictors

To identify meaningful predictors, we included variables known to be related to outcome after therapeutic intervention (18, 19) and those suspected of clinical relevance, but not yet confirmed. Demographic characteristics [age, sex, time since onset, stroke subtype, stroke lesion (cortical, subcortical, or combined cortical and subcortical), and hemiplegic side], clinical measures [FMA-UE score, MI, Medical Research Council Scale for Muscle Strength (MRC) score, MAS grade at the elbow flexor muscle of the hemiplegic side, Hand Movement Scale (HMS), and Brunnstrom Recovery Stage (BRS)], and robotic kinematic measures [smoothness, reach error (RE), path error (PE), and independence] were selected for analysis.

The assessments of FMA-UE, MI, MAS, smoothness, RE, PE, and independence were conducted by experienced occupational therapists before the first RT session and after the last session. The evaluations of MRC-shoulder flexion, extension, abduction, and adduction; MRC-elbow flexion and extension; MRC-wrist flexion and extension; MRC-finger flexion and extension; HMS; and BRS were performed at admission.

Clinical Measures

The FMA-UE is a quantitative measure of motor impairment following a stroke and consists of 33 items rated on a three-point scale (maximum score, 66), with higher scores indicating less severe impairment (20). The scale is composed of sub-scores: 36 for the shoulder/elbow (FMA-A), 10 for the wrist (FMA-B), 14 for the hand (FMA-C), and 6 for coordination (FMA-D). These can be distributed into sub-scores of 42 for the proximal unit of the shoulder/elbow and coordination (FMA-Prox) and 24 for the distal unit of the wrist and hand (FMA-Dist).

The MI is based on the ability to move the upper extremity segment through a range of motion and to resist the force. The MI-upper limb consists of three domains (pinch grasp, elbow flexion, and shoulder abduction). Each domain is scored between 0 and 33, and the total upper limb score (maximum score, 100) is calculated by adding one to the sum of the three domain scores (21).

The MRC score ranges from 0 to 5, with higher scores representing greater muscle strength (22). The MRC-upper extremity score was calculated by summing the MRC-shoulder, MRC-elbow, MRC-wrist, and MRC-finger scores, whereas the MRC-shoulder score was calculated by adding the MRC-shoulder flexion, extension, abduction, and adduction scores. The MRC-elbow, MRC-wrist, and MRC-finger scores were each calculated as the sum of the MRC-elbow flexion and extension, MRC-wrist flexion and extension, and MRC-finger flexion and extension scores, respectively.

The MAS measures spasticity, with a higher grade indicating higher spasticity (23). The MAS spasticity grades of 1+, 2, 3, and 4 were converted to 2, 3, 4, and 5, respectively, while grade 1 remained the same.

The HMS ranges from 1 to 6 and evaluates the ability to perform hand movements of different degrees of difficulty, with a higher number representing better hand movement (24).

The BRS ranges from 1 to 6 and describes the stereotypical stages of motor recovery, starting with flaccidity to full recovery of motor function (25). The BRS consists of different parts; the two parts concerning the upper arm (BRS-upper arm) and the hand (BRS-hand) were used herein.

Robotic Kinematic Measures

Robotic kinematic measures (e.g., smoothness, RE, PE, and independence) were used as potential predictors. Assessments of kinematic measures consist of point-to-point reaching movements and circle drawing movements (26). The point-to-point reaching movement assessment was used to calculate smoothness, RE, and PE, while the circle drawing assessment was conducted to calculate independence. Smoothness was calculated as the mean of the speed divided by the peak speed and is expressed as a value ranging from 0 to 1, where a value closer to 1 indicates better control of movement speed (27). RE and PE represent the ability to move accurately along a straight path toward the center of targets and toward targets, respectively. RE was calculated as the normalized summed difference of the end of the reach from the center of the target with respect to time. PE was calculated as the normalization of the summed deviations from the desired straight path and the participant's actual path from one point to another with respect to time. RE and PE are expressed as a value ranging from 0 to 1, with a value closer to 0 indicating better performance (28). Independence was calculated as the ratio between the major and minor axes of the ellipse that best represents the path drawn by the hand during the circle drawing assessment. Values range from 0 to 1, where values closer to 1 represent fitting ellipses that are closer to a circle, and indicate better coordination of shoulder and elbow movements (29).

Outcome Measure

Since RT focuses upon upper limb impairment, we chose the FMA-UE as the primary outcome measure and calculated the difference in the FMA-UE score before and after RT (ΔFMA-UE). We considered 9 and 5.25 as the MCID for patients with subacute and chronic stroke, respectively (30, 31). As such, patients with subacute stroke who had a ΔFMA-UE value $\geq$9 and patients with chronic stroke who had a ΔFMA-UE value $\geq$5.25 were classified as responders in this study. Those with values below the aforementioned were classified as non-responders.

Statistical Analysis

The sample size calculation estimated that 58 subjects would provide 80% power with 5% α and an odds ratio of 2.5 (power analysis using logistic regression according to the guidelines of Lipsey & Wilson and G Power 3.1.9.7 software) (32).

Continuous variables are presented as means and standard deviations, and categorical variables are presented as numbers and percentages. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Meaningful

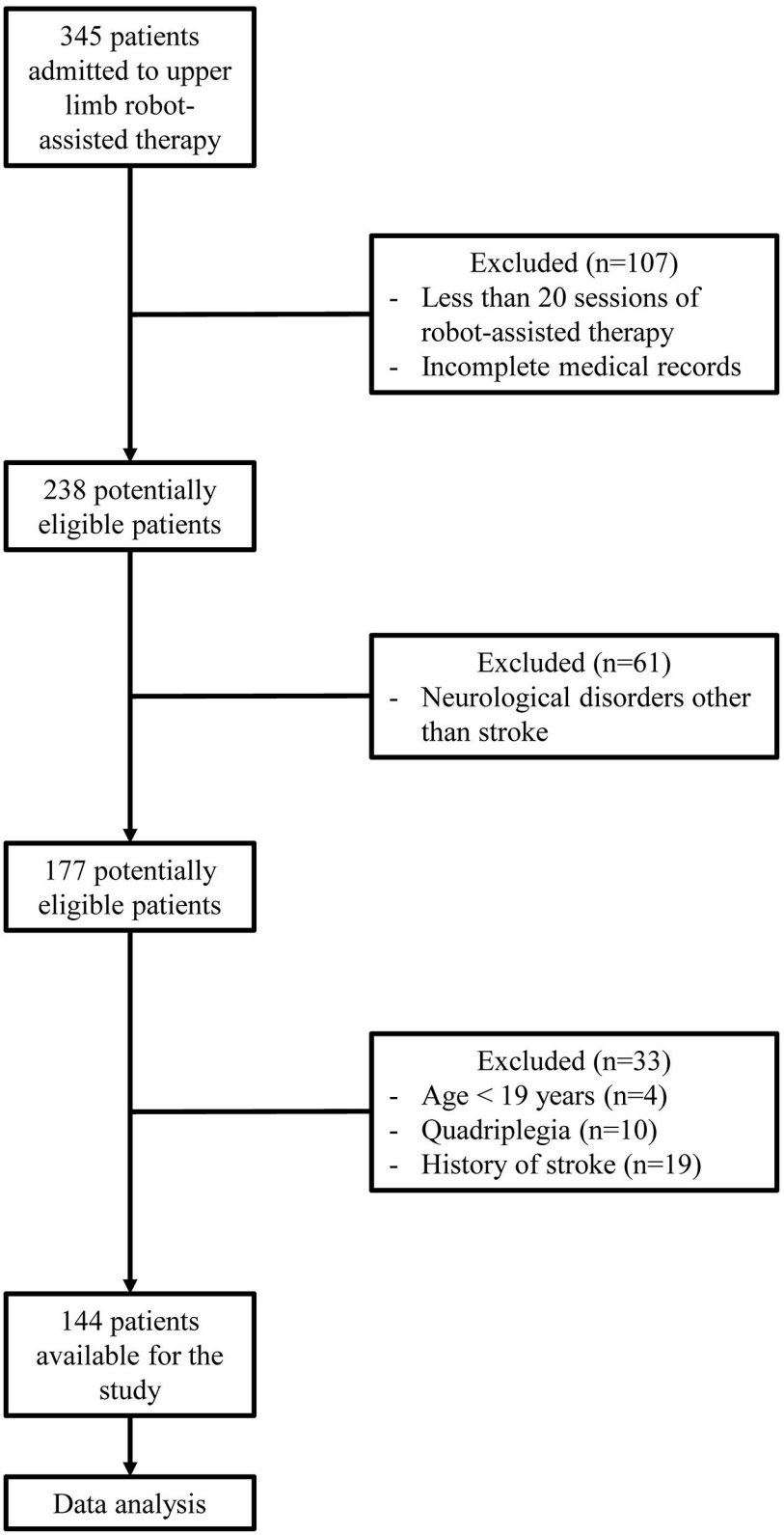

FIGURE 1 | Flow diagram of the selection procedures of stroke patients.

TABLE 1 | Baseline characteristics of responders and non-responders according to stroke phase.

Characteristics	Subacute phase		Chronic phase	
	Responder ($n = 25$)	Non-responder ($n = 61$)	Responder ($n = 12$)	Non-responder ($n = 46$)
Demographic characteristic				
Age, years	56.3 (12.2)	54.7 (14.0)	57.3 (13.6)	56.0 (12.9)
Sex, male	19 (76.0)	38 (62.3)	10 (83.3)	35 (76.1)
Female	6 (24.0)	23 (37.7)	2 (16.7)	11 (23.9)
Time since onset, days	91.8 (44.0)	110.1 (34.0)	280.3 (64.9)	417.3 (228.4)
Stroke subtype, ischemic	14 (56.0)	30 (49.2)	4 (33.3)	23 (50)
Lesion, cortical	1 (4.0)	3 (5.0)	0 (0.0)	1 (2.1)
Subcortical	19 (76.0)	40 (65.5)	10 (83.3)	30 (65.2)
Combined	5 (20.0)	18 (29.5)	2 (16.7)	15 (32.7)
Hemiplegic side, right	14 (56.0)	26 (42.6)	5 (41.7)	22 (47.8)
Clinical measure				
FMA-UE	20.5 (7.9)	20.4 (8.7)	20.2 (9.5)	18.9 (9.3)
MAS	0.9 (0.9)	1.1 (0.7)	1.3 (0.78)	1.5 (0.8)
HMS	2.6 (1.3)	2.1 (0.9)	3.0 (1.8)	2.2 (0.7)
Robotic kinematic measure				
Smoothness	0.425 (0.072)	0.421 (0.070)	0.460 (0.063)	0.440 (0.068)
Reach error	0.064 (0.058)	0.061 (0.0445)	0.062 (0.060)	0.062 (0.052)
Path error	0.031 (0.025)	0.027 (0.017)	0.026 (0.026)	0.028 (0.023)
Independence	0.548 (0.179)	0.526 (0.167)	0.538 (0.134)	0.538 (0.188)

Values are the mean (standard deviation) for continuous data, and the number (percentage) for categorical data.
FMA-UE, Fugl-Meyer Assessment-Upper Extremity; MAS, Modified Ashworth Scale; HMS, Hand Movement Scale.

predictors were determined using univariable and multivariable logistic regression analyses (33). We performed univariable logistic regression analyses to assess the relationship between potential predictors and the outcome measure, and extracted variables for which the *P*-value was <0.25 (34). These variables were further tested for correlations among variables using the Pearson or Spearman correlation test depending on the distribution (normal or not). We excluded variables that had a high correlation ($|R| > 0.7$) (35) and a low odds ratio. To prevent overfitting, we calculated outcome events per predictor variable (EPV) using the number of selected variables. It is recommended that the EPV should be at least 10:1 (36). Next, multivariable stepwise logistic regression analysis was used to determine meaningful predictors. Subsequently, meaningful predictors with a significance level of <0.05 were included in the final prediction model. The goodness-of-fit of the final model and each meaningful predictor was tested with the Hosmer-Lemeshow test. Finally, receiver operating characteristic curves were used to assess the predictive capacity of the developed prediction model and to determine the most reliable cut-off score of each meaningful predictor in relation to responders of RT. Herein, 95% confidence intervals (CIs) are reported for the area under the receiver operating characteristic curves (AUCs). A P-value < 0.05 was considered reflective of statistical significance. Statistical analyses were conducted using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

Three hundred forty-five patients underwent RT using InMotion2 between January 2015 and September 2019. Among them, 107 were excluded because of termination of the RT due to medical abnormalities, pain, decreased patient motivation, unexpected discharge, or the absence of evaluation following RT and incomplete medical records. Upon exclusion of 61 patients who underwent RT for a diagnosis other than stroke, 4 patients who were <19 years old, 10 quadriplegic patients, and 19 patients who had a history of stroke, a total of 144 patients were enrolled (**Figure 1**).

Overall, there were 86 patients with subacute stroke and 58 with chronic stroke. Among patients with subacute stroke, there were 25 responders and 61 non-responders. Among those with chronic stroke, there were 12 responders and 46 non-responders. The characteristics of responders and non-responders by stroke phase are shown in **Table 1**.

Potential and Meaningful Predictors

Subacute Phase

Variables identified through univariable logistic regression analysis of the relationship between potential predictors and responders of RT with a P-value < 0.25 were sex; time since onset; FMA-C score; MRC-wrist flexion, MRC-wrist extension, MRC-finger extension, and MRC-wrist scores; MAS grade; HMS; and BRS-hand (**Supplementary Table 1**). Among these variables,

TABLE 2 | Multivariable analyses using the MCID of the FMA-UE as the outcome measure according to stroke phase.

	Subacute phase					Chronic phase				
Baseline characteristics	**Unstandardized coefficient**	**Odds ratio**	**95% CI**		***P*-value**	**Unstandardized coefficient**	**Odds ratio**	**95% CI**		***P*-value**
Time since onset	−0.014	0.99	0.97	1.00	0.043*	−0.008	0.99	0.98	1.00	0.066†
HMS	0.451	1.57	1.01	2.44	0.045*	0.497	1.65	0.95	2.85	0.076†
Constant	−0.520	0.60			0.543	−0.078	0.93			0.958

MCID, minimal clinically important difference; FMA-UE, Fugl-Meyer Assessment-Upper Extremity; CI, confidence interval; HMS, Hand Movement Scale.
**P < 0.05; †P < 0.1 in the multivariable analysis.*

a high correlation was demonstrated between MRC-wrist flexion and MRC-wrist extension scores, MRC-wrist flexion and MRC-finger extension scores, MRC-wrist flexion and MRC-wrist scores, MRC-wrist extension and MRC-finger extension scores, MRC-wrist extension and MRC-wrist scores, and between the MRC-finger extension score and the HMS. We excluded the MRC-wrist flexion and MRC-wrist scores that had a low odds ratio. However, if an MRC-finger extension score had a low odds ratio, it was not excluded, as it was presumed to be a major potential predictor. Eight potential predictors were selected and the EPV was >10 (EPV = 10.75). Multivariable stepwise logistic regression analysis of selected potential predictors followed by application of a backward elimination procedure revealed the time since onset and HMS as significantly meaningful predictors (**Table 2**).

Chronic Phase

In the univariable logistic regression analysis of the relationship between potential predictors and responders of RT, the variables with a *P*-value < 0.25 were time since onset; MI-upper limb, MRC-wrist extension, MRC-finger flexion, MRC-finger extension, and MRC-finger scores; HMS; and BRS-hand (**Supplementary Table 1**). Among these variables, a high correlation was demonstrated between the MRC-finger flexion and MRC-finger scores, and between the MRC-finger extension and MRC-finger scores. The MRC-finger scores that had a low odds ratio were excluded. Seven potential predictors were finally selected. The EPV was <10, but was in line with the recommended range of ≥5–9 EPV (EPV = 8.3) (37). Multivariable stepwise logistic regression was conducted on the selected potential predictors, and the time since onset and HMS were identified as meaningful predictors using the backward elimination procedure (**Table 2**).

Final Prediction Model and Meaningful Predictor Cut-Off Score

In the final prediction model, the time since onset and HMS were included in each subacute and chronic stroke model. Below are the final logistic regression equations.

$$\begin{aligned} &\textit{Subacute phase: Logit } P\,(\Delta FMA - UE \geq 9) \\ &\quad = -0.520 - 0.014 \times (\textit{time since onset}) + 0.451 \times (\textit{HMS}) \\ &\textit{Chronic phase: Logit } P\,(\Delta FMA - UE \geq 5.25) \\ &\quad = -0.078 - 0.008 \times (\textit{time since onset}) + 0.497 \times (\textit{HMS}) \end{aligned}$$

Both models showed a good fit (Hosmer-Lemeshow test, $P > 0.05$), and the corresponding AUC values were calculated and plotted as receiver operating characteristic curves (**Figure 2**). AUC values with 95% CIs were 0.658 (95% CI, 0.520–0.797) for the subacute phase model and 0.739 (95% CI, 0.606–0.872) for the chronic phase model.

Every meaningful predictor showed a good fit (Hosmer-Lemeshow test, $P > 0.05$). The sensitivity and specificity for the cut-off score of the meaningful predictors were calculated and plotted as receiver operating characteristic curves (**Figure 3**) for patients with subacute and chronic stroke. Corresponding AUC values with 95% CIs are shown in **Table 3**.

DISCUSSION

This study demonstrated that the HMS and time since onset were significant predictors for clinically significant motor improvement in upper limb impairment, as represented by the FMA-UE score after RT with InMotion2 alongside CT in patients with subacute stroke. Similarly, the HMS and time since onset were meaningful predictors with borderline statistical significance in patients with chronic stroke.

This study demonstrated that the HMS is a meaningful predictor among patients with subacute and chronic stroke. A baseline HMS that exceeds 2.5, i.e., ≥3 was indicative of a favorable outcome post-RT. An HMS of 3 indicates possible active flexion and extension of all fingers in synergy. Active finger extension has been revealed as an indicator of better recovery of arm function in patients with stroke in multiple studies. Fritz et al. (38) confirmed that active finger extension could predict recovery following constraint-induced movement therapy. Additionally, Smania et al. (39) demonstrated that an MRC-finger extension score >3 could be a predictor of the subacute and chronic stroke phase recovery, and that an HMS >3 could predict recovery in the chronic phase; these results are supportive of the findings of our study. The HMS had a low sensitivity but a high specificity in the present study. Therefore, healthcare professionals can perform HMS when determining the beginning of RT in patients with a subacute or chronic stroke. In cases where the HMS score is ≤2, it can be explained to the patients or caregivers that it is difficult to expect the complete therapeutic effect of RT. This may lead to increased cost efficiency for RT, and the efficient use of hospital resources. The HMS is

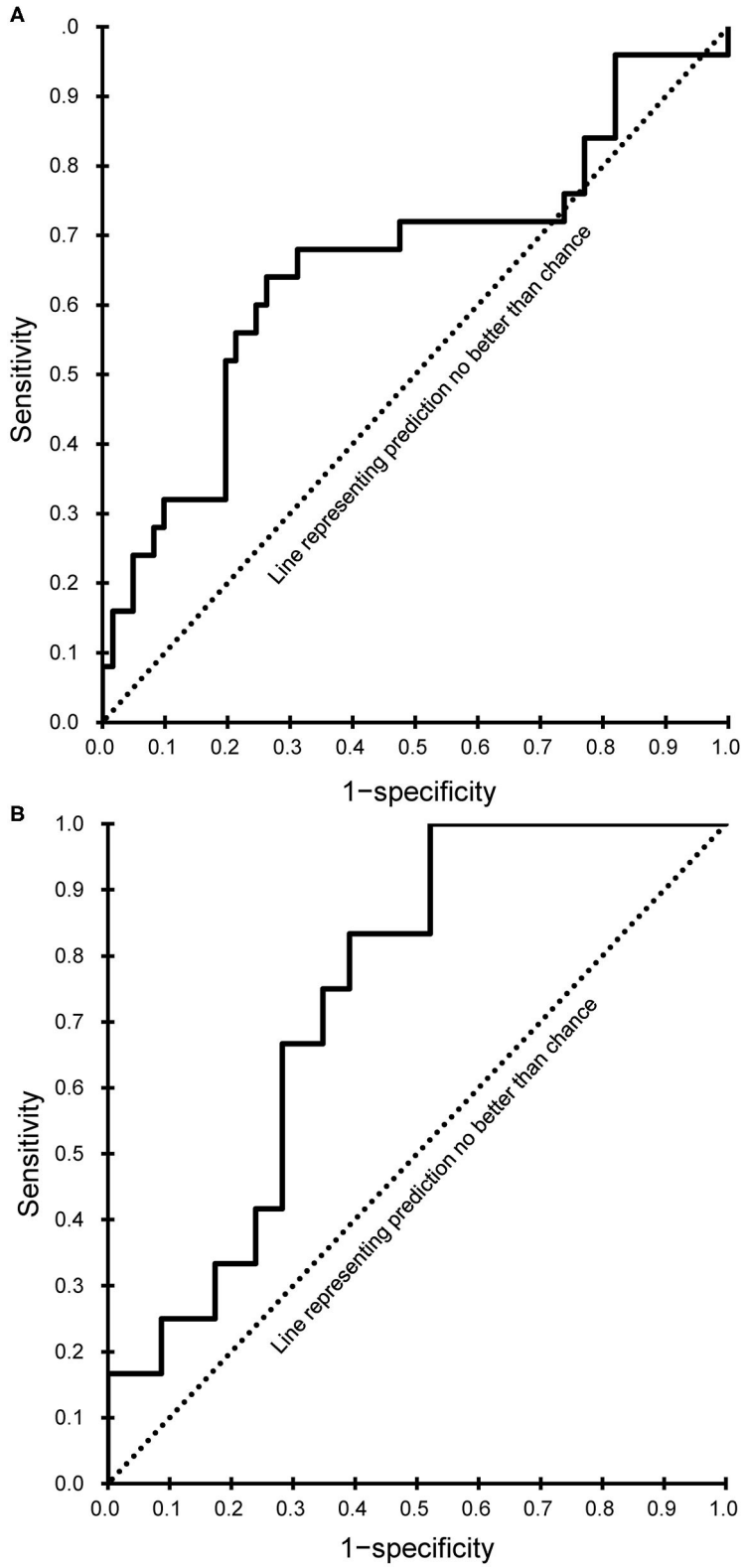

FIGURE 2 | Receiver operating characteristic curves of the final prediction model. **(A)** Subacute phase. **(B)** Chronic phase.

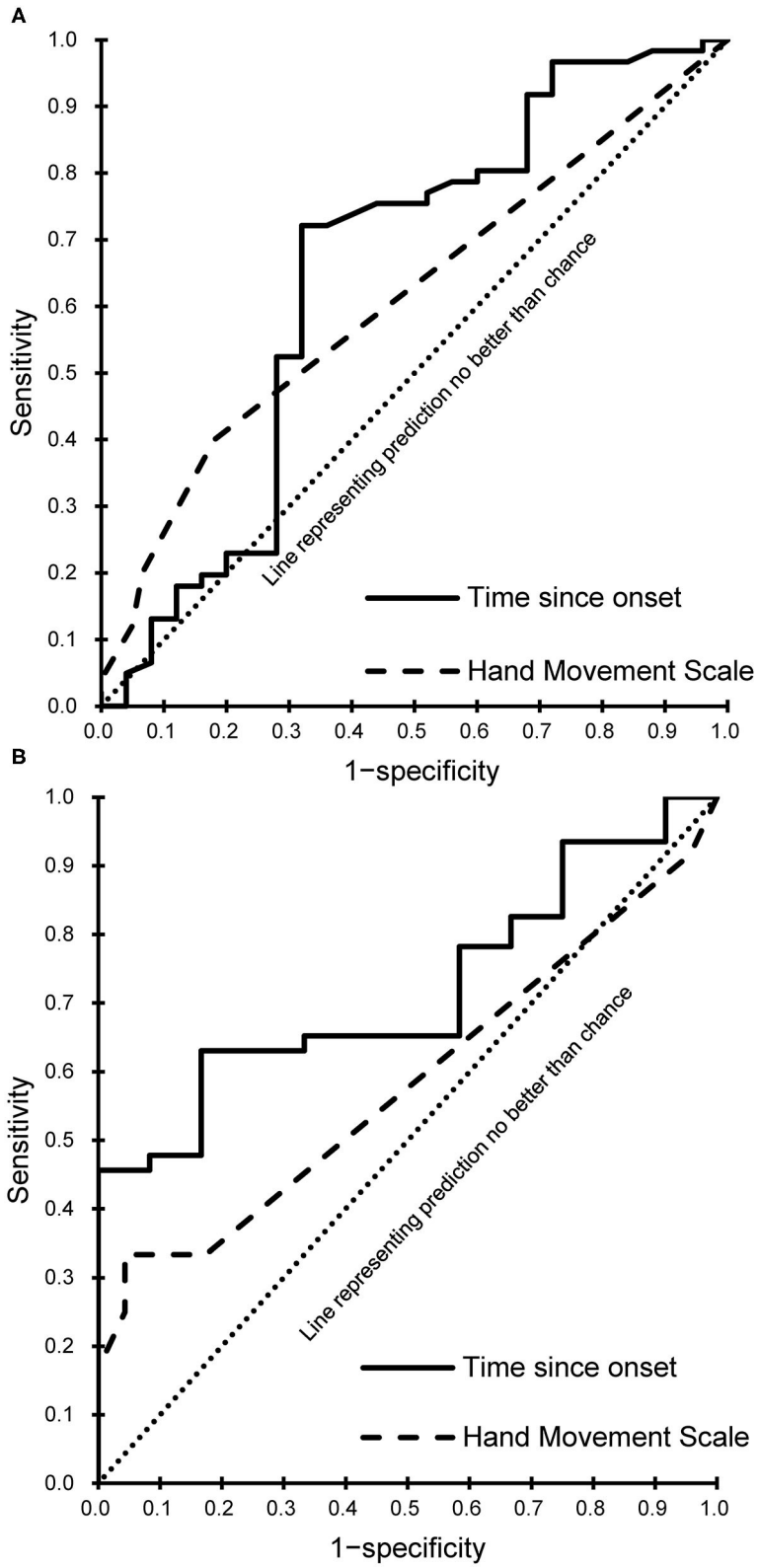

FIGURE 3 | Receiver operating characteristic curves of the meaningful predictors. **(A)** Subacute phase. **(B)** Chronic phase.

TABLE 3 | The sensitivity and specificity for the cut-off score of the meaningful predictors according to stroke phase.

Phase	Meaningful predictor	AUC	95% CI		Cut-off	Sensitivity	Specificity
Subacute	Time since onset	0.65	0.50	0.79	97.5	68.9%	68%
	HMS	0.61	0.47	0.75	2.5	40%	82%
Chronic	Time since onset	0.72	0.58	0.86	299.5	65.2%	66.7%
	HMS	0.58	0.37	0.79	2.5	33%	82.6%

AUC, area under the receiver operating characteristic curve; CI, confidence interval; HMS, Hand Movement Scale.

also easy to perform. For these reasons, the HMS is likely to be a suitable and convenient criterion for responders of RT.

The outcomes of this study are consistent with those of several prior studies showing that baseline dexterity is a major predictor of post-RT upper limb recovery. Hsieh et al. (9) and Huang et al. (10) demonstrated that the Box and Block Test score in patients with chronic stroke was a predictor of motor and functional outcomes following RT, whereas Franceschini et al. (11) confirmed that the Box and Block Test score was a predictor of post-RT functional outcome in patients with subacute stroke. Baseline hand movement, not baseline proximal upper limb function, predicts a favorable outcome; this may be explained by the fact that distal upper limb function is mostly represented unilaterally in the brain, whereas proximal upper limb function is represented bilaterally. Therefore, preservation of hand movement is more related to the degree of sparing of corticospinal pathways than it is to proximal upper limb function and represents a higher recovery potential (40, 41).

Herein, the time since onset was likewise identified as a meaningful predictor of a favorable outcome following RT. Undergoing RT at a shorter time since onset was more effective, specifically before 97.5 days since onset and 299.5 days since onset for patients with subacute and chronic stroke, respectively. Previous studies have confirmed that earlier intervention can predict favorable post-intervention outcomes in such cases. Duret et al. (12) and Mazzoleni et al. (42) suggested that early administration of RT could provide greater functional improvement. Paolucci et al. (18) demonstrated that CT was more effective in patients for whom it was initiated soon after stroke onset, compared to CT in those for whom it was initiated later. The predictive capability of the time since onset may not be surprising, because a shorter time after stroke may be associated with a greater potential for recovery, possibly improving the response to RT. Although stroke recovery is heterogeneous and the long-term effects of stroke are determined by the site and size of the initial stroke lesion, almost all stroke recovery follows a logarithmic pattern time course; in many stroke patients, motor recovery is almost complete after 8 to 12 weeks (1, 43). The time period of 97.5 days since onset that we identified is in line with the results of these prior studies. Moreover, the administration of RT within 299.5 days since onset in patients with chronic stroke was promising for significant recovery, albeit to a lesser degree than that observed for patients in the subacute phase. There is a growing body of evidence supporting the argument that the potential for neuroplasticity and adaptation continues and that motor function improves over time in chronic stroke (16, 44).

The MCID of the FMA-UE has been established 5.25 for patients with chronic stroke (31). For subacute stroke, we selected an FMA-UE score of 9 as the MCID (30). Although another study found an MCID of 4 for patients with subacute stroke (45), we chose 9 because motor recovery in the subacute phase is better than that in the chronic phase. Additionally, mean time since onset in our population was closer to that of Narayan Arya et al. (30) than that of Lundquist et al. (45).

Interestingly, the predictors found in responders of RT among patients with subacute and chronic stroke, were HMS and time since onset. Although both predictors were statistically significant for patients with subacute stroke, they had borderline statistical significance for patients with chronic stroke. This can be explained by combining the characteristics of the two variables. As demonstrated earlier, although a high HMS demonstrates a high potential for recovery due to relatively well-preserved corticospinal pathways following a stroke, RT may have not been as effective in the chronic phase as it was in the subacute phase, and other factors, such as muscle atrophy, fatigue, and pain, may have had a greater effect than the neural substrate related to neural plasticity.

No robotic kinematic measure examined in this study was able to predict responders of RT. This finding is supported by the study of Duret et al. (12), in which predictors of a favorable motor outcome in patients with subacute stroke were identified. However, robotic kinematic measures were unable to predict favorable post-RT outcomes because the measures currently being used are insufficient. Schwarz et al. (46) conducted a systematic review on the kinematic assessment of upper limb movements and demonstrated that the reliability, correlation with the FMA-UE score, and ability to detect longitudinal changes of the kinematic measures used were low. However, Krebs et al. (47) reported that a standard clinical outcome measure and significant correlation was observed when kinematic and kinetic measures were included simultaneously. As such, if an upgraded standardized kinematic measure or kinematic and kinetic measure is developed, additional research using it as a potential predictor may be needed.

This study has several limitations. First, as this was a retrospective study, potential confounding factors that could have affected the clinical outcomes were not accounted for, and because patients of just one rehabilitation hospital were studied, there may have been selection bias. Nonetheless, given that

a relatively standardized rehabilitation therapy was conducted, and as all study subjects were patients admitted to the same rehabilitation hospital, environmental factors were minimized. Additionally, this study was conducted with a sufficient number of patients with subacute and chronic stroke. Second, it is difficult to say whether the identified predictors solely predicted favorable post-RT outcomes, as CT was administered along with RT. However, considering that CT and RT were administered to all patients and that RT is rarely administered without CT, the outcomes of this study can be used as realistic predictors. Third, early and late subacute phases were not divided despite the chances of the influence of these phases on recovery and outcome. Fourth, aside from the chronic phase prediction model and the time since onset in the chronic phase, the AUC values of the remaining prediction model and meaningful predictors were <0.7, indicating insufficient discrimination ability. Lastly, other kinematic measures such as movement duration, peak velocity and peak acceleration known to be related to outcome after RT (48), and neuropsychological impairments such as aphasia and neglect known to be related to post-stroke motor recovery (49, 50), psychosocial, and emotional factors, which may have affected the outcome, were not included as potential predictors. Therefore, controlled, prospective, and multicenter studies including a more comprehensive set of potential predictors are required to validate and improve our results in the future.

CONCLUSIONS

Better hand movement and a shorter time since onset can realistically serve to predict clinically significant motor improvement in upper limb impairment after RT with InMotion2 alongside CT, in patients with subacute and chronic stroke, whereas other demographic characteristics and robotic kinematic measures cannot predict responders of RT. These findings may assist healthcare professionals in discerning optimal patients for RT and in accurately informing patients and caregivers about the outcomes of RT.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of the Institutional Review Board of the National Rehabilitation Center in South Korea. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JJL and J-HS contributed to conception and design of the study, performed the statistical analysis, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.668923/full#supplementary-material

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A Comparative Efficacy Study of Robotic Priming of Bilateral Approach in Stroke Rehabilitation

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Background: Stroke survivors can remain impaired in body functions, activity, and participation. A novel rehabilitation regimen is required to obtain scientific evidence and to help clinicians determine effective interventions for stroke. Mirror therapy (MT) and bilateral upper limb training (BULT) are based on the tenet of bilateral movement practice; however, the additional effect of bilateral robotic priming combined with these two therapies is unclear.

Objectives: This study examined the effects of two hybrid therapies, robotic priming combined with MT and robotic priming combined with BULT, in stroke survivors.

Methodology: The study randomized 31 participants to groups that received robotic priming combined with MT ($n = 15$) or robotic priming combined with BULT ($n = 16$). Outcome measures included the Fugl–Meyer Assessment (FMA), the revised Nottingham Sensory Assessment (rNSA), the Chedoke Arm and Hand Activity Inventory (CAHAI), and accelerometer data.

Results: Both groups showed statistically significant within-group improvements in most outcome measures. Significant between-group differences and medium-to-large effect sizes were found in favor of the group that received robotic priming combined with MT based on the FMA distal part subscale scores, FMA total scores, and accelerometer data.

Conclusion: Robotic priming combined with MT may have beneficial effects for patients in the improvements of overall and distal arm motor impairment as well as affected arm use in real life. Additional follow-up, a larger sample size, and consideration of the effect of lesion location or different levels of cognitive impairment are warranted to validate our findings in future studies.

Clinical trial registration: www.ClinicalTrials.gov, identifier NCT03773653.

Keywords: priming, mirror therapy, bilateral upper limb training, mirror visual feedback, motor learning, stroke

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INTRODUCTION

Rehabilitation of stroke patients is a long process that takes several months or even years. More than 30% of stroke patients admitted to the hospital remain impaired in autonomy, engagement, and fulfillment of societal roles (1). Rehabilitation methods are needed to allow individuals to continue to maximize gains in arm impairment and function more than 3 months after stroke. Priming, an implicit learning technique, can be used to prepare the brain for a more plastic response before task-based rehabilitative therapy, thereby leading to improved functional outcomes (2). Bilateral robotic priming, an extended application of robotic therapy involving bimanual, repetitive, mirror-symmetric movement practice, is a type of movement-based priming with a low-tech robot device (3). It can normalize cortical inhibition, prepare the brain for subsequent rehabilitative therapies, and facilitate recovery through a task-oriented approach (2, 4, 5).

In recent years, reports on task-oriented approaches have increased. Mirror therapy (MT) and bilateral upper limb training (BULT) are bimanual strategies for stroke recovery and can be applied as task-oriented approaches (3, 6). BULT is performed intensively and simultaneously with both arms in a symmetrical or alternating pattern. According to the classical definition, BULT is typically symmetrical, both temporally and spatially, and can exploit the coupling effect of both arms to improve movement of the affected arm, for example, in simultaneously lifting two soft drink bottles (3, 7–11). Asymmetrical movement with different temporal and spatial relationships for the achievement of common goals, such as opening a jar of coffee or drying one's own back with a towel, has also been viewed as a kind of BULT in recent studies. BULT focuses on facilitating the coordination of a variety of different real-world tasks (12–14). For comprehensive effects, rehabilitation regimens should include not only classical definitive bilateral arm training but also the bilateral synergy framework.

MT is a promising approach in which a mirror is positioned vertically between the two arms so that the reflected image of the less affected arm gives the appearance of normal movement in the affected arm (15). The possible mechanism for the success of this therapy is that it could induce primary motor cortex cortical activations (16). Compared with BULT, MT has been proposed to provide significant benefits to distal hand function and superior improvements in sensory deficits, quality of life, and the amount of use of the affected arm (6, 17). A previous study found that BULT integrated with bilateral robotic priming was more effective than unilateral hybrid therapy for improving motor function. The efficacy was believed to result from inter limb coupling and the priming effects of bilateral symmetric practice (18). MT and BULT are both bimanual strategies for stroke; however, the distinct effect of bilateral robotic priming combined with MT and BULT is unclear.

In summary, bilateral robotic priming, MT, and BULT have been considered to be types of bilateral approaches (3, 6) and are based on the tenet of bilateral movement practice. MT and BULT can be provided as task-oriented approaches involving both arms. When combined with bilateral robotic priming, the effects of MT and BULT may be increased and differentiated. Bilateral hybrid therapy (bilateral robotic priming plus BULT) yielded a better effect on motor improvement (18). However, if bilateral robotic priming is followed by MT, which is also a type of bilateral approach but involves mirror visual feedback, the regimen may enhance the recovery effect.

This study compared the efficacy of these two different hybrid approaches that are both based on the tenet of bilateral movement practice. We hypothesized that within-group differences in the robotic primed MT (RMT) and robotic primed BULT (RBULT) groups would be found after the intervention. Furthermore, we hypothesized that sensorimotor function recovery would be better in the RMT group than in the RBULT group.

MATERIALS AND METHODS

Research Design

This was a single-blind randomized controlled trial. An independent research assistant performed randomization by using a computer-generated random-sequence table with four permuted blocks stratified by the total Fugl–Meyer Assessment (FMA) upper arm pretest score (<35 or ≥ 35) (19) and the side containing the lesion (right or left). The ethics review board at each participating site approved the study protocol.

Instruments

The primary outcome measure, the FMA, quantitatively measures the recovery of motor impairment and has high reliability, validity, and responsiveness in stroke patients (20, 21). Motor impairment levels were classified as severe (score 0–15), severe to moderate (16–34), moderate to mild (35–53), or mild (54–66) (19). The proximal (0–42), distal (0–24), and total (0–66) FMA–upper extremity (UE) scores were used to compare different UE elements in the current study.

The secondary outcome measures were the revised Nottingham Sensory Assessment (rNSA), the Chedoke Arm and Hand Activity Inventory (CAHAI), and accelerometry.

Based on the superior effects of MT on sensory improvement as reported in a previous study (8), we used the rNSA to assess sensory impairments (22). For this test, we measured (1) tactile sensation, including light touch, temperature, pinprick, pressure, tactile localization, and simultaneous bilateral touch; (2) proprioception; and (3) stereognosis. Higher rNSA scores indicate lower impairment.

RMT and RBULT are based on the tenet of bilateral movement practice; therefore, the CAHAI was chosen to assess the performance of the affected arm in 13 daily activities requiring bilateral arm function, such as opening a jar of coffee and drying one's own back with a towel. Higher scores indicate higher quality of performance (23).

To monitor the amount of use of the affected arm in real life, mean counts were collected from a wrist accelerometer, the triaxial wearable sensor GT3X+ or wGT3X-BT (ActiGraph Corporation, Pensacola, FL, USA), which was worn on the first 3 and the last 3 days of the intervention period, except when bathing. We used the vector magnitude average count, which

is the average vector magnitude of all three axes during the scored time. In our case, the scored time was 3 days. During this period, activity that caused the acceleration signal was "counted" as activity. The accelerometer sampling rate was 100 Hz, and data were summed over 60-s epochs; this device has been suggested for use outside of the clinic (24, 25).

Participant Selection

Patients were recruited by clinical staff or investigators from four outpatient clinics. A patient who was willing to join the current study could also contact the investigators *via* clinical staff. The Committee on Human Research approved the study. In accordance with the institutional review board approval, the experimental procedures, risks, and benefits of the study were explained to the potential participants after they were identified. Our recruitment procedures ensured the participants were not coerced to join the study. Patient privacy and data security were handled appropriately.

After the participants provided informed consent verbally and in writing, the study assessor conducted further eligibility and baseline assessments. A standard imaging method was used to confirm the stroke diagnosis. The inclusion and exclusion criteria were selected based on a review of the relevant literature in which potential factors were considered (6, 26). The inclusion criteria were (1) $\geq$3 months after the onset of a first-ever unilateral stroke; (2) patients aged 18–80 years old; (3) baseline FMA UE score between 16 and 53 (19, 27); (4) baseline spasticity score on the Modified Ashworth Scale of $\leq$3 (28); (5) ability to follow study instructions; (6) no serious vision, neurologic, orthopedic, or medical problems based on medical history data and physical examinations; (7) no Wernicke's aphasia in which the participant may have difficulty following the instructions for assessments and intervention; and (8) no participation in other studies.

To date, no published research has compared the effects of RMT with RBULT among stroke patients. Thus, the sample size required for this study was estimated based on a previous study (6). Based on the smallest sample size needed for achieving a statistical power of 0.80 with a one-sided type I error of 0.05, we deemed a total sample size of 28 with 14 subjects for each group was sufficient to validate the advantages of MT on somatosensory function.

Procedures

All participants received 40–45 min of bilateral robotic priming and 40–45 min of MT or BULT. As determined from the designs of previous studies on bimanual strategies and the feasible number of clinical patient visits to the hospital (6, 18), the schedule for both groups was 3 days/week for 6 weeks. The intervention was delivered by three licensed and certified occupational therapists. To confirm that the intervention was provided as intended, practice guidelines were used, and the principal investigator supervised these sessions.

The Bi-Manu-Track robot (Reha-Stim Co., Berlin, Germany) was used for bilateral robotic priming practice. The robot enables two symmetric movements (forearm pronation/supination and wrist flexion/extension) in three treatment modes (passive–passive mode, active–passive mode, and active–active mode). A computer task was supplied with the robot practice to enhance the participant compliance. The participants performed ~11,200–1,600 repetitions of the movements each day.

During MT, a wooden mirror box ($41 \times 50 \times 33$ cm^3) was placed so that the mirrored side was in the midsagittal plane of the participant (29). The participant was then guided to watch the mirror image of the movement of the less affected arm and move both arms as symmetrically as possible. To ensure that the participants watched the mirrored image, the less affected arm was hidden by a bed tray table (30) (**Figure 1**). The intervention activities involved task-oriented activities such as picking up and putting down items in a box, lifting two soft drink bottles, and other functional tasks involved in daily activities.

During BULT, the participants performed different types of tasks, including (1) common goal activities that depend heavily on cooperation between both arms, such as pulling up the trousers or spooning soup out of a bowl, and (2) independent goal practice tasks in which the arms are not necessarily interdependent, such as simultaneously lifting two soft drink bottles or manipulating two coins (**Figure 1**) (12, 14).

In addition to the clinic-based RMT or RBULT, each participant practiced the transfer package at home for 5 days/week to transfer the improved abilities to real-life situations. The transfer package included a behavioral contract, three home skills practices (e.g., lifting two soft drink bottles, picking up and putting down items in a box, or lifting a plate with both hands) for a total of 30 min, six important daily activities involving the affected arm (e.g., taking clothes out of the closet, eating snacks, or turning on the light), and a home diary to record the amount of use of the affected arm (**Figure 3**). The therapists helped participants with compliance management and problem solving at each clinic visit (6, 31).

All interventions were graded and designed according to the level of impairments and life experience of the participants as well as their individual needs and rehabilitation goals (5, 6, 18, 29). To foster engagement in the practice of transfer tasks, we interviewed the participants to identify the main problem areas and set their three prioritized goals. For example, a 48-year-old housewife who sustained a left hemispheric stroke set kitchen activities as one of her prioritized goals of functional recovery. Because the participant experienced difficulty in flexing her affected arm during kitchen activities, the therapist instructed her to practice lifting a hot water kettle to make a cup of tea. As she improved in task performance, the kettle was filled with more water to make the task more challenging. The treating therapists worked with the participants to identify the skills needed for practice to ensure the transfer package fit into the personal needs of the participants as they progressed overtime. Any other routine interdisciplinary rehabilitation without emphasis on arm training continued as usual.

Data Collection

Outcome assessments were conducted at baseline and immediately after the intervention. The fully trained assessor was a licensed occupational therapist blinded to the group assignments, and the participants were blinded to the study hypotheses.

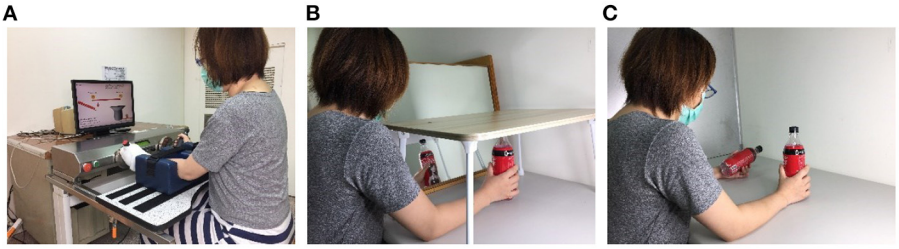

FIGURE 1 | Intervention setup for Bi-Manu-Track robot **(A)**, mirror therapy **(B)**, and bilateral upper limb training **(C)**.

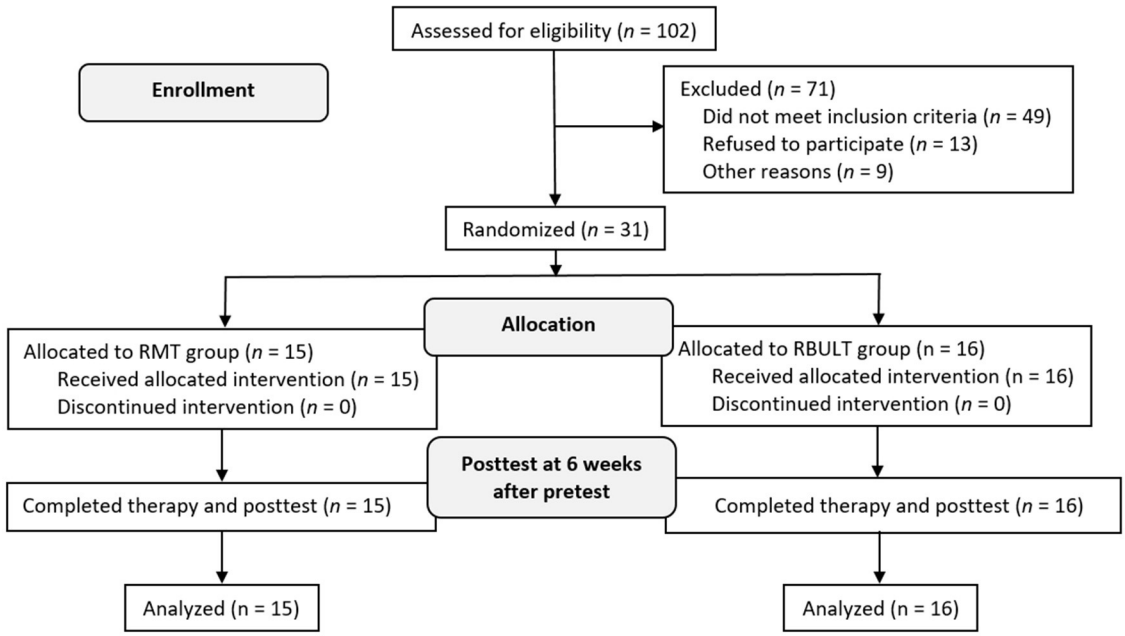

FIGURE 2 | Consolidated standards of reporting trials flowchart of the study.

Data Analysis

Depending on the data type, within-group data and between-group data were analyzed using χ^2 tests, paired *t*-tests, or independent *t*-tests. The treatment assignment in this randomized controlled trial depended on the baseline score; therefore, analysis of covariance was used to achieve higher power (32). The effect size between the two groups, eta-squared (η^2), was calculated by analysis of covariance, and large, moderate, and small effect sizes were represented by η^2 values of at least 0.14, 0.06, and 0.01, respectively (33). The baseline score was the covariate, the group was the independent variable, and the posttreatment score was the dependent variable. For each subscale of the rNSA, only participants who had less than a perfect score at baseline (demonstrating sensory impairment) were included in the data analysis. The significance (α) level was set at 0.05. The analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) software.

RESULTS

The study recruited 31 patients [19 men (61.29%)] who were randomly assigned to the RMT (15 patients) or RBULT (16 patients) group (**Figure 2**). The cohort has a mean age of 55.53 (SD, 12.16) years and a mean of 19 (SD, 16.80) months after stroke. The two treatment groups were statistically equivalent in baseline demographics and clinical characteristics, motor impairment level, and stroke severity (**Table 1**). All participants finished the 6-week intervention and posttreatment assessment.

The post treatment evaluation showed statistically significant within-group improvements in most outcome measures in both groups, including the FMA score, temperature perception, touch localization, tactile total scale score, proprioception, and the CAHAI score. Statistically significant within-group improvements in light touch perception, pinprick perception, and accelerometer data were shown only in the RMT group, whereas significant improvements in stereognosis were shown

FIGURE 3 | Diagram of the study design.

only in the RBULT group (**Table 2**). Moreover, statistically significant intergroup differences with medium to large effect sizes in favor of the RMT group were found in the FMA distal part subscale score ($p = 0.03$), FMA total score ($p = 0.01$), and accelerometer data ($p = 0.02$). These results reflected the distinctive effects of RMT in improving motor function and the actual amount of functional arm use.

After the adaptation phase of the study, no intolerable adverse events related to treatment were reported. In light of our findings, with a one-sided type I error rate of 0.05 and an effect size (η^2) of 0.07 to 0.14, the power of our study was 31–58%.

TABLE 1 | Demographics and baseline clinical characteristics.

Characteristics	RMT ($n = 15$)	RBULT ($n = 16$)	*p*-value
Age, mean (SD), years	55.71 (9.2)	55.36 (14.72)	0.94
Sex, *n* (%)			
Male	8 (53.33)	11 (68.75)	0.47
Female	7 (46.67)	5 (31.25)	
Side of lesion, *n* (%)			
Right	9 (60.00)	9 (56.25)	>0.99
Left	6 (40.00)	7 (43.75)	
Type of stroke, *n* (%)			
Hemorrhage	8 (53.33)	5 (31.25)	0.29
Ischemia	7 (46.67)	11 (68.75)	
Months after stroke, mean (SD)	18.13 (15.11)	20.00 (18.69)	0.76
FMA-UE, mean (SD)	34.93 (7.7)	32.44 (7.68)	0.37
NIHSS, mean (SD)	5.67 (2.02)	6.31 (2.89)	0.48

FMA-UE, upper extremity motor subscale of the Fugl–Meyer Assessment; NIHSS, National Institutes of Health Stroke Scale; RBULT, robotic primed bilateral upper limb training; RMT, robotic primed mirror therapy; SD, standard deviation.

DISCUSSION

Prior studies have noted the additional effect of priming combined with a task-oriented approach. For chronic stroke patients, combining movement-based priming and task-oriented approaches can be a promising intervention strategy for recovery in the arms (34). The objective of the study was to identify the efficacy of RMT and RBULT, two different hybrid approaches that are based on the tenet of bilateral movement practice. The study results indicate that both groups of stroke survivors showed significant benefits in the recovery of most sensorimotor functions. Furthermore, RMT may significantly improve distal and total arm motor impairment as well as the actual amount of functional arm use, in accordance with previous findings. However, this study was unable to demonstrate consistent evidence of sensory recovery.

Studies have demonstrated that MT is a promising method to restore motor function in the distal arm (21, 29, 35). Superior motor recovery in the distal arm with RMT can be explained by the following factors. First, in our study, the participants in the RBULT group involuntarily watched the performance of the affected hand during therapies, whereas the use of the bed tray table in the RMT group forced participants to look at the reflected movement of the less affected arm. The forced visual perception of the arm movement of the less affected arm may contribute to motor learning and elicit increased therapy effects (36). In addition, the conflicting spatial relationship between real and reflected objects reinforces the difficulty of MT task-oriented activities. The participants in the RMT group needed to focus more intently on performing activities carefully and correctly and therefore may have achieved better performance and recovery.

TABLE 2 | Descriptive and inferential statistics of the outcome measures at baseline and posttest per treatment group.

Outcome measures	Baseline, mean (SD)		Post treatment, mean (SD)		ANCOVA	
	RMT ($n = 15$)	RBULT ($n = 16$)	RMT ($n = 15$)	RBULT ($n = 16$)	p-value between groups	Effect size η^2 (95% CI)
FMA-UE						
Proximal	27.4 (4.03)	26.63 (4.57)	31.53 (3.62)**	29.94 (5.12)**	0.12	0.05 (0–0.25)
Distal	7.53 (4.53)	5.81 (4.04)	11.93 (6.8)**	8.5 (5.37)**	0.03§	0.07 (0–0.28)
Total	34.93 (7.7)	32.44 (7.68)	43.47 (9.43)**	38.44 (9.67)**	0.01§	0.13 (0–0.35)
rNSA[a]						
Light touch	7.86 (4.38)	8.33 (4.27)	9.71 (4.79)*	9.67 (4.55)	0.34	0.01 (0–0.28)
Temperature	9.82 (6.21)	9.3 (5.7)	11.91 (5.52)**	11 (5.62)**	0.29	0.02 (0–0.25)
Pinprick	8.86 (4.45)	9.83 (5)	11.71 (6.34)*	12.83 (4.49)	0.54	<0.01 (0–0.10)
Pressure	11.33 (5.09)	11.4 (4.93)	12.5 (5.54)	15.6 (5.37)	0.93	0.24 (0–0.55)
Localization	7.62 (4.03)	9.47 (6.46)	10.08 (4.55)*	11.2 (6.57)**	0.20	0.02 (0–0.21)
Bilateral simultaneous touch	7.33 (6.92)	4.2 (3.03)	10.83 (5.04)	7.4 (8.32)	0.47	0.01 (0–0.31)
Tactile total scale	74.86 (27.69)	79.73 (31.2)	83.14 (23.09)**	86.67 (24.96)*	0.35	<0.01 (0–0.08)
Proprioception	16.1 (5.13)	14.36 (3.98)	17.8 (4.59)*	15.91 (4.85)*	0.43	<0.01 (0–0.18)
Stereognosis	9.73 (9.13)	12.62 (7.96)	12.55 (9.15)	13.85 (8.55)**	0.14	0.06 (0–0.29)
CAHAI	39.2 (11.59)	37.25 (12.74)	51.4 (13.98)**	47 (13.63)**	0.07	0.07 (0–0.28)
Accelerometer	453.32 (206.37)	443.64 (188.73)	541.2 (247.22)*	433.38 (197.15)	0.02§	0.14 (0–0.36)

Values are presented as the mean (standard deviation).

CAHAI, Chedoke Arm and Hand Activity Inventory; RBULT, robotic primed bilateral upper limb training; RMT, robotic primed mirror therapy; rNSA, revised Nottingham Sensory Assessment.

[a]*Only those participants who scored less than full scores at baseline, indicating sensation impairments, were included in the data analysis. The numbers of individuals in the RMT group and RBULT group were 7 vs. 6, 11 vs. 10, 7 vs. 6, 6 vs. 5, 13 vs. 15, 6 vs. 5, 14 vs. 15, 10 vs. 11, and 11 vs. 13 for the analysis of light touch, temperature, pinprick, pressure, localization, bilateral simultaneous touch, tactile total scale, proprioception, and stereognosis, respectively.*

§*p-value <0.05 in the between-group analysis. *p-value <0.05 in the within-group analysis. **p-value <0.01 in the within-group analysis.*

In addition, the participants with good proprioceptive function could directly correct their movements by comparing the visual input from the reflected image superimposed on the affected arm and the proprioceptive inputs from that arm. On the other hand, for the participants with impaired proprioceptive function, observing the action of the superimposed reflection may have guided the movements of the affected arm more directly and reduced their motor impairment. However, in the current study, the limited space available for movement under the bed tray table may also have limited the recovery of the proximal part in the RMT group, preventing any significant between-group benefit in favor of RMT for the proximal limb.

Another clinically significant finding was that the mean differences in the FMA and CAHAI scores of both groups after the study intervention were higher than the minimal clinically important differences (37–39). Compared with other recent studies with a comparable time since stroke and comparable baseline impairment as indicated by the FMA, this study showed a mean difference in the RMT group that was much larger than the minimal clinically important differences and the mean difference in robotic therapies without MT (40). Higher mean differences were also found in the comparison of the CAHAI scores between this study and our previous study (41). However, there were similar findings on the combination of robot-assisted therapy and constraint-induced therapy (42). In addition, numerous priming techniques can be combined with task-oriented approaches. Similar findings have been reported for stimulation-based and manipulation input sensory priming techniques assessed with the FMA (34, 43, 44). This may indicate the efficiency of combining contemporary therapies with priming techniques and the need to clarify the best combination regimen in future studies.

A previous MT study that used motor activity logs to investigate the self-perceived assessments of patients of their use of the affected arm found only a non-significant trend in increased arm use (6). To the best of our knowledge, this is the first study investigating the effect of MT on the objective amount of use as an outcome variable. The RMT group in our study demonstrated a significant improvement, the causes of which may include the following: first, in contrast to self-perceived assessment with a motor activity log, accelerometers can capture all activity without over- or under-reporting results due to recall bias; therefore, these devices can objectively quantify the true improvement in the amount of affected arm use after the RMT. Second, this improvement may have been the result of significant recovery of the distal arm, enhancing the participants' motivation to use their affected arms. Learned nonuse was thus reduced, and the use of the affected arm was increased.

Finally, the significant between-group effects for somatosensory function were not consistent with previous studies. Findings on the recovery of sensory function have varied across randomized controlled trials of MT. Some studies found beneficial effects on the degree of improvement in cutaneous sensitivity, temperature perception, or pain perception, whereas

other studies did not find any differences (6, 45). Different MT regimens involve different active or passive sensory stimulation protocols that may have different effects on sensory recovery. These findings may need to be clarified in a well-designed study.

Limitations and Future Research

Our study has limitations. First, the results of priming may be evident at follow-up (2, 4, 46). Without a follow-up evaluation, we could not determine whether the greater immediate effects in the RMT group were maintained. Second, the sample size was small. A minimum total sample size of 56 with 28 subjects for each group would have provided a statistical power of 0.80 with a two-sided type I error threshold of 0.05 in improving motor impairment (i.e., the FMA total score). Third, we did not consider the effect of lesion location or different levels of cognitive impairments. These factors should be taken into account in future studies.

In recent years, the age of stroke patients has a decreasing trend (47). The average age of the participants in this study was much lower than the average age of stroke patients, and age may influence activities of daily living improvement (48). In addition, the participants had moderate to mild impairment on average, and the therapy administered may be more limited or more beneficial to stroke survivors with different levels of impairment. These limitations imply that a careful interpretation of the study results is needed. Finally, combining bilateral robotic priming and task-oriented approaches to arm treatment could be a promising intervention strategy for reducing motor impairment and enhancing affected arm use. However, regarding the activity level in the International Classification of Functioning, Disability, and Health domains, for other types of priming (e.g., stimulation and sensory priming), there is no conclusive evidence to support the combined use of priming with task-oriented approaches (36). Our study may serve as basis for future studies.

CONCLUSIONS

Stroke survivors can remain impaired at least 3 months after onset. This is the first study to compare the efficacy of robotic priming of MT and BULT for stroke; it provides scientific evidence as well as a reference for clinicians in determining effective interventions. The results suggest that both hybrid therapies provide benefits in motor improvement; however, RMT may promote better recovery in the distal parts of the arm and the entire arm as well as lead to a greater increase in the actual amount of functional arm use. In individually tailored rehabilitation therapy plans involving bilateral practice, RMT may be a better option if improvements in motor impairment or increases in the use of the affected arm are the goal of treatment. The results of this study warrant further research with a larger sample to address the retention of therapeutic benefits.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because based on the Personal Information Protection Act enacted in Taiwan, individualized data cannot be released for the protection of privacy. Requests to access the datasets should be directed to kehchunglin@ntu.edu.tw.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee, National Taiwan University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

K-CL, C-LC, GY, Y-JC, and Y-YL contributed to the conception of the work. K-CL designed the experiments. Y-CL performed the experiments. K-CL and Y-CL analyzed the data and wrote the manuscript. C-TL contributed materials. All authors contributed to the article and approved the submitted version.

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Peer Support to Enhance Social and Emotional Self-Management Following Acquired Brain Injury Rehabilitation: Design of a Pre–post Study With Process Evaluation

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Background: Specialized rehabilitation following acquired brain injury provides intensive multidisciplinary treatment to individuals with complex disabilities for optimizing recovery and supporting a safe transition to the community. Post-specialist rehabilitation, patients and caregivers have reported a need for support. We present the design of an implementation study to evaluate a new self-management support service for individuals with acquired brain injury and their caregivers.

Methods: This is a pre–post intervention study with a mixed-method design. The study population comprises individuals aged ≥18 years with acquired brain injury living independently following specialized rehabilitation in the Southern part of the Netherlands. All participants receive a post-rehabilitation support service. The support service consists of several house visits by a peer support volunteer in the first weeks after specialized rehabilitation treatment. The peer support volunteers are trained according to an adapted version of the previously developed Self-Management Support (SMS) program. The SMS program is directed at improving social and emotional self-management. Patient outcomes are assessed by questionnaire pre-, directly post-, and 6 months post-intervention. The primary patient outcome measure is self-efficacy. Secondary outcomes are perceived autonomy, quality of life, and psychological well-being. A process evaluation will be performed to gain insight into barriers and facilitators for the implementation of peer-led SMS by combining both quantitative, questionnaire data and qualitative data derived from focus groups with peer supporters and patients. In a workshop with relevant stakeholders, possibilities for dissemination and sustainability will be explored.

Discussion: This paper describes the design of a practice-based study on feasibility, barriers, and facilitators to the implementation of a home-based, peer-led self-management support intervention for patients with acquired brain injury. We will

quantitatively and qualitatively evaluate the change in relevant patient outcomes pre- and post-intervention and the barriers and facilitators related to the implementation of the intervention. Following a positive evaluation, the final stage of the study aims to facilitate deployment and utilization of the intervention.

Keywords: self-management, SMS, peer support, rehabilitation, acquired brain injury, self-efficacy, follow-up

INTRODUCTION

Advances in acute and critical care management have increased the number of people surviving acquired brain injury. As a sudden, severe event, acquired brain injury can cause persistent, even life-long consequences for the patients' participation. This burden affects the daily life of survivors and their families. In the Netherlands, at current, an estimated 650,000 people and their families are dealing with the consequences of acquired brain injury, accounting for 25% of total healthcare costs, not to mention relevant social costs (1).

Specialized rehabilitation care provides intensive multidisciplinary care to individuals with complex disabilities following acquired brain injury to optimize their recovery after hospital admission and support a safe transition to the community (2, 3). Post-specialist rehabilitation, the intensity of formal care, treatment, and support is strongly reduced. The transition from inpatient or outpatient rehabilitation to living at home independently is considered difficult by many patients (4–6).

Previous studies revealed that there is a need for support of patients and their informal caregivers when returning home after rehabilitation, and a need for the potentially added value of hands-on experts, such as peers, in providing this support (4, 6–8). Peer supporters have an exclusive expertise that can be useful, because they have experienced these difficulties themselves. In addiction and mental healthcare services, peer supporters have proven to be beneficial to the patients' activation; patients become healthier and have a better quality of life (9).

Tailored self-management interventions are of crucial importance for patients and informal caregivers to further optimize the path of care toward independent living and are expected to be of value post-rehabilitation (10). A widely applied self-management strategy in healthcare developed by Lorig et al. (11) focuses on three self-management tasks: medical management, role management, and emotional management. Self-management is closely linked to self-efficacy, as self-efficacy reflects the person's confidence in the belief in their own abilities (12). We previously studied Lorig's self-management strategy in the primary care setting (13). This Self-Management Support program (SMS) includes principles of problem solving and cognitive behavioral change (13). Although nurse-led SMS effectively improves self-efficacy, daily functioning, and social participation in multiple chronic conditions, its implementation in practice turned out to be difficult (14). A challenge has been the often disease-focused context in which SMS has to be integrated. More recently, we performed a pilot study among people that reached out to the municipality for support with social participation, in which SMS was provided by trained volunteers; that appeared to be successful (15). These volunteers showed that they could perform the intervention as well, in contrast to what is often expected by healthcare professionals (15).

The study presented here will focus on patients with acquired brain injury. Typically, an acquired brain injury is not hereditary; it is congenital, degenerative, or induced by birth trauma. Essentially, this type of brain injury occurs suddenly, leaving those who are severely affected struggling with everyday function and adaptation and facing challenges in everyday functioning (16). Improving these patients' problem solving skills and acquiring an active coping style are known to improve their health-related quality of life (3). Indeed, self-management interventions carried out by peer supporters have been successful (7, 17, 18). Previous studies, however, did not take into account the problems of the transition following rehabilitation, in the path of care toward living independent.

We present the design of a mixed-method pre–post study to evaluate the implementation of SMS provided by peer support volunteers (hereafter referred to as "peer supporters") to adults with acquired brain injury following specialist rehabilitation in a large rehabilitation center in the South of The Netherlands. Besides the evaluation of patient outcome, a thorough process evaluation will be performed to investigate barriers and potential facilitators for the implementation of peer-led SMS for patients with acquired brain injury.

Research Questions

Pre–post Evaluation

1. Does the degree of self-efficacy of individuals with brain injury improve after peer-led SMS?
2. Does self-efficacy improve more in patients who had a more optimal "dose" of peer-led SMS?

Process Evaluation

A process evaluation of the SMS intervention is directed toward the following research questions:

1. What are the reach, dose, and fidelity of the peer-led SMS intervention?
2. How is SMS experienced by patients, their informal caregivers, peer supporters, and health professionals?
3. What are barriers and facilitators of the peer-led SMS intervention?
4. How does the intended cooperation between health professionals and peer supporters evolve during their involvement with patients?
5. What is necessary for definitive implementation of the peer-led SMS intervention in the rehabilitation center?

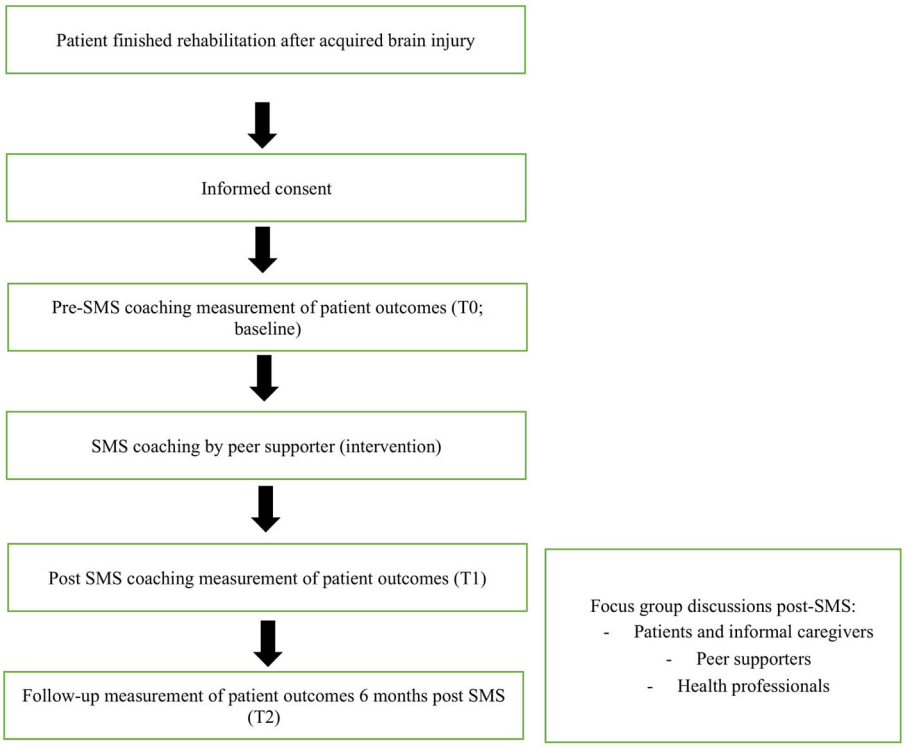

FIGURE 1 | Schematic representation of the study design.

Dissemination

In addition, implementation strategies for regional and national implementation will be explored:

1. What is, according to relevant stakeholders, necessary to successfully implement and disseminate cooperation between professionals and (volunteer) peer supporters?

METHODS/DESIGN

Study Design

This is a pre–post intervention study with a mixed-method design. The peer-led SMS intervention starts 4 weeks after completion of the rehabilitation treatment at the patient's home. Participants will be followed up to 6 months post-intervention. Three questionnaire measurements will be conducted (pre-, directly post-, and 6 months post-intervention). In addition, in-depth qualitative data on the experiences with the intervention will be gathered by focus-group discussions post-intervention. A schematic representation of the study design is depicted in **Figure 1**. The study has been approved by the institutional Medical Ethics Committee (METC azM/UM 2018-0930).

Study Population and Recruitment

Individuals with acquired brain injury, potentially with their informal caregivers, who have recently finished their rehabilitation program, were eligible. The rehabilitation center is a healthcare organization providing rehabilitation care with five locations in the South of the Netherlands.

Types of acquired brain injury could be any of the following: traumatic brain injury, cerebrovascular accident, or brain injury as a result of anoxia, infection, or tumor. The inclusion and exclusion criteria are listed in **Table 1**. Partners, spouses, or significant others who are most closely related to the patient are considered informal caregivers.

Patients will be recruited from June 2019 to September 2020. Annually, around 750 patients with acquired brain injury are admitted to the center. Inpatient as well as outpatient treatments are offered.

By the end of the treatment in the rehabilitation center, the multidisciplinary rehabilitation team discusses the preferable subsequent trajectory after dismissal, including the type of primary or home care for the patient and their informal caregivers. At this point, SMS coaching by a peer supporter is offered to eligible patients (**Table 1**).

If the patient is willing to participate, a written informed consent is obtained and the patient will be matched with a peer supporter.

Peer Supporters

Potential peer supporters are recruited both by recommendation of the multidisciplinary rehabilitation team of the rehabilitation center and by patient associations in the area. Important criteria to become an SMS coach are for the peer supporter to: have processed his or her own condition, be a good listener, have

TABLE 1 | Inclusion and exclusion criteria for patients.

Inclusion criteria	- Individuals with acquired brain injury who completed their rehabilitation treatment (including day rehabilitation).
	- Age 18 years or older
	- Dismissal to their own home after rehabilitation
	- Desire for peer support at home (provided by patient after consultation)
	- Some preserved learning ability
Exclusion criteria	- Discharge to a destination other than home
	- Severe mental health problems, defined as severely increased scores on the Four-Dimensional Symptom Questionnaire (4DSQ) (distress >20, depression >5, anxiety >9, somatization >20)
	- Sufficient professional support at home according to the rehabilitation team
	- Life expectancy <6 months
	- Chronic (>4 months) use of psychotropic medication

sufficient speech possibilities, and be able to travel to the home of the patients. The six-half-day course that the peer supporters follow to become a trained SMS coach is adapted to their cognitive and physical possibilities, including sufficient breaks, frequent repetition, and written information. The three theoretical concepts (exploration, cognitive-behavioral change, and problem solving) are discussed and practiced in role-play with the trainers and the other peer supporters. In the last session, the peer supporters show their skills during a session with a simulation client.

Intervention

SMS by the peer supporter will be provided during visits at the patient's home. In previous SMS studies, the frequency of visits ranged from 5 to 8 (15). Trained peer supporters will provide SMS to patients that have just finished their rehabilitation treatment and are dismissed home. The patient's rehabilitation physician will offer the SMS by a peer supporter. The intervention starts with exploration. Exploration is a phase in which the peer supporter discusses problems in daily life activities of the patient. Exploration features asking open-ended questions to gather information on this topic and providing insight in the level of psychological burden that the patient experiences with these problems. Cognitive–behavioral change is characterized by challenging irrational thoughts that the patients might have, that are holding them back from performing everyday tasks (e.g., how other people perceive the patient while there are visible limitations, like walking with a walker). Those thoughts are challenged by the peer supporter to check their value and perhaps change these thoughts. For more practical problems, such as outside transportation, problem solving is a possibility for the patient to come up with an action plan. The peer supporter will use a stepwise approach that discusses the advantages and disadvantages of several solutions. This way, the patient can choose the best possible solution for the problem.

The peer supporters are trained to act upon changes in psychosocial well-being of the participants. If specific physical or psychosocial problems appear to be persistent and serious over time, the peer supporter will apply a step-wise approach that starts with verbal administration of the Daily Functioning Thermometer (DFT), a visual analog scale of overall burden (range 0–10). If DFT < 6, the Distress Screener (DS) will be verbally administered. This is a quick-scan instrument to identify potential underlying mental health problems (19). If DS > 3, the Four-Dimensional Symptom Questionnaire (4DSQ) will be used to identify the level of psychological well-being. If at least one of the 4DSQ subscale scores is above the cutoff point (distress $>$ 20, depression > 5, anxiety > 9, somatization > 20) or the peer supporter considers that the psychological situation of the patient is not stable, professional care is necessary. If the patient still has a connection to the rehabilitation center, a healthcare professional at the rehabilitation center will be consulted. Otherwise, the patient will be advised to contact the general practitioner.

Data Collection

Patient Outcomes Pre–post Evaluation

Written questionnaire data will be collected at baseline, i.e., 2–4 weeks after having ended the rehabilitation treatment (T0), immediately after the peer-led SMS intervention (T1), and 6 months later (T2). The degree of self-efficacy, measured by the 12-item Dutch version of the General Self-Efficacy Scale (ALCOS12), consists of three subscales: taking initiative, competence, and perseverance when a setback occurs (20). The *Four-Dimensional Symptom Questionnaire (4DSQ)* is a questionnaire consisting of 50 items that measures psychological well-being in four domains: psychosocial complaints, distress, depression, and anxiety (19). The *MPAQ* is a 16-item questionnaire used to measure the degree of personal autonomy. It consists of three scales: the degree of experienced autonomy, the effort made to achieve autonomy, and dilemmas that doing what is best for the illness might not match a person's valued activities and social roles (21). The *QOLIBRI* measures the health-related quality of life in people with acquired brain injury with 37 items from 6 subscales (22). An overview of the primary and secondary outcome measures is presented in **Table 2**.

Patient characteristics that will be collected are age, sex, subtype of acquired brain injury, time since injury, educational level, income, and whether the patient will receive professional care at home after dismissal.

Process Evaluation

To determine the reach of the intervention, frequencies and characteristics of the patients who either accepted or declined the SMS support will be collected. **Table 3** provides an overview of the variables collected in the process evaluation. After each visit, peer supporters complete a tailored questionnaire to determine the extent of implementation of the SMS coaching, which is the quantification of the fidelity. Quantitative data through a questionnaire will be gathered on dose delivered, i.e., the number of house visits by peer supporters. Dose received (satisfaction) will be measured with both quantitative methods through the overall grade of the intervention by the patients, whether or not the patients would recommend the intervention to other patients, and the usefulness experienced by the patients, as with qualitative

TABLE 2 | Patient outcome domains and questionnaires.

Domain	Instrument	Measurement		
		T0	*T1*	*T2*
Demographic factors	Specific questions about age, sex, education level, and socioeconomic status	X		
Psychological well-being	Four-Dimensional Symptom Questionnaire (4DSQ)	X	X	X
Self-efficacy	Dutch version of the General Self-Efficacy Scale (ALCOS12)	X	X	X
Brain injury-specific quality of life	Quality of Life after Brain Injury (QOLIBRI)	X	X	X
Personal autonomy	Maastricht Personal Autonomy Questionnaire (MPAQ)	X	X	X
Satisfaction with the SMS coaching	Tailor-made questionnaire		X	

T0, immediately after dismissal from the rehabilitation center (baseline measurement).
T1, post SMS coaching measurement.
T2, follow-up measurement 6 months post SMS coaching.

TABLE 3 | Implementation measures, barriers, and facilitators.

Domain	Stakeholders	Data source	Method	
			Quantitative	Qualitative
Reach: proportion of the intended target population that participated in the intervention	Patients	Descriptive statistics on the number of patients that were given the offer to receive the intervention, compared to patients that refused, dropped out, or completed the intervention	X	
Fidelity: to what extent was the intervention performed as planned	Peer supporters	Checklist that is filled out after every house visit that describes the components of the intervention that were performed. Focus group	X	X
Dose delivered: amount of house visits that took place	Peer supporters	Checklist describing the amount of house visits	X	
Dose received: satisfaction of the patients, peer supporters, and professionals with the intervention	Professionals	Focus group		X
	Patients	- Overall grade of the intervention	X	X
		- Recommendation to others by the patient	X X	
		- Usefulness experienced by the patient		
		- Focus group		
	Peer supporters	Focus group		X
Barriers and facilitators: problems that were encountered while implementing the intervention	Peer supporters	- Quantitative data concerning the amount of peer supporters trained compared to peer supporters that signed up	X	X
		- Descriptive information about traits that the succeeded peer supporters possess		
		- Focus group		
	Patients	Focus group		X

methods through focus groups among professionals, patients, and peer supporters.

Post-intervention, focus groups will be held to gather in-depth qualitative data about the experiences with the intervention. One group will be individuals (i.e., patients and informal caregivers) that received SMS by peer supporters. The second group will be peer supporters themselves. The main goal of both focus groups is to gather in-depth qualitative data of the experiences with the intervention, and the barriers and facilitators that the users may have encountered. In addition, the focus-group discussions may be used to provide deeper insight in the mechanisms of the intervention. This information is gathered in the focus group by asking the participants how the intervention has helped them. A third focus group will be held among professionals that are

experts in the field of acquired brain injury; qualitative data will be collected on the cooperation between peer supporters and professionals at the rehabilitation center, as well as on the implementation in clinical practice.

Implementation

To optimize implementation, an evaluation of an implementation pilot phase of 3 months will be held at the rehabilitation center. The peer supporter will be embedded in usual care at the rehabilitation center. This phase will take place after the recruitment of participants in order to discover how implementation of the peer-led SMS intervention can be improved. This will be evaluated through a group interview and a questionnaire among healthcare professionals and peer supporters. Topics of this group interview will include their experiences with this implementation, the implications for usual care, and possibilities for improvement.

Dissemination

Relevant stakeholders in rehabilitation after acquired brain injury (i.e., health insurance financiers, volunteer organizations, and content specialists) will be gathered in a workshop. The goal of this workshop is to discuss what is necessary for a successful implementation of cooperation between healthcare professionals and peer supporters. With this information, the target population for the peer-led intervention can be disseminated to other regions and people with acquired brain injury who do not necessarily receive specialized rehabilitation.

After completion of the study, the data will be publically accessible for further research and verification from a data repository platform (Dataverse NL).

Statistical Analysis

The mixed-method design of this implementation study aims to triangulate the findings of quantitative and qualitative analyses (23). One aspect of the quantitative analyses is the evaluation of patient outcomes with the degree of self-efficacy as the primary outcome. As a guideline, a required sample size of 90 participants was calculated based on an effect size of 0.3 (24, 25), an α of 0.05, and a statistical power (1-β) of 0.80. Furthermore, the qualitative data collection in two focus groups will be held among eight participants for both groups.

Standard descriptive statistics will be used to present the data concerning the participants, dropouts, losses-to-follow-up, and their characteristics. Comparisons of the mean values in patient-reported outcomes over time will be analyzed using paired *t*-tests, or non-parametric tests in case of a skewed distribution and, if possible, multilevel repeated analyses. Furthermore, we will conduct subgroup analyses to study whether the change in self-efficacy over time differs according to demographic characteristics, such as age, sex, educational level, and socioeconomic status, or the "dose" of peer-led SMS received by the patient.

Equally important, with our interest in matters of implementation, there is a qualitative part in the study. Within the focus groups, we will seek for new information until saturation is reached. The qualitative data will be coded and analyzed by two individuals.

DISCUSSION

We present the protocol of a mixed-method study to evaluate the implementation of a peer-led self-management intervention following acquired brain injury rehabilitation. In a pre–post evaluation, quantitative changes in patient outcome pre–post intervention are complemented with qualitatively derived patient experiences post-intervention. To evaluate the process of implementation, registrations during the intervention and post-intervention focus-group discussions with patients, informal caregivers, peer supporters, and health professionals are used to investigate the extent of implementation and the barriers and potential facilitators. A workshop with relevant stakeholders will be held to gather recommendations for successful dissemination of the peer-led intervention.

Self-management and peer support by volunteers are the core components of the current SMS intervention. Self-management interventions have proven effective in patients with chronic diseases, and various approaches have been described (9–11). For improving active coping and the patient's self-efficacy and mastery, these interventions have shown to be supportive for patients with an acquired brain injury (10, 11, 13, 14). Patients with acquired brain injury that demonstrate active coping mechanisms have shown more positive results regarding health-related quality of life and participation after following a self-management intervention (26). Furthermore, it is increasingly common to involve peer supporters in the treatment of mental health problems. Only few studies evaluated the implementation of peer support programs for people with an acquired brain injury. These show promising results, and patients report positive experiences with peer supporters (7, 17, 18, 27). Furthermore, support provided by volunteers is a low-cost method.

The results of the previous SMS studies in the primary care setting were promising. Unfortunately, the implementation of SMS progressed slowly and eventually stagnated due to the high workload of healthcare professionals and the disease-oriented context that they work in (14, 15). As mentioned, the adaptation phase after brain injury is challenging for many patients and their informal caregivers, and there are unmet care needs (4). Introducing a self-management intervention in this phase is recommended by both the patients and their informal caregivers (28, 29). Peer supporters are believed to be of added value in addition to professional care, because they recognize and can relate to the patients' needs more by experience (4). Both the SMS intervention itself and the unique qualities of peer supporters who provide the intervention have shown to be promising components of support programs and are therefore believed to constitute a strong base for implementation (6, 7, 10, 17, 18).

In summary, this paper describes the design of a study on the barriers and facilitators related to the implementation of a home-based, peer-led self-management intervention for patients with an acquired brain injury. We will quantitatively and qualitatively evaluate the change in relevant patient

outcomes pre- and post-intervention. Equally important, quantitative registrations and qualitative research among patients, their informal caregivers, peer supporters, and respective professionals will provide insight into the barriers and facilitators related to the implementation of the intervention. Enrollment of patients and informal caregivers has started in June 2019 and will continue until September 2020. Currently, we experience substantial problems in patient recruitment due to the corona pandemic.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by METC aZM/UM. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB-D has drafted the manuscript. SS designed the study and substantively revised the manuscript. JV designed the study and substantively revised the manuscript. HB made substantial contributions to the conception, designed the study, and substantively revised the manuscript. JE made substantial contributions to the conception, designed the study, and substantively revised the manuscript. All authors have read and approved the manuscript.

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STUDY PROTOCOL
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Deficit of Inhibition as a Marker of Neuroplasticity (DEFINE Study) in Rehabilitation: A Longitudinal Cohort Study Protocol

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Background: Brain plasticity is an intrinsic property of the nervous system, which is modified during its lifetime. This is one mechanism of recuperation after injuries with an important role in rehabilitation. Evidence suggests that injuries in the nervous system disturb the stability between inhibition and excitability essential for the recuperation process of neuroplasticity. However, the mechanisms involved in this balance are not completely understood and, besides the advancement in the field, the knowledge has had a low impact on the rehabilitation practice. Therefore, the understanding of the relationship between biomarkers and functional disability may help to optimize and individualize treatments and build consistent studies in the future.

Methods: This cohort study, the deficit of inhibition as a marker of neuroplasticity study, will follow four groups (stroke, spinal cord injury, limb amputation, and osteoarthritis) to understand the neuroplasticity mechanisms involved in motor rehabilitation. We will recruit 500 subjects (including 100 age- and sex-matched controls). A battery of neurophysiological assessments, transcranial magnetic stimulation, electroencephalography, functional near-infrared spectroscopy, and magnetic resonance imaging, is going to be used to assess plasticity on the motor cortex before and after rehabilitation. One of the main hypotheses in this cohort is that the level of intracortical inhibition is related to functional deficits. We expect to develop a better understanding of the neuroplasticity mechanisms involved in the rehabilitation, and we expect to build neurophysiological "transdiagnostic" biomarkers, especially the markers of inhibition, which will have great relevance in the scientific and therapeutic improvement in rehabilitation. The relationship between neurophysiological and clinical outcomes will be analyzed using linear and logistic regression models.

Discussion: By evaluating the reliability of electroencephalography, functional near-infrared spectroscopy, transcranial magnetic stimulation, and magnetic resonance imaging measures as possible biomarkers for neurologic rehabilitation in different neurologic disorders, this study will aid in the understanding of brain plasticity mechanisms in rehabilitation, allowing more effective approaches and screening methods to take place.

Keywords: disability, biomarkers, brain plasticity, stroke, spinal cord injury, amputation, osteoarthritis, neuronal plasticity

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INTRODUCTION

The brain is designed and molded by environmental changes, pressures, and experiences (1). In this context, brain plasticity is understood as an intrinsic and permanent property of the nervous system, which is in constant modification during the human lifetime (1–3). This property allows the partial or total recovery after injuries to the human nervous system, and it involves recovery or compensation and motor adaptation with assistive technologies (3). Throughout life, the human brain is flexible, adapts quickly to environmental changes, and simultaneously, preserves a relatively stable balance between the long-term potentiation and the long-term depression or excitability and inhibition (4, 5). However, evidence suggests that injuries in the nervous system unbalance neural stability (6). For example, recently, evidence has shown that a deficit in neuronal inhibition is detected in patients with a disability regardless of etiology (7–9), and this lack of inhibition is associated with more disability (10). The understanding of brain plasticity has advanced; however, this knowledge has had a low impact on the rehabilitation practice (1). Furthermore, the mechanisms involved in the excitability and the inhibition balance and in brain plasticity regulation are not completely understood, as the biomarkers would be able to measure these processes. Also, there is a lack of studies designed to understand the mechanisms of brain plasticity in the context of rehabilitation, and there are no reliable biomarkers in the rehabilitation field nowadays. Therefore, this study's objective is to identify, through transcranial magnetic stimulation (TMS), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS), biomarkers that represent the imbalance in the cerebral activity and its impact on rehabilitation, optimizing, and individualizing treatments and resources. Consequently, this project looks to understand the relationship between the biomarkers and the functional impairment related to the disability, regardless of the etiology. For that reason, we designed this cohort study with four conditions in neurorehabilitation: stroke, spinal cord injury, limb amputation, and knee osteoarthritis (OA). We selected these four conditions to represent conditions with different levels of neural lesions (i.e., stroke for central lesions, spinal cord injury to central lesion but in spinal cord, phantom limb pain for peripheral lesion but more proximal, and OA for peripheral lesion and more distal). Subjects included in this cohort are tested in the baseline with comprehensive neurophysiological assessments to assess different measures of neuroplasticity and especially inhibitory activity of the motor cortex and also a comprehensive clinical assessment to correlate to functional deficits.

METHODS AND ANALYSIS

Participants and Study Design

This is a prospective cohort study made up of four groups with a specific diagnosis (stroke, spinal cord injury, knee OA, or lower limb amputation) and a group of healthy volunteers.

Patients admitted to the conventional rehabilitation program of the Instituto de Medicina Física e Reabilitação (IMREA) will be invited to participate in the study and included after signing the informed consent form previously approved by the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Ethics Committee for Research Protocol Analysis CAAE: 86832518.7.0000.0068. For this study, 400 patients will be recruited, 100 patients with a stroke diagnosis, 100 with knee OA, 100 with spinal cord injury, and 100 amputee patients. The control group will be made up of 100 healthy subjects paired by sex and age.

Patients who agree to participate in the study will undergo a series of assessments at two time points: before and after the IMREA rehabilitation program. An individualized approach characterizes this program, considering the injury's etiology, the type of disabilities the patient has, general clinical conditions, likely prognosis, and the patient's socioeconomic factors. The control group will only perform neurophysiological (EEG, fNIRS, and TMS) and functional assessments once.

It is important to note that all patients involved in the research will receive the same type of treatment as patients who are not participating in the research.

Sample Size

The sample size of 100 patients for each type of injury was determined, given this is an observational study (prospective cohort) and, thus, the primary analysis being a linear regression. Therefore, 100 participants in each group will allow for the modeling of 10 covariates, which will yield an effect size of ∼0.3, which we believe is enough, mainly due to the use of neurophysiological variables and our knowledge of previous studies. Our group recently performed two studies with multivariate analyses, one with 35 and another with 55 patients, to assess neurophysiological markers (EEG and TMS), which allowed us to identify the role of these markers in the rehabilitation of conditions such as stroke.

Thus, using a larger sample (100 subjects), compared with our previous studies, associated with a larger detailing of clinical and neurophysiological information, will aid in the better comprehension of cerebral plasticity. We also believe this sample size will yield similar results for patients with knee OA, spinal cord injury, and amputation. Furthermore, it will allow for the identification of transdiagnostic markers, not aiming to compare the different injury groups but to determine the neurophysiological alterations they have in common.

Inclusion Criteria

Participants of both sexes will be included in the study if they are older than 18 years, have confirmed clinical stability verified by medical evaluation, have signed the informed consent form, and if they fulfill the eligibility criteria for the IMREA rehabilitation program. To be included in the specific injury groups, patients will have to have a clinical, and radiological [magnetic resonance imaging (MRI) or computerized tomography; or bilateral knee radiography] diagnosis of stroke (confirmed by computed tomography scan and/or MRI), spinal cord injury, or knee OA (clinically confirmed) or a clinical diagnosis of bilateral or unilateral lower limb amputation.

Exclusion Criteria

Subjects will be excluded if they are pregnant, have active OA with clinical manifestations in joints other than the knee, or if they have any other clinical or social conditions that interfere with the patient's participation in the rehabilitation treatment.

Clinical and Functional Assessments

At the beginning of the study, on the participant's first visit, a trained physician will take the patient's history, perform a physical examination, and review the eligibility criteria for that patient. The obtained information from the patient's history such as age, sex, height, weight, ethnicity, education level, medications in current use, comorbidities, and the specific characteristics of each injury will be used as covariates in the final linear regression model.

Several instruments that allow the global assessment of participants, general or specific to each condition, were selected (**Table 1** and **Appendix 1**). Some scales, such as cognitive, sleep, and mood scales, will be used to characterize the study's sample, as well as for the management of confounding variables on the multivariate statistical model.

The same evaluator will preferably carry out assessments. Evaluators will be trained to standardize questionnaire applications to reduce assessment subjectivity.

A detailed explanation of all the scales and tests used in this study under **Supplementary Material**.

Neurophysiological Assessment Methods

Transcranial Magnetic Stimulation

The Magstim Rapid® stimulator (The Magstim Company Limited, United Kingdom) and a 70-mm coil in figure-of-eight will be used, positioned tangentially to the skull and at an angle of 45° in relation to the sagittal line will be used. The muscular response to the stimulus applied to the motor cortex will be recorded using surface electromyography with Ag/AgCl electrodes positioned on the target muscle and the grounding electrode positioned on the wrist. We will follow the methods established in the literature for physiological and clinical studies (50).

Bilateral upper limb assessment (first dorsal interosseous muscle of the hand) will be performed. The motor area corresponding to the first dorsal interosseous is the most used motor cortical area in cortical excitability studies in addition to presenting a greater accuracy of the method due to the local anatomy and penetration of the TMS pulse. To locate the cortical area of the hand, it will initially be identified from the vertex (intersection between the nasion–inion lines and zygomatic arches). Then, for the identification of the probable hot spot, a mark will be made 5 cm from the vertex toward the ear tragus in the coronal plane. The hot spot will be defined as the location as the lowest resting motor threshold and with the greatest amplitude of the motor evoked potential in the target muscle for a given intensity of the upper threshold stimulus.

The resting motor threshold (rMT) will be defined as the minimum intensity necessary for a single TMS pulse on the hot spot to generate an evoked motor potential (EMP), with at least 50 μV peak-to-peak amplitude, in 50% of attempts. rMT will be used as an indirect measure of cortical excitability. In addition, the following measures will be used: resting EMP, in which motor 10 EMPs will be recorded, with an interval of ∼7 s between stimuli; silent period (SP), which represents the temporary suppression of electromyographic activity during a sustained EMP voluntary contraction; intercortical inhibition (SICI), which will be assessed by interstimulus intervals of 2 ms. The conditioned stimulus intensity (CS) will be set at 80% rMT and the test stimulus intensity (TS) adjusted to induce MEPs of ∼1 mV peak-to-peak amplitude. Also, finally, intracortical facilitation (ICF) will also be measured by 10-ms interim stimulus intervals, and CS intensity will be the same as it was for the SICI evaluation.

Electroencephalography

EEG is a useful tool for inhibitory network assessment. This study aims to understand better the effects of inhibitory networks on the rehabilitation process. Successful inhibition is associated with increased EEG power in theta and delta bands (51, 52). Thus, we hypothesize that a better functional state will be related to the increase in power in the EEG delta and theta bands in the resting state, as well-modifications of others EEG bands (alpha, beta, and gamma).

We will use the same methodology of our other trial also looking at the inhibitory activity using EEG (53). EEG will take place over ∼45 min: 25 min of participant and software preparation, 10 min of EEG recording divided into a resting EEG condition (5 min with eyes open and 5 min with eyes closed), and a task-related condition (8 min). Participants will be asked to relax in the resting condition; the investigator will ensure they do not fall asleep.

The task-related condition will include movement observation, movement imagery, and movement execution. This will be recorded by connecting the Net Station software (for EGI) with E-Prime. The entire task-related condition part will consist of 60 trials, with 20 trials for each of movement observation, movement imagery, and movement execution in a randomized order.

We will record the EEG in a standardized way using the 64-channel EGI system (EGI, Eugene, USA). The EEG will be recorded with a band-pass filter of 0.3–200 Hz and digitized at the sampling rate of 250 Hz by connecting the Net Station software (for EGI) with E-Prime.

Electroencephalography Data Assessment

The EEG data will initially be analyzed visually by a specialist clinical neurophysiologist who will identify and signal the artifacts, in addition to possible clinical changes in the EEG. Then, the data will be exported and analyzed offline with EEGLab (54) and MATLAB (MATLAB R2014b, The MathWorks Inc. Natick, MA, 2000). The following standard bands and frequencies will be analyzed: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), and beta 2 (20–30 Hz). Sensory inhibition will also be analyzed through the methods already described in this protocol.

Furthermore, a coherence analysis will be carried out through the MATLAB "mscohere" function, which calculates

TABLE 1 | Assessment instruments used for each study group.

Category	Instrument	Amp.	Stroke	OA	SCI	CG*
Independence	Functional Independence Measure (FIM) (11)	X	X	X	X	X
Independence (Specific to SCI)	Spinal Cord Injury Independence Measure (SCIM III) (12)				X	
Cognition	Montreal Cognitive Assessment (MOCA) (13)	X	X	X	X	X
Cognition (speach)	Semantic verbal fluency test (14)		X			
Pain	Conditioned Pain Modulation (CPM) (15)	X	X	X	X	X
Pain	Pressure Pain Threshold (PPT) (16)	X	X	X	X	X
Pain/Sensitivity	Monofilament Sensitivity Test (17)	X	X	X	X	X
Pain/Sensitivity	Tuning Fork Vibration Sensitivity Test (18)	X	X	X	X	X
Pain	Pain Catastrophizing Scale (19, 20)	X	X	X	X	
Pain	McGill Pain Questionnaire (Brazilian Version) (21)	X	X	X	X	
Pain	Visual Analogue Scale (VAS) for Pain (22)	X	X	X	X	
Lower Limb Motor Function	6-min and 10 meters gait test (23)	X	X	X	X	X
Lower Limb Motor Function	Timed Up and Go (TUG) (24)	X	X	X	X	X
Lower Limb Motor Function	Lower Limb Isokinetic Dynamometer (25)	X	X	X	X	X
Lower Limb Motor Function	Walk Index for Spinal Cord Injury (WISCI-II) (26)				X	
Upper Limb Motor Function	Fugl–Meyer Assessment (FMA) (27)		X		X	
Upper Limb Motor Function	Hand Grip and Pinching (28–30)		X		X	X
Upper Limb Motor Function	Purdue Pegboard Test (PPBT) (31)		X		X	X
Upper Limb Motor Function	Robot-Measured Kinematic Variables (32)		X		X	X
Upper Limb Motor Function	Finger Tapping (FT) (33)		X		X	X
Upper and Lower Limb Motor Function	Medical Research Council Scale (MRC) (34)		X	X	X	
Balance	Force platform (35)	X	X	X	X	X
Balance	Berg Balance Scale (36)	X	X	X	X	
Spasticity	Modified Ashworth (37)		X		X	
Sleep	Epworth sleepiness scale (38)	X	X	X	X	X
Mood	Hamilton Depression Rating Scale (HAM-D) (39)	X	X	X	X	X
Mood	Hospital Anxiety and Depression Scale (HADS) (40)	X	X	X	X	X
Pain, rigidity, and daily activities	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (41)			X		
Lower limb	Amputee Mobility Predictor (AMP) (42)	X				
Amputation	Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0) (43)	X				
Stroke	National Institutes of Health Stroke Scale (NIHSS) (44)		X			
SCI	American Spinal Injury Association Impairment Scale (ASIA) (45)				X	
OA	Kellgren-Lawrence Radiographic Classification of OA (46)			X		
OA	Ultrasound Assessment (US)			X		
Quality of life	Stroke Impact Scale (SIS) (47)		X			
Quality of life	Medical Outcomes Short-Form Health Survey (SF-36) (48)	X	X	X	X	X
Polymorphisms	Genetic Polymorphism Analysis (49)	X	X	X	X	X

**Control group.*

the estimate of coherence squared of magnitude, which is a function of power spectral density and the cross power spectral density of two channels. A coherence value between 0 and 1 will be calculated for each frequency point for the selected channel pairs. High coherence between two EEG signals has been considered as evidence of the possible existence of a structural and functional connection between two cortical areas.

Initially, only the electroencephalographic activities related to the primary motor cortex (CZ, C3, and C4) will be used for multivariate regression models, in addition to transversal inter-hemispheric coherence (C3–C4) and front-central

intra-hemispheric coherence, F3–C3, and F4–C4. The data referring to the other EEG channels will be stored for future exploratory analyzes.

Functional Near-Infrared Spectroscopy

The relative changes in the concentration of oxy- and deoxyhemoglobin will be evaluated for each condition (left-hand grip, right-hand grip, and both hands grip), including rest (interval between each activity block). An average of the 10 trials will be made for each condition to improve the signal-to-noise ratio. A correlation analysis (seed-based correlation analysis) will also be carried out, estimating the strength of the neural connections related to the channels positioned on the M1 brain area, which can help elucidate the null hypothesis.

Functional Near-Infrared Spectroscopy + Electroencephalography Recording Protocol

EEG recording will be carried out concurrently with fNIRS. There will be 10 min of recording at rest (the first 5 min with the eyes closed and the last 5 min with the eyes open). Then, the patient will be asked to open and close his hands at a frequency of 1 Hz, using a video to guide the frequency of their movements. For fNIRS, the patient will be asked to open and close his hands at a frequency of 1 Hz, using a video to guide the frequency of their movements. There will be five 30-s blocks in which the patient will execute right-hand movements and five 30-s blocks imagining the right-hand movements, with an interval of 30 s between blocks. The same protocol will be repeated for the left hand and with simultaneous movements of both hands resulting in a total fNIRS collection time of ∼30 min.

Magnetic Resonance Imaging

Diffusion tensor imaging with fractional anisotropy (FA) will be used to collect the MRIs. The regions of interest will be the bilateral primary motor cortices and fibers of the corpus callosum and corticospinal tract. After obtaining the diffusion tensor imaging data, FA values will be determined for all corpus callosum and corticospinal fibers. The FA value of 0.15 will be considered as a reliable threshold to isolate the white matter from the rest of the brain (55). The volumetric measurement of the motor cortex will also be taken.

Initially, only the primary motor cortex thickness will be used for the analysis. We will select 10% of the sample, resulting in a total of 40 patients. These results will be analyzed with multivariate models, including only these patients in a subgroup analysis.

Statistical Analysis

For this analysis, we will use the multivariate regression model in which motor improvement will be the dependent variable and changes in inhibitory activity (resulting from neurophysiological assessments performed before and after treatment) will be the independent variables.

To control the impact of different conditions on the multivariate model, we will create a "dummy variable" for each disease etiology. Moreover, demographic characteristics (age, education, sex, and ethnicity) and clinically relevant characteristics (duration of illness, comorbidities, and the use of medications) will be tested, as well as specific aspects for each disease, such as the stroke side, the level of spinal cord injury, the degree of bone deformity of knee OA, and the level of lower limb amputation. The neurophysiological biomarkers described earlier will be tested in the same model.

Although this study's aim is not to test interventions but to identify changes in biomarkers related to functional improvement (regardless of the therapy performed), the different therapies performed by patients will be quantified, including information such as the number of sessions, frequency, duration, among others, which can be used in future analyses.

For secondary analyzes, functional improvement can be assessed by the several, general and specific, scales used depending on the evaluated disease. In this situation, we will use the calculation of the functional modification's effect size and not the absolute values of the scale for the analysis in the multivariate model.

Also, the motor function of the upper limb will only be assessed for patients with stroke and spinal cord injury, the main scale used being the Fugl–Meyer Assessment. In this case, an analysis similar to the one described earlier will be performed but only including these two populations.

Some of the scales, such as those for mood, pain, cognition, and sleep, will be used to characterize the sample, in addition to possibly being used to control confounders in the multivariate model. Besides, mood, pain, and cognitive disorder are commonly present in these populations, so we will perform an exploratory analysis using a similar statistic method but with scales related to these aspects as dependent variables.

In the statistical analysis for the results of the obtained polymorphisms, classical methods of case–control studies' epidemiological analysis will be applied. Odds ratio and the respective 95% confidence intervals will be estimated by unconditional logistic regression to simultaneously control potential confounding variables. To assess the relationship between the dependent variable (stroke and its subtypes) and the independent variables (polymorphisms of the evaluated genes, smoking, lipid variables, etc.), the statistical technique used will be logistic regression analysis, which allows the evaluation of disease risk associated with a given variable considering all other independent variables in the model.

DISCUSSION

This study will help understand the relationship between the brain plasticity biomarkers and functional disability not related to a specific etiology but related to central and peripheral neural injury. In addition, we expect that this study is going to build a better understanding of the brain modification associated with prosthesis adaptation and movement adaptation assisted technologies in patients with stroke and spinal cord injury. We also expect that we are going to be able to understand better the relationship between these biomarkers and motor deficit and other functional disabilities. Thus, the current challenge is to identify in human beings how multiple aspects of brain

plasticity that happens in an integrated way influence the process of rehabilitation and to understand how different types of lesions in the peripheral and central nervous system modify the balance of brain plasticity.

We chose these four different conditions (stroke, spinal cord injury, OA, and amputation), as in all of them, we can find patients passing through maladaptive neuroplasticity regarding pain and disability (56–60). This approach may allow us to explore the possible transdiagnosis markers linked with plasticity in disability and pain regardless of the diagnosis label usually touched by the literature. One of the justifications that aim to explore these biomarkers is that chronic pain and disability conditions may share similar maladaptive changes regarding neuronal plasticity (61, 62).

In this study, we are looking to test and explore the neural inhibition through TMS, EEG, fNIRS, and MRI that have an impact on the rehabilitation clinical practice. We will also classify biomarkers as follows: (i) substitute, which indicates the biomarkers are modified with the "successful" rehabilitation; (ii) prognosis, which indicates the biomarkers indicate functional recovery regardless of rehabilitation therapy; and (iii) predictive, which indicates the biomarkers predict treatment response. We will investigate the activity of theta, delta, and beta waves on EEG, rMT, EMP, SICI, ICF, CS, and SP on TMS, the brain metabolic activity on fNIRS, and the motor cortex's volumetric mass on MRI to assess these aspects as potential biomarkers, characterizing them as either substitute, prognostic, or predictive (63).

The development of (i) substitute results for functional recovery and the understanding of the factors that influence the rehabilitation process will be possible to develop consistent and feasible studies. Currently, the majority of the studies in this field have low statistical power, without control of confounding variables, and reproducibility problems (64). In addition, the lack of substitute markers has allowed the approval of therapies without the background of consistent methodological studies. These distortions are not harmless and overwhelm the health system.

Another biomarker that we expect to identify is (ii) prognostic. The current models to determine the functional prognosis of patients with stroke or spinal cord injury are not accurate, making the therapeutic approach difficult. These biomarkers could specify the patient's recovery potential, providing earlier hospital discharges and avoiding unnecessary treatments. One example is a pain biomarker in spinal cord injury using intracortical inhibition. Studies have shown that subjects with spinal cord injury and pain have decreased intracortical inhibition (65, 66).

The final biomarker that we aim to identify is (iii) predictive of functional recovery. In this case, we are going to identify the plastic brain modifications that are related to functional recovery and that are induced by rehabilitation therapy (67). This understanding will allow the individualization of the treatment and potentialize future insights about the new approaches of rehabilitation.

To our knowledge, there is a lack of studies designed to understand brain plasticity in the rehabilitation context, and there is too little knowledge in the mechanisms involved in the balance between neural inhibition and excitability and in brain plasticity regulation. Also, the current literature has had a low impact on the rehabilitation practice.

In this context, TMS is a widely used tool to measure corticomotor excitability in patients with motor deficit conditions such as stroke. It has been found that motor deficit severity is highly associated with the level of corticomotor excitability measured by rMT depicted in TMS results. Given that rMT reflects neuronal membrane excitability, functional modifications that occur after motor deficit conditions, such as inhibitory circuit malfunctions, are reflected as rMT alterations in TMS (68). We expect to find a reduction in inhibitory brain activity associated with a decrease in rMT, SICI, and SP due to the direct relationship between these biomarkers and motor inhibitory pathways of the brain. Moreover, study findings show that ICF and MEP are mediated by different interneuronal pathways than those of rMT, SICI, and SP; thus, it is expected that as inhibitory circuits increase their activities, ICF and MEP amplitudes will be decreased (69).

Several studies have conveyed brain plasticity alterations in the primary motor cortex. These changes have been thus identified through the use of biomarkers such as EEG and fNIRS, for instance, strong correlations between theta and delta band activities in the hippocampus and successful inhibitory mechanisms in rodent models (70). The use of EEG as a biomarker "tracker" thus becomes important because sensory inhibition reflects an automatic cortical inhibition function, which can be used as a measure of the brain's inhibitory status (71–74). These findings support one of the study's main hypotheses that motor function deficits are associated with lower cerebral inhibitory activity when compared with a healthy control group. Studies that have performed electrophysiological evaluations of patients with chronic pain conditions such as OA, spinal cord injury, and neurogenic pain have found a decrease in theta and delta wave activity and an increase in beta wave activity due to deficient brain inhibitory circuits (75). Thus, an increase in the activity of theta and delta bands, as well as a decrease in beta bands, is a reflection of increased inhibitory activity, which can be achieved through rehabilitation in patients with pain conditions. Therefore, given these findings, we expect a diminished event-related desynchronization in patients with motor dysfunctions.

The association of EEG and fNIRS have been used in many studies to analyze cortical activation and plasticity connections in the context of rehabilitation (76). Both tools are practical, non-invasive methods of measuring brain activity; however, fNIRS lacks good spatial and temporal resolution and cannot assess deep brain structures (75). Thus, its association with EEG provides a more holistic understanding of cortical activation in the conditions being studied. Moreover, it has been shown that electrophysiological variations have the ability to predict hemodynamic activation in motor regions of the brain (77).

Different studies have found an inverse relationship between fNIRS results and efficient inhibitory networks, given that efficient inhibitory networks depict less cortical activation in prefrontal regions during executive function tasks. Therefore,

we hypothesize that, as patients undergo rehabilitation, their inhibitory networks will be strengthened, which will then be depicted on the fNIRS as a decrease in activity, bolstering the use of fNIRS as a tool for plasticity biomarker measurement (78). However, evidence on this relationship is still conflicting. For instance, a study evaluating the feasibility of fNIRS as an assessment mechanism for patients with spinal cord injury has conveyed enhanced activation of motor cortical areas after rehabilitation with robot-assisted gait training (78). Given that fNIRS produces blood-oxygen-level-dependent images, this suggests a link between the brain's metabolic activity in the motor cortex and recovery of gait-impairing conditions such as SCI and stroke, which is still unclear. Thus, the use of fNIRS to evaluate neuroplasticity biomarkers in this study will help to further elucidate the relationship between neuroplasticity and brain hemodynamic activity.

Moreover, the use of more conventional imaging methods, such as MRI to evaluate the transdiagnostic nature of plasticity biomarkers, has become very promising given the association between cortical thickness and chronic pain (79, 80), amputations (81, 82), spinal cord injury (83, 84), and stroke (85, 86). These correlations support the analysis of volumetric measurements of the motor cortex to yield a better understanding of this relationship.

This is a novel and feasible observational study that will help the understanding, improvement, and development of the rehabilitation field and allows for the identification of several biomarkers at once, providing further insight for clinical practice in rehabilitation. Furthermore, this study was designed to answer our hypothesis in an optimized way, with a rigorous methodology. Besides that, one of the limitations is that our results will not provide a causal relationship between neurophysiological markers and functional and clinical outcomes. Also, the study may be underpowered, as there are four groups of intervention; to minimize that, we performed a sample size calculation based on the expected effect size regarding previous studies; the neurophysiological surrogate variables are something that could help to address this limitation also. The differences between severities of conditions could lead to different dropout rates in one of the more severe group conditions; this may unbalance the groups' size. Another limitation is that the variability of the clinical phenotypes of the conditions approached by this study could generate some noise in our results. To minimize this limitation, we are planning to do a multivariate analysis, which could minimize relevant confounders that may interfere with our results. Finally, our study may lack generalizability, as the study will be performed in only one center.

On the other hand, this is a novel and feasible observational study that, as mentioned before, will help the understanding, improvement, and development of the rehabilitation field.

In conclusion, understanding brain plasticity in the context of rehabilitation allows for more effective approaches and provides screening evaluations of current rehabilitation techniques. The future results of this study will help to better understand brain plasticity and its mechanisms and its reliable representative biomarkers as well. This knowledge will lead to the development of rehabilitation as has occurred in other fields, such as cardiology. In this context, simple questions such as the posology of the treatment will start to be answered when we have markers to measure the functional recovery and feasible and powered studies will be able to be performed in an extensive and consistent manner.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Medical School of University of São Paulo (CAPPESQ). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

In this study protocol, FF conceived the initial idea, MS, MI, and LB designed the study, and PM, AM, MS, and FF drafted the manuscript article. All authors reviewed and approved the final version of the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.695406/full#supplementary-material

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Differences Between Exergaming Rehabilitation and Conventional Physiotherapy on Quality of Life in Parkinson's Disease: A Systematic Review and Meta-Analysis

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Parkinson's disease (PD) is a neurodegenerative condition with both motor and non-motor symptoms affecting the quality of life (QoL) of older adults. Exergaming rehabilitation allows the interaction of the subject with digital games through the implementation of repetitive functional activities. Conventional physiotherapy uses patient-centered programs that include a variety of active exercises. The aim of this review was to look into the effectiveness of exergaming rehabilitation on the QoL of people with PD and compare it with conventional physiotherapy. Five electronic databases were searched for eligible studies until February 2021. For the statistical analysis, the mean, standard deviation, and 95% confidence interval were used to calculate effect sizes between groups. To determine heterogeneity, statistical index I^2 was used. A total of 548 participants were included in 14 studies. Exergaming rehabilitation related with improved QoL ($p = 0.687$, 95% CI: −1.682 to −0.734), balance ($p = 0.039$, 95% CI: 0.364–13.689), ($p = 0.018$, 95% CI: 0.446–4.830), and gait ($p = 0.005$, 95% CI: 0.351–1.924). No significant difference was found between groups regarding the Unified Parkinson's Disease Rating Scale ($p = 0.196$, 95% CI: −5.970 to 1.225) and for the Timed Up and Go Test ($p = 0.12$, 95% CI: 0.446–4.830). Exergames as a rehabilitation method can be used to provide alternative interactive intervention with positive results for QoL in people with PD. Further investigation is needed to assess the effect on mental health in this population group.

Keywords: Parkinson's disease, conventional physiotherapy, quality of life, functionality, exergaming

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects older people after the sixth decade of life. It involves motor and non-motor signs and symptoms (1, 2) and it is characterized by degeneration and progressive loss of dopamine neurons in the pars compacta of the substantia nigra (SNc), leading to disorganization, and dysfunction of the basal ganglia (3).

PD is the second most common neurodegenerative disease after Alzheimer's disease (4), affecting 1% of people older than 60 years of age (5). Countries with high industrial development,

like the European countries and the USA, show high percentages of the disease in comparison with lower industrial development countries (6, 7). Until 2016, around 6.1 million cases of PD had been recorded worldwide, with 3.2 million showing disability problems and around 211,296 deaths recorded in 2016 (8).

Due to PD being a progressive disorder, treatment can be ongoing, adding to the cost that also depends on the severity of the condition and the needs of each patient. The total direct and indirect cost in Europe is around €14 billion per year (4), while in the USA, it is around $25.4 billion (9). It becomes obvious that this condition is an economic challenge for health services.

The main symptoms of the disease include cardinal signs that involve a number of complex motor signs (10) including resting tremor (4–6 Hz), rigidity, bradykinesia/akinesia, and loss of postural reflexes (5, 10). The existence of the cardinal signs limits function and activities of daily living (ADL), leading to a reduction in quality of life (QoL) (1). ADL limitations reduce social interaction function and independence (11, 12). Furthermore, a number of psychomotor, cognitive, and sensorial symptoms like pain, hyposmia, reduction of proprioception and kinesthesia, and decrease in memory and concentration have been reported (2). A large percentage of patients (40–50%) show emotional changes including anxiety disorders and depression, which lead to themselves noticing the symptoms and recognizing the disorder (13).

Physiotherapy can use a variety of interventions to treat psychomotor symptoms in PD based on the needs and goals set for each patient (4). Conventional physiotherapy (CPT) is one of the most common healthcare management methods used in PD (14) that provides a specified program of active exercises that use changes in the center of gravity (CG) and balance aerobic exercises (14, 15).

Exergaming rehabilitation (ER) is a broad spectrum that includes all the types of therapeutic immersion to project interactive digital exercises (16). As a rehabilitation method, it provides digital games and the user does exercises in order to achieve the game's outcomes (17). Adams et al. (17) defined ER as "videogames that use exertion-based interfaces to promote physical activity, fitness, and gross motor skills development". ER is available with every equipment that projects digital exercise programs including non-immersive consoles, semi-immersive hybrid systems, and immersive virtual reality (VR) tools. In order for ER to function, the use of platforms, pads, video-consoles, and, most recently, VR headset and controller is essential (18).

The combination of ER with the use of a treadmill by patients with PD has shown positive results on gait, as stride length and balance were increased (19–21) and improvement in upper limb movement in particular oscillation of the arms (20). Finally, rehabilitation with the use of ER is found to significantly improve mental health in people with PD (21–23).

As patients with this specific health condition deteriorate with time, the constant burden on the psychomotor level can be unavoidable and can increase treatment cost (24). Exergaming methods have been used for rehabilitation purposes in recent years (25). This systematic review aims to identify, meta-analyze, and present the outcomes on ADL, physical and cognitive function, and QoL when using ER in the rehabilitation of people with PD. A comparison between ER and CPT results is a main goal of this review. Results are expected to aid understanding of the value to use ER, which will help clinicians and researchers in their decision-making.

METHODS

Search Strategy

This systematic review is registered with the PROSPERO database (CRD42020196946). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement principles, using the population, intervention, control, and outcomes (PICO) model, have been followed (guidelines 2020). The following electronic databases, with no timeline or language restrictions, were searched: Medical Literature Analysis και Retrieval System Online (MEDLINE/PUBMED), Physiotherapy Evidence Database (PEDro), Cochrane Controlled Trials Register (CENTRAL/CCRT), and Scientific Electronic Library Online (SciELO). **Figure 1** presents details of the search procedure followed.

Inclusion Criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs); (2) diagnosis of PD; (3) the experimental intervention to have used ER that included exergaming tools [This should involve video-consoles (Nintendo, X-box, etc.) for non-immersive tools, 3D programs with computers and cockpits for semi-immersive tools, and VR environment with headset for fully immersive tools.]; (4) the control group to have practiced CPT, which included any type of active exercise; (5) the study assessed QoL, physical function, and cognition.

Quality Assessment of Studies

Data were extracted by one reviewer (PE) and revised by a second independent reviewer (SD). The studies that met the inclusion criteria were transferred onto the CADIMA system, which is an electronic tool that facilitates documentation in systematic reviews (26). The two reviewers (PE, SD) separately evaluated the studies, in two different timelines, June and August 2020, and then re-searched the literature for new studies in December 2020 and February 2021. The studies were evaluated in two phases. Phase 1 was conducted by reviewer PE, who screened the titles and abstracts for eligibility. Phase 2 was completed by reviewer SD who reviewed the full text of the previously selected studies. For assessing study bias, the PEDro Scale was used by both reviewers. The PEDro assessment tool was developed to evaluate methodological quality of clinical trials (27). No discrepancies were found during the study quality assessment, and results are presented in **Table 1**.

Data Synthesis and Analysis

For the analysis, the statistical software SPSS 25.0 was used. Analysis was based on the mean, standard deviation (SD), and confidence interval (CI) for the evaluation of the effect sizes

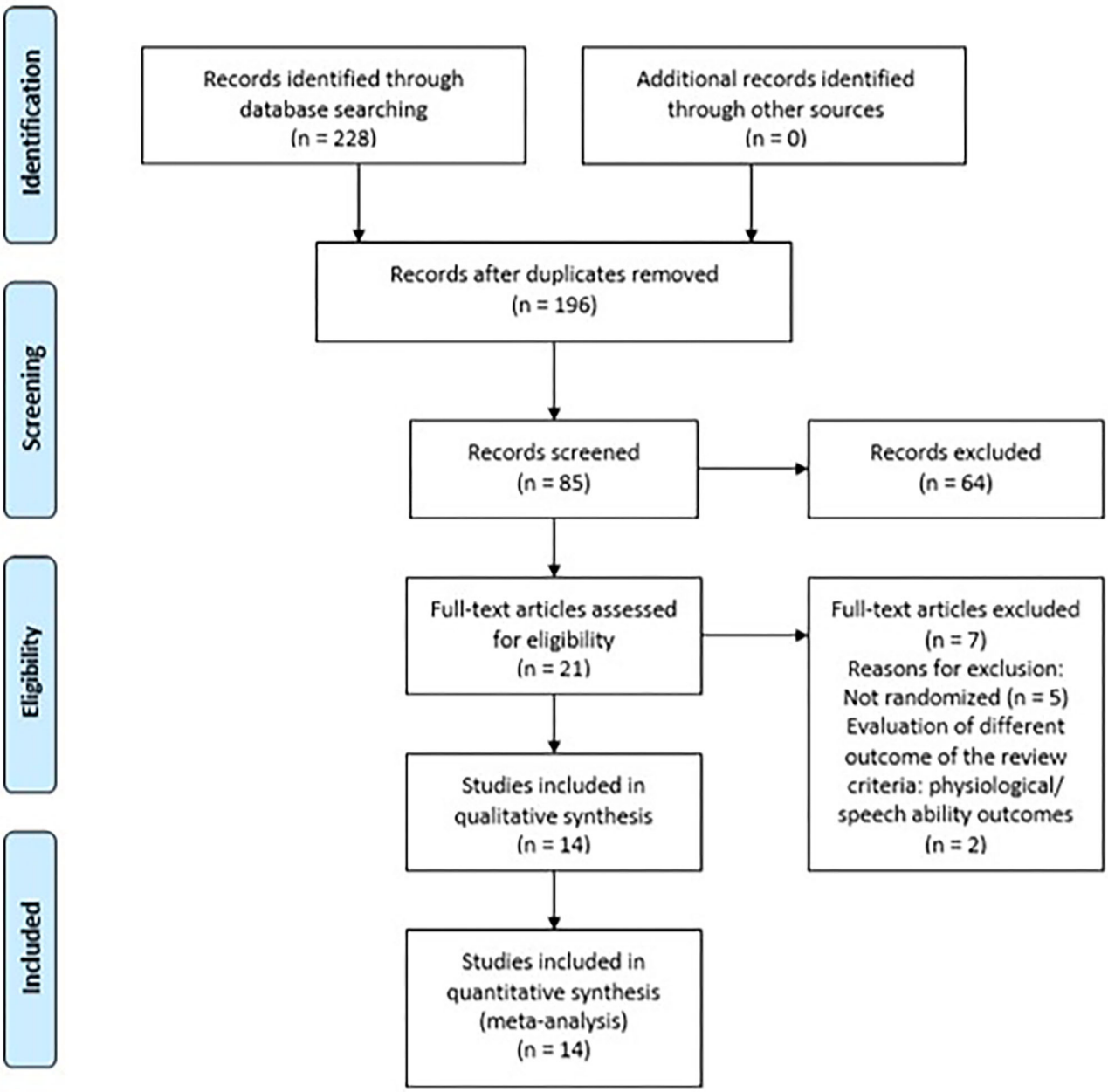

FIGURE 1 | Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart for the selection of the included studies.

between groups. Statistically significant difference was set at <0.05 (42).

For the examination of homogeneity, Levene's test was applied. In order to have homogeneity, groups had to be equal, which means that homogeneity Sig index, or *p*-value, was set at >0.05. All types of immersion for exergames and VR programs were grouped together in the meta-analysis and compared against the control group.

A random-effects meta-analysis was performed with the use of the OpenMeta-analyst software (37). More specifically, the continuous random-effects DerSimonian and Laird model with 95% CI was used. To determine heterogeneity, statistical index I^2 for the description of the variation between the studies was used. Significant level of heterogeneity of the index I^2 was set at $>75\%$. The weight assigned to each study was based on the variance and t^2 value of each study. Furthermore, forest plots were used to illustrate the mean difference and CI between the experimental group and control group for each of the included studies. Multiple meta-analyses were performed in order to evaluate scales and outcomes used.

TABLE 1 | PEDro assessment for the included RCTs.

Study identification number	Eligibility criteria	Randomly allocated to groups	Concealed allocation	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability provided	Total score
Pompeu et al. (28)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	7
Pedreira et al. (29)	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	5
Pazzaglia et al. (30)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	6
Liao et al. (31)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	8
Gandolfi et al. (32)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Fontoura et al. (33)	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	7
Feng et al. (34)	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	6
Allen et al. (35)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Pavez-adasme et al. (36)	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	5
Santos et al. (37)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	7
Shen and Mak (38)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	8
Shih et al. (39)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	6
Yang et al. (40)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Tollar et al. (41)	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	7

PEDro, Physiotherapy Evidence Database; RCT, randomized controlled trial.

RESULTS

Study Selection

The initial literature search detected 228 studies, but following screening of the title and abstract, only 21 remained for further examination. Following reading of the full text, seven studies were excluded. In particular, five studies were pilots of a clinical trial and two did not match the inclusion criteria for this review. One of the studies evaluated physiological variables and the other visuospatial and speech ability variables. Following the exclusion of these studies, 14 studies met the inclusion criteria of this systematic review (28–41).

Based on the PEDro Scale, an average score of 6.7/10 for the included studies was found. The total score of the scale ranged from 0 to 10, with scores of 9–10 considered "excellent," 6–8 "good," 4–5 "fair," and 0–3 "poor" (43). In this systematic review, as shown in **Table 1**, only two studies were given a "fair" score (29, 36), while the rest of the studies received a "good" quality score (28, 30, 32–35, 37, 39, 41). The highest score was 8/10, and it was given to three studies (31, 38, 40).

The Levene's test, done to examine the clinical characteristics of the studies, found homogeneity ($p > 0.05$) between the studies, which allowed the meta-analysis to be performed. Six different group analyses had a heterogeneity score of $p > 0.05$ and thus were further meta-analyzed for QoL, ADL, and physical function. Cognitive function did not pass the set value for heterogeneity ($p = 0.039$) and was thus not included in any further analysis. **Table 4** presents the results of the meta-analysis of the outcomes that passed heterogeneity examination.

Participant Characteristics

In total, 548 people with PD were included in this review from 14 different studies (248 in the experimental group, 249 in the control group, and 51 in a different third group). A total of 59.9% (328 patients) were males, and 37.8% (207 patients) were females. In the study of Pedreira et al. (29), the gender for 13 participants was not reported. The mean age of the target group was 67.3 years ($\pm$2.877), while the mean grade of the severity of the disease, as evaluated by the Hoehn and Yahr scale (44), ranged between 1 and 3. The mean duration of the disease in years was 6.75 ($\pm$1.488), as summarized in **Table 2**.

Interventions

All the included studies used exergaming training as a rehabilitation intervention for the experimental group. Nine studies applied non-immersive equipment (28, 30–32, 34, 35, 38, 39, 41), while four studies used semi-immersive tools (29, 36, 37, 44). Only one study fully utilized immersive equipment (30). Details are summarized in **Table 3**. All studies used CPT for their control groups, with one of them (39) offering an additional one-off fall prevention education session. Two of the studies (37, 41) contained a third interventional group. In particular, in one study (39), the third group was told to continue with their ADL and they did not receive any physiotherapy intervention. In the other one (37), the third group received a combined ER and CPT interventional program. Details of all groups are presented in **Table 3**.

TABLE 2 | Demographic characteristics of the participants.

Study	Country	Gender	Age (SD)	Disease Duration	Disease Classification
Pazzaglia et al. (30)	Italy	Female = 16 Male = 35	71 (8.5)	6 (± 6.29)	UPDRS III 24
Pavez-adasme et al. (36)	Chile	Female = 3 Male = 5	66.6 (8.1)	4.5 (± 2.6)	H&Y 1–3
Tollar et al. (41)	The Netherlands	Female = 38 Male = 36	69.3 (4.35)	7.4 (± 2.04)	H&Y 2–3
Santos et al. (37)	Brazil	Female = 14 Male = 31	64.2 (8.5)	7.1 (± 0.5)	H&Y 1–3
Feng et al. (34)	China	Female = 12 Male = 16	67.1 (4.71)	6.8 (± 1.44)	H&Y 2–4
Allen et al. (35)	Australia	Female = 15 Male = 23	67.9 (7.9)	5.6 (± 5)	UPDRS III 40
Fontoura et al. (33)	Brazil	Female = 4 Male = 16	63 (7)	n/g	H&Y 1–3
Gandolfi et al. (32)	Italy	Female = 25 Male = 51	68.6 (8.2)	6.8 (± 3.85)	H&Y 2.5–3
Yang et al. (40)	Taiwan	Female = 9 Male = 14	75.2 (7.35)	10 (± 3.85)	H&Y 2–3
Shih et al. (39)	Taiwan	Female = 4 Male = 18	68.1 (9.81)	4.6 (± 4.29)	H&Y 1–2
Liao et al. (31)	Taiwan	Female = 19 Male = 17	65.6 (7.46)	7 (± 2.83)	H&Y 1–3
Shen and Mak (38)	China	Female = 24 Male = 27	64.3 (8.25)	7.3 (± 4.15)	H&Y 1–3
Pedreira et al. (29)	Brazil	Female = 9 Male = 22	63.65 (8.25)	7.9 (± 5.6)	H&Y 1–2.5
Pompeu et al. (28)	Brazil	Female = 15 Male = 17	67.4 (8.1)	n/g	H&Y 1–2

The characteristics of the intervention, including setting, frequency, and duration of the intervention, as well as number and age of participants, showed homogeneity ($p = 0.98$, 1.01, 0.58, 0.98, and 0.89, respectively). The majority of the studies (85.7%) took place in an outpatient setting.

The duration of interventions ranged between 40 and 60 min, while one study did not provide information about the duration of the intervention (35). Half of the studies practiced the rehabilitation program twice a week (28, 32, 33, 35–38), five studies three times per week (29, 31, 34, 39, 41), and two studies five times per week (30, 40). The total duration of the rehabilitation program ranged between 4 and 12 weeks, with the most common total duration being 6 weeks (28.6%).

Quality of Life: Parkinson's Disease Questionnaire-39

Seven studies (28, 30, 33, 39, 41, 43, 44) were included in the meta-analysis of QoL (207 participants in total). All studies used the Parkinson's Disease Questionnaire-39 (PDQ-39), and all applied exergames for the experimental group. For the control group, all of them (30, 33, 41, 43, 44) offered active exercises as a rehabilitation program. To examine the effects of the interventions, the post-intervention data presented in these publications were meta-analyzed. As shown in **Figure 2**, this meta-analysis had zero percentage of heterogeneity ($I^2 = 0\%$, Het. $p = 0.604$), and a statistically significant difference in favor of the experimental group ($p < 0.001$, 95% CI: −1.682 to −0.734) for the QoL was found. Results are presented in **Table 4**.

Activities of Daily Living: Activities-Specific Balance Confidence Scale

Two studies (30, 35) used the Activities-Specific Balance Confidence Scale (ABC) to assess ADL. There was null heterogeneity ($I^2 = 0\%$ Het. $p = 0.368$, **Figure 3**), and in total, 115 participants were extracted from these studies. The results (**Table 4**) showed a significant improvement for the ER group ($p = 0.039$, 95% CI: 0.364–13.689).

Activities of Daily Living: Unified Parkinson's Disease Rating Scale II

Three studies (29, 32, 38) used the Unified Parkinson's Disease Rating Scale Part II (UPDRS II) to assess ADL. Heterogeneity,

TABLE 3 | Characteristics of the interventions.

Study	Participants (*N*) Experimental/control group	Length of intervention in minutes	Frequency of intervention	Duration of intervention (weeks)	ER intervention	CPT intervention	Follow-up
Pazzaglia et al. (30)	51 25/26	40	3	6	VR NIRVANA (function and coordination exercises)	Joint mobilization, respiratory balance and coordination exercises, gait	n/g
Pavez-adasme et al. (36)	8 4/4	45	2	6	Nintendo Wii Fit (Strength, balance, aerobic and stretching exercises)	Muscle strength, aerobic exercises, balance and stretching exercises	n/g
Tollar et al. (41)	74 25/25/24	60	5	5	Microsoft X-Box Kinect(motor control and stability exercises, balance)	CYC Group: Balance and aerobic exercises CG: Continuation of ADL	n/g
Santos et al. (37)	45 15/15/15	50	2	8	Nintendo Wii Fit (games of boxing, soccer heading)	NWCE group: Combination of EG and CG training CG: PNF exercises, gait	n/g
Feng et al. (34)	28 14/14	45	5	12	VR training (Balance, coordination and stretching exercises, gait)	Aerobic exercises, coordination, balance and stretching exercises, gait	n/g
Allen et al. (35)	38 19/19	n/a	3	12	VR Unity games (coordination and cognitive training)	General exercises and continuation of ADL	n/g
Fontoura et al. (33)	20 10/10	60	2	5	Microsoft X-Box Kinect (Functional, muscle strength, ROM and coordination exercises)	Stretching, muscle strength and balance exercises, gait	n/g
Gandolfi et al. (32)	76 38/38	50	3	7	TeleWii, Nintendo Wii, balance board (Stretching, balance and functional exercises)	Stretching and balance exercises	70
Yang et al. (40)	23 11/12	50	2	6	VR training balance board (Stretching, balance and functional exercises)	Balance and object manipulation exercises	20
Shih et al. (39)	22 11/11	50	2	8	Microsoft Kinect Sensory (Balance and coordination exercises, gait)	Balance, coordination, muscle strength exercises, gait	n/g
Liao et al. (31)	36 12/12/12	60	2	6	Wii Fit exergaming (yoga, balance and muscle strength exercises)	TE group: Muscle strength, balance and stretching exercises CG: Fall prevention education program	35
Shen and Mak (38)	51 26/25	60	3	12	Computerized Dancing System, Smart-EquiTest Balance Master (Postural control and coordination exercises, gait, sit to stand and gait at home)	Lower limb muscle strength and physical condition exercises, gait at home	35

(Continued)

TABLE 3 | Continued

Study	Participants (*N*) Experimental/control group	Length of intervention in minutes	Frequency of intervention	Duration of intervention (weeks)	ER intervention	CPT intervention	Follow-up
Pedreira et al. (29)	44 22/22	40	3	4	Nintendo Wii (boxing)	Balance and muscle strength exercises, gait	n/a
Pompeu et al. (28)	32 16/16	60	2	7	Wii Fit Exergaming (balance and cognitive training)	Balance, trunk rotations and transition of CB	32

n, number of participants; ER, Exergaming rehabilitation; VR, virtual reality; ROM, range of motion; EG, experimental group; CG, control group; ADL, activities daily living; NWCE, Nintendo Wii Conventional exercise; TE, traditional exercise; CB, central body; n/g: not given.

though high, passed the set criteria for inclusion in this meta-analysis ($I^2 = 89\%$, Het. $p < 0.001$; **Figure 4**). A total of 101 participants were included in these studies, and there was no significant difference between the groups ($p = 0.196$, 95% CI: −5.970 to 1.225).

Function: Berg Balance Scale

Seven studies (29, 31, 33, 38, 40, 41, 43) used the Berg Balance Scale (BBS) to assess function. In the **Figure 5** studies showed a relatively high heterogeneity ($I_2 = 71\%$, Het. $p = 0.002$). Based on the data extracted, a significant improvement was observed in the experimental group in comparison to the control group ($p = 0.018$, 95% CI: 0.446–4.830).

Function: Timed Up and Go

The Timed Up and Go (TUG) scale was used in six studies (31, 33, 37, 39, 41, 43). As seen in **Figure 6**, heterogeneity was relatively small ($I^2 = 39.9\%$, Het. $p = 0.139$). Meta-analysis did not indicate any significant difference in favor of any of the groups ($p = 0.12$, 95% CI: 0.446–4.830).

Function: Dynamic Gait Index

Three studies (38, 40, 43) used the Dynamic Gait Index (DGI) to evaluate function. The studies showed null percentage of heterogeneity ($I^2 = 0\%$, Het. $p = 0.975$) as presented in **Figure 7**. The results of the meta-analysis found a statistically significant improvement in function for the experimental group ($p = 0.005$, 95% CI: 0.351–1.924).

DISCUSSION

This review and meta-analysis aimed to evaluate the effects of ER on QoL, ADL, and physical and cognitive function in comparison with CPT in people with PD. Following a systematic examination of the major literature databases, 14 studies met the inclusion criteria and were meta-analyzed. All the included studies were published within the last 10 years, and they were RCTs using ER and CPT as their intervention rehabilitation methods. The data were checked for homogeneity, and several statistical tests were used to conduct the meta-analysis. The total pooled participant size was 548 people with PD.

The primary outcome evaluated in this systematic review was QoL, and secondary outcomes were ADL, cognitive function, and physical function. The identified studies used different evaluation scales to assess outcomes of their populations, and as such, several meta-analyses were conducted. To assess QoL, seven studies used the PDQ-39 scale (28, 30, 32, 33, 36, 38, 41), one study used the SF-36 (30), and one used the PDQ-8 scale (32). All studies used baseline and post-intervention evaluations. Follow-up evaluations were conducted in five studies (32, 34, 37, 38, 41). Most specifically, three studies had a 1-month follow-up (30, 37, 40), two studies had a 2-month follow-up (32, 38), and the longest follow-up duration was 12 months for one study (38).

The results of the meta-analysis showed that ER significantly improved QoL in comparison with CPT in people with PD

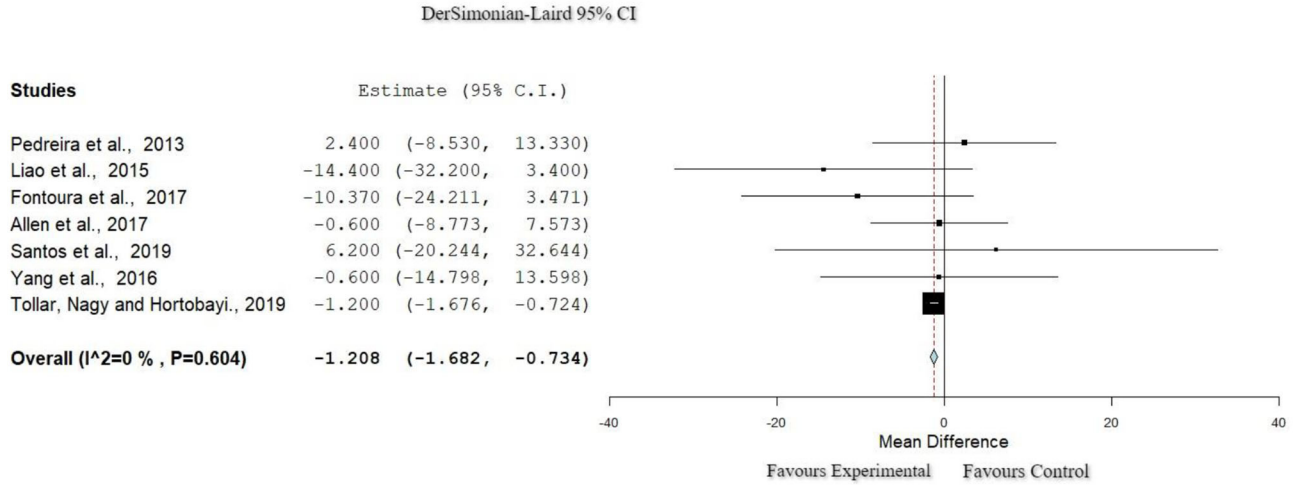

FIGURE 2 | Forest plot for QoL: PDQ-39. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. PDQ-39, Parkinson's Disease Rating Scale-39; QoL, quality of life.

($p < 0.001$), which is in agreement with studies found in the literature (32, 33, 35, 40, 45). Other published systematic reviews that used VR methods (but did not compare with CPT) used the PDQ-8 scale to assess QoL and found significant improvements (32, 39, 41). In the current systematic review, only one study (35) used the PDQ-8, and they reported improvements in QoL as well. For the control group, only one study, which used the PDQ-39, showed a significant improvement in QoL (35).

The study of Pazzaglia et al. (30) used the SF-36 to assess QoL and was the only study not to find any significant difference between the experimental group and the control group. The mentioned assessment tool is a commonly used questionnaire for the evaluation of psychomotor variables. On the other hand, application of the PDQ-39 questionnaire seems to be more useful for the evaluation of the QoL, as it presents higher Cronbach's alpha index (0.76–0.93) regarding the correlation of the emotional changes of the people with PD with their status of health (46, 47). This concludes with the necessity of similar highly confident reliability use of the appropriate evaluation scales between clinical trials.

Three studies included a third intervention group using different approaches to improve QoL for the target group (28, 30, 32). The study of Santos et al. (37) combined ER with CPT for the intervention program of the third group, where the results showed no statistical difference for the effect size but an important magnitude of improvement of the combined group in comparison with the other groups. The combination of the two programs offers alternative solutions that cover the goals of the intervention in a multifactorial way. The reported study was the only RCT that applied this combined rehabilitation method, demonstrating the need for the evaluation of the effectiveness of the addition of ER to CPT for the QoL of the people with PD.

PD includes a large spectrum of symptoms that affect in a multifactorial way the QoL of this population group. The type of clinical setting can reveal different results to the wellbeing of the people with PD, since the outpatient setting follows an emotional approach for the mental improvement of the people (48). As mentioned by Gumber et al. (49), hospitalization of people presents an economic and emotional burden that affects their QoL. Furthermore, the outpatient setting resulted in a lower symptom burden on the population group and enhancement of the health-related quality of life (HRQoL) of the neurological patients and their families (50), confirming the findings of the studies that used outpatient setting in this systematic review. More specifically, 12 of the included studies (28–30, 32, 33, 35–41) took place in outpatient settings and only two in inpatient settings (31, 34). The two studies conducted in an inpatient setting showed improvement on the measured outcomes as the outpatient setting. More specifically, the study of Liao et al. (31) that used inpatient setting presented an increase of physical, emotional, and social function of the population group. In contrast to the findings of this systematic review, the study of Rajan et al. (51) showed positive effects on the reported QoL of the participants who received outpatient care in comparison with the standardized inpatient model setting (51). However, these results can be explained by the fact that the authors used different methodological approaches and they did not include studies with exergaming rehabilitation.

Physiotherapy can play a crucial role in the health management of people with PD (52). Multiple techniques can be applied in order to achieve goals aiming to improve motor skills and gait. Interventions that include exergaming methods seem to enhance both balance and QoL (53). These findings are supported by the current systematic review. The usage of ER intervention results in important improvements in function, as progress is found in balance and gait (48, 54).

TABLE 4 | Results of the meta-analysis.

Study	Weights	PDQ-39
QoL		
Pedreira et al. (29)	0.18%	1.20 [1.682, −7.34]
Liao et al. (31)	0.07%	(0.242)
Fontoura et al. (33)	0.11%	$p < 0.001$
Allen et al. (35)	0.33%	
Santos et al. (37)	0.03%	
Yang et al. (40)	0.11%	
Tollar et al. (41)	99.14%	
Study	**Weights**	**ABC**
ADL		
Gandolfi et al. (32)	61.58%	7.02 [0.364, 13.68]
Shen and Mak (38)	38.41%	(3.39) $p = 0.039$
		UPDRS II
Pompeu et al. (28)	32.51%	−2.37 [−5.97, 1.225]
Fontoura et al. (33)	31.45%	(1.83)
Tollar et al. (41)	36.03%	$p = 1.96$
Study	**Weights**	**BBS**
Function		
Pompeu et al. (28)	19.06%	2.63 [0.446, 4.83]
Pazzaglia et al. (30)	10.08%	(1.11)
Feng et al. (34)	14.08%	$p = 0.018$
Santos et al. (37)	13.47%	
Shih et al. (39)	18.17%	
Yang et al. (40)	9.50%	
Tollar et al. (41)	15.60%	
		TUG
Liao et al. (31)	15.21%	−0.97 [−2.212, 0.258]
Feng et al. (34)	8.11%	(0.63)
Pavez-adasme et al. (36)	33.99%	$p = 0.121$
Santos et al. (37)	24.19%	
Shih et al. (39)	16.90%	
Yang et al. (40)	1.56%	
		DGI
Pazzaglia et al. (30)	8.58%	1.13 [0.351, 1.924]
Santos et al. (37)	9.66%	(0.40)
Tollar et al. (41)	81.75%	$p = 0.005$

QoL, quality of life; ADL, activities of daily living; PDQ-39, Parkinson's Disease Rating Scale-39; ABC, Activities-Specific Balance Confidence Scale; UPDRS II, Unified Parkinson's Disease Rating Scale Part II; BBS, Berg Balance Scale; TUG, Timed Up and Go; DGI, Dynamic Gait Index.

Data are presented as standardized mean difference [95% CI], (standard error), p-value.

For the function, seven studies (28, 30, 34, 37, 39–41) used the BBS to measure the balance of the population. All the included studies showed a significant improvement of the balance through the application of ER comparing the pretest and posttest measurements. However, other studies found that function was not significantly more improved when using ER in comparison with when using CPT (29, 32, 34, 36, 39). In the study of Feng et al. (34), a significant improvement for the control group, in comparison with the CPT group, was found when using non-immersive VR. The application of immersive exergaming in a fully virtual environment showed a significant improvement for the experimental group with increase of function (34) in contrast to previous studies where non-immersive tools of ER programs were used (35, 40). Furthermore, three studies with high homogeneity used the DGI scale for the evaluation of the dynamic gait, presenting improvement of the mentioned outcome for the experimental group (30, 37, 41). The repetitive provision of sensory–motor stimulus with ER facilitates the interaction of the user with the environment, provoking enhancement of the functional outcomes like dynamic gait (30), as has been reported by the results of this systematic review.

The improvement in QoL and function when using exergaming programs leads to improvements in mental health by decreasing stress and depression (55, 56). People with PD have difficulties in executing ADL, which impact their QoL, leading to further emotional and physical limitations (57, 58). For the assessment of ADL, the most commonly used scale is UPDRS (51, 52), which is a valid scale to examine the relationship between disease severity and ADL (59). The usage of an appropriate evaluation questionnaire is considered to be of high importance in order for aspects that can limit the autonomy and functional ability of the target group to be identified (60).

The study of Hariz and Forsgren (61) indicated that changes to posture and balance limit motor capacity and communication skills, leading to a decrease in ADL capability. As found in this analysis, improvements in QoL and function related to improvements in ADL of the experimental groups (33, 35, 37, 38, 40, 41), while there was no such correlation with the improvement in the control group (29, 33, 38).

The small number of studies identified, in this systematic review, to have examined cognition used a variety of assessment scales not allowing a meta-analysis to be conducted. The effectiveness on cognitive function for people with PD is, thus, ambiguous, since only two studies showed improvement with ER and CPT (36, 39). The study of Pedreira et al. (29) did not show any significant improvement for cognition. The studies used different evaluation scales to measure outcomes, as two of them used the Montreal Cognitive Assessment (MoCA) scale (36, 39) and one used the PDQ-39 (29). The systematic review of Triegaardt et al. (54) mentioned improvement in the measurements of the MoCA scale for cognition, confirming the findings of this review on the cognitive function of people with PD, especially when using ER.

ER creates a safe environment that offers physical and cognitive training. The cognitive interaction can lead to cognitive improvements and better ADL skills (59). Active exercises in combination with visual and auditory stimuli offered by the ER increase skill repetitions and velocity and raise endurance (62). The kind of immersion created by VR differs based on

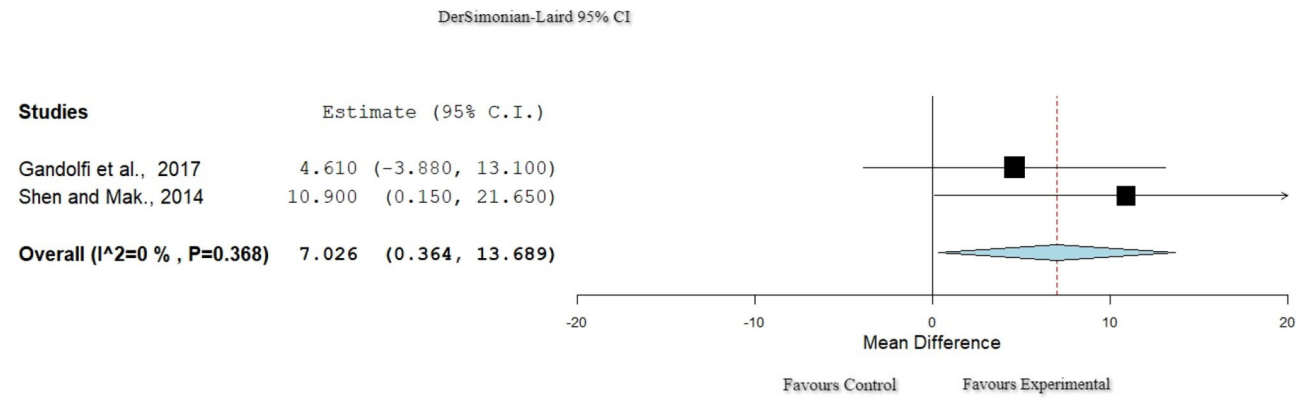

FIGURE 3 | Forest plot for ADL: ABC. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. ABC, Activities-Specific Balance Confidence Scale; ADL, activities of daily living.

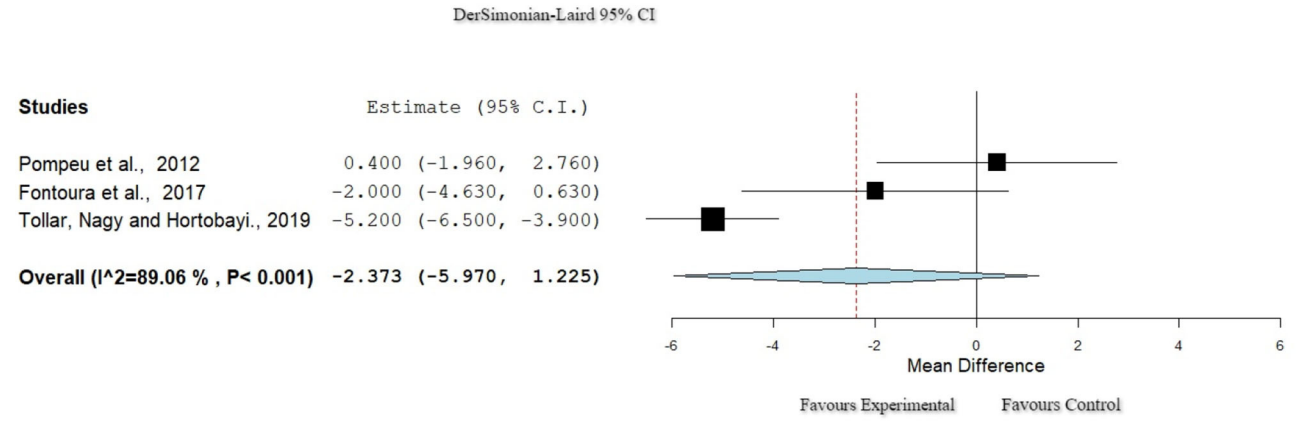

FIGURE 4 | Forest plot for ADL: UPDRS II. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. ADL, activities of daily living; UPDRS II, Unified Parkinson's Disease Rating Scale Part II.

the cost and the features of the equipment. Non-immersive applications have significantly lower cost compared to the fully immersive tools, which provide more realistic gamification. The non-immersive equipment and semi-immersive equipment are easier to apply as a means of therapy and can be used as home care intervention (61, 63). Even though this variable was not evaluated in this review, currently, the ER intervention especially with VR equipment is more expensive than CPT, but in the future, financial affordability is expected, which will enable easier access for the population overall and will facilitate its usage as a rehabilitation method (64, 65).

In summary, the studies included in this systematic review applied a variety of immersion tools for the experimental intervention. Most of the studies used non-immersion application (29, 30, 33–35, 38, 40–42, 62). A semi-immersion intervention tool, aiming to provide more realistic and accurate stimuli during training (40) or aiming to produce multiple tactile and auditory stimuli simultaneously (38), was also used. Only one study used full-immersion program as intervention (30), which limits conclusions to be made.

ER offers a wide range of options, based on users' needs, aiming to promote rehabilitation and offer psychomotor benefits (25). As an interventional tool, ER can be applied for people with disabilities, where the subjects experience functional activities within digital or virtual environment, without external constraints (66). Exergaming and virtual rehabilitation could facilitate tele-physiotherapy sessions and promotes access to rehabilitation (66). Exergaming ensures multiple and targeted repetitions and offers the opportunity to apply home based therapy (37, 64, 67). The combination of ER with CPT, can contribute to patients' education while promoting physical activity, improving psychomotor behaviors, an thus advances health (68–71).

The average PEDro score in this review was 6.7, which is considered to be good (43). Lack of double blinding and

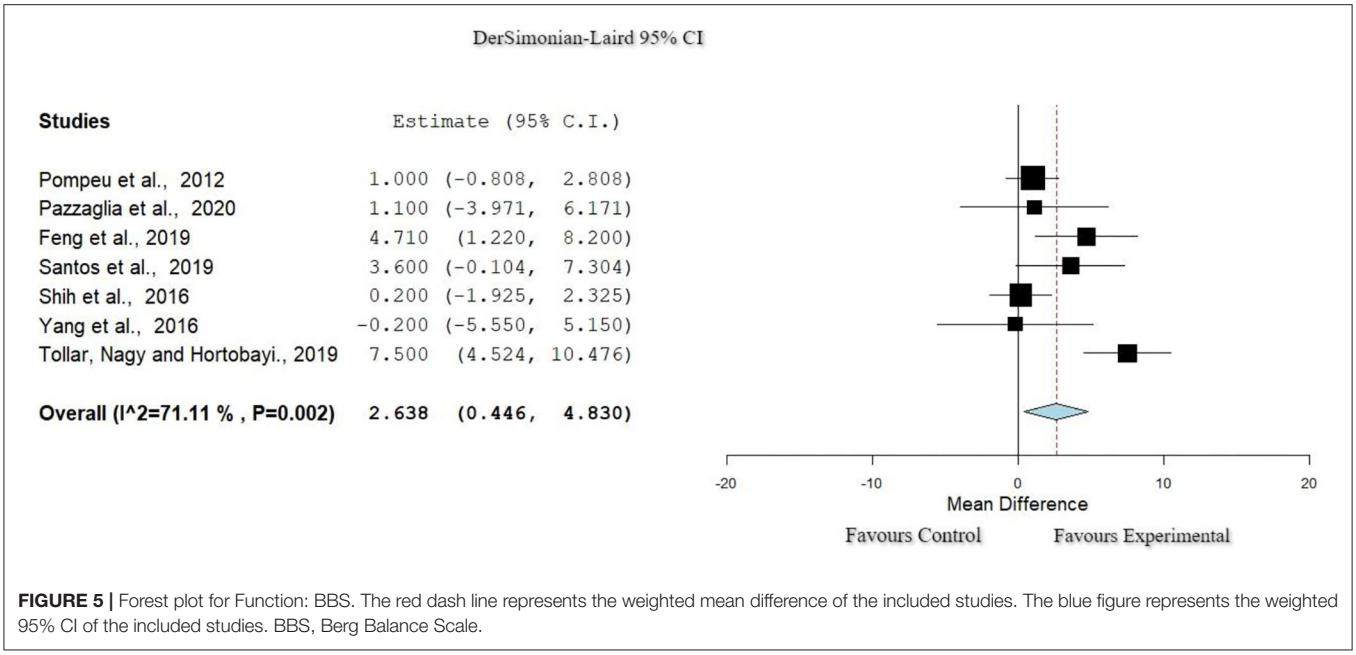

FIGURE 5 | Forest plot for Function: BBS. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. BBS, Berg Balance Scale.

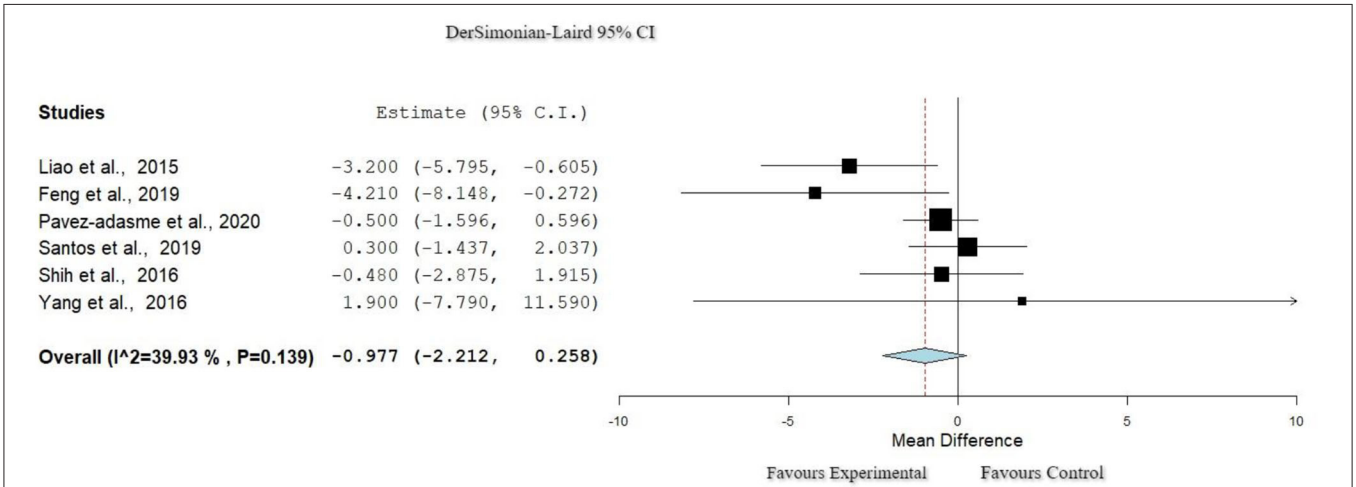

FIGURE 6 | Forest plot for Function: TUG. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. TUG, Timed Up and Go.

intention to treat in some of the studies is a methodological limitation and needs to be considered when designing future studies. Because of the small number of studies that compared the two different intervention techniques, a conclusion on the most efficient treatment cannot be made. The included studies presented numerous and interesting findings for the use of ER, although the different types of immersions that have been used did not provide a clear picture of the most adequate.

Multiple ER can be used to provide alternative interactive interventions. More future research is essential to further evaluate the benefits of this type of intervention in PD rehabilitation. The application of more advanced technological ER systems provides variability of gamification and simultaneous combination of exergaming programs that allow the execution of more realistic activities, raising the physical and emotional interaction between the individual and the environment. This gives the opportunity to evaluate the use and effectiveness of the intervention in mental health and motivation for people with PD, which should be considered in future studies.

In conclusion, the use of ER as an intervention tool can meet the needs and abilities of people with PD, as these systematic review and meta-analysis have found positive results

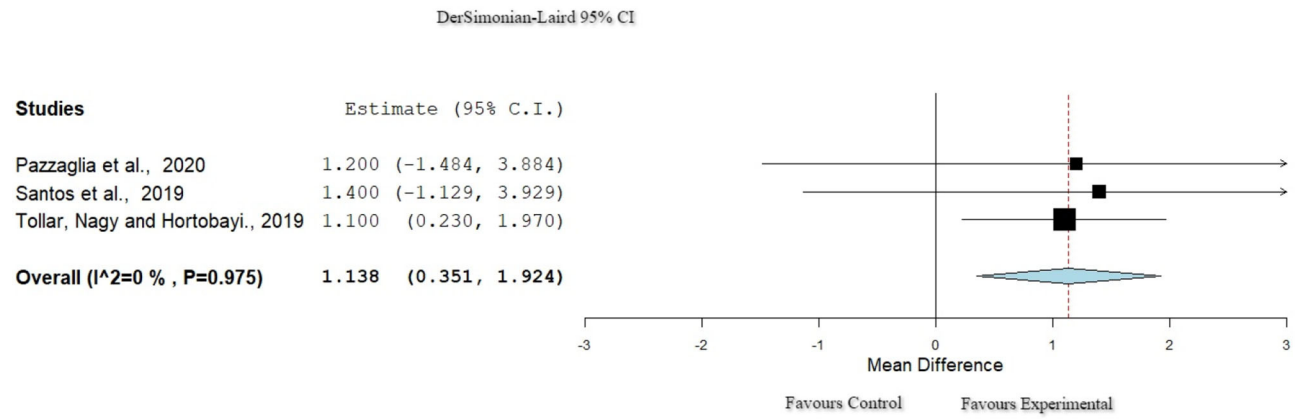

FIGURE 7 | Forest plot for Function: DGI. The red dash line represents the weighted mean difference of the included studies. The blue figure represents the weighted 95% CI of the included studies. DGI, Dynamic Gait Index.

in function and QoL. Only a small number of studies compared ER with CPT, and thus, future studies should follow such comparison designs. In addition, few studies examined the QoL in patients with PD and an even smaller number of studies compared it with the use of CPT. It is essential that more research is done in order to have more accurate data on this particular topic.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

PE, SD, and MC contributed to conception and design of the study. SD and PE organized the database. PM and PE performed the statistical analysis. PE wrote the first draft of the manuscript. PE and MC wrote sections of the manuscript. MC reviewed the writing and organization of the study. All authors contributed to manuscript version, read, and approved the submitted version.

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

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Improvement of Apraxia With Augmented Reality: Influencing Pantomime of Tool Use via Holographic Cues

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Background: Defective pantomime of tool use is a hall mark of limb apraxia. Contextual information has been demonstrated to improve tool use performance. Further, knowledge about the potential impact of technological aids such as augmented reality for patients with limb apraxia is still scarce.

Objective: Since augmented reality offers a new way to provide contextual information, we applied it to pantomime of tool use. We hypothesize that the disturbed movement execution can be mitigated by holographic stimulation. If visual stimuli facilitate the access to the appropriate motor program in patients with apraxia, their performance should improve with increased saliency, i.e., should be better when supported by dynamic and holographic cues vs. static and screen-based cues.

Methods: Twenty one stroke patients and 23 healthy control subjects were randomized to mime the use of five objects, presented in two *Environments* (Screen vs. Head Mounted Display, HMD) and two *Modes* (Static vs. Dynamic) resulting in four conditions ($Screen^{Stat}$, $Screen^{Dyn}$, HMD^{Stat}, HMD^{Dyn}), followed by a real tool demonstration. Pantomiming was analyzed by a scoring system using video recordings. Additionally, the sense of presence was assessed using a questionnaire.

Results: Healthy control participants performed close to ceiling and significantly better than patients. Patients achieved significantly higher scores with holographic or dynamic cues. Remarkably, when their performance was supported by animated holographic cues (e.g., striking hammer), it did not differ significantly from real tool demonstration. As the sense of presence increases with animated holograms, so does the pantomiming.

Conclusion: Patients' performance improved with visual stimuli of increasing saliency. Future assistive technology could be implemented upon this knowledge and thus, positively impact the rehabilitation process and a patient's autonomy.

Keywords: virtual reality, apraxia, pantomime of tool use, stroke, hologram, sense of presence, visual cues

INTRODUCTION

Apraxia occurs in 30–50% of patients after left brain damage (LBD) (1, 2) and frequently co-occurs with other syndromes, such as aphasia or neglect (3–6). Limb apraxia refers to a higher-order motor disorder of learned purposive movement skills not caused by deficits of elemental motor or sensory systems (7) that may also affect activities of daily living (ADL) (8, 9). Patients show impairments in planning or producing motor actions. Typically, they have problems with gesture imitation, pantomimed tool use, and actual tool use (4, 10, 11). In the pantomime of tool use task patients are asked to produce an action without holding the object in their hand (12). Pantomiming requires both, motor-cognitive (e.g., the spatial configuration of the body, hands and movements) and communicative processes, including the simulative demonstration and integration of semantic and motor features of the underlying tool use action, requiring a heightened demand on the working memory processes (5, 10, 13, 14). Pantomime of tool use is considered as very sensitive in detecting the presence of limb apraxia; typically the pantomime mode appears more sensitive as compared to actual tool use mode (3, 15), however performance measures across these modes correlate and individual patterns appear stable (16, 17). While both modes may retrieve similar concepts, differences may be represented by missing visuotactile feedback, i.e., the absence of mechanical interaction and cues from real objects, the heightened demand on imagery and the translation from mental images to motor execution (5, 10, 11, 16, 18, 19). Contextual information may provide critical cues facilitating the access to an adequate motor concept and may constrain the possibilities for action production (15–17). While tactile feedback alone, such as a stick that resembles the handle of a tool, seems to be inefficient in evoking the correct motor program of an action (20, 21), several studies underlined the role of visual feedback (11, 17, 22). In this regard, it has been shown that the perception of object affordances (i.e., action possibilities offered by the environment and the object's properties) and its visual attributes is influenced by its visuo-perceptual context, such as thematic and functional properties but also by space (23).

Augmented reality (AR) technology provides a unique way to study the contributions of visual information during pantomiming and may help understand the underlying mechanisms of apraxia. This new technology allows manipulating the experimental setting by providing different contextual information. In contrast to virtual reality, in which the user is often immersed in a completely synthetic environment, in AR the user's real environment is not replaced but rather enriched by spatially aligned virtual objects (24). In mixed reality training scenarios, a higher sense of presence, defined as the psychological product of technological immersion (25), is suggested to enhance motor performance (26–28). AR systems are advantageous over virtual reality in providing a better sense of presence and reality judgments because users can still see their body parts when interacting with virtual objects (29). These virtual objects or holograms, herein referred to as the perception of a computer generated object through stereo imaging, can provide detailed visual contextual information about the properties of the object (e.g., size or structure) and its functioning (e.g., a moving hologram showing its intention) by creating a realistic illusion in three dimensions (30). Practicing in a salient environment by using meaningful and context-specific cues is related to induced plasticity, increased motor learning and a transfer to other tasks (31). Saliency is a strong predictor of attention and gaze allocation and as such a crucial factor in most everyday visual tasks and everyday functioning (32–34). While visual salience refers to objective attributes compared to its surroundings (e.g., object color and structure), semantic salience defines associations with an object (e.g., memories or personal importance) and depends on the user (35). We suggest holograms to function as cues with high visual and semantic salience, which might support motor actions in patients with apraxia. This is in line with the most recent concept of "action reappraisal" by Federico and Brandimonte (23), a reasoning-based approach in human tool-use processing, suggesting that tool use actions utilize multiple sources of information, including affordances and contextual conditions.

The main objective of this study was to test the hypothesis that the disturbed movement execution in stroke patients with apraxia can be mitigated by AR stimulation during pantomime tasks. If visual stimuli facilitate the access to the appropriate motor program in patients with apraxia, the performance should improve with cues of higher saliency and more contextual information. Specifically, we consider dynamic holographic tools presented through a Head Mounted Display (HMD) as stimuli with higher salience because the moving character on the one side and the holographic nature (i.e., three-dimensionality) on the other side should attract more attention than two-dimensional static images of a tool, enhancing the perception of the object in this way (33, 36). The enriched contextual environment (e.g., detailed object features such as structure) and the overall realism that is conveyed by these properties should provide more cognitive cues (37). Further, little is known yet as to the impact of the induced sense of presence in virtual environments on motor performance in stroke rehabilitation (26). We suggested the enriched conditions to evoke higher presence, and expected to observe an association between increased presence and pantomime performance. A better understanding of the technological properties (e.g., visual saliency) and user attributes (e.g., presence) that contribute to motor performances in augmented environments may further inform decisions about their use in overall stroke rehabilitation.

METHODS

Participants

This study was conducted at the neurorehabilitation hospital Schoen Clinic Bad Aibling (Germany). From April 2019 to December 2019, we included a total of 49 participants (25 patients

Abbreviations: ADL, Activities of Daily Living; AR, Augmented Reality; DILA-S, Diagnostic Instrument for Limb Apraxia – Short Version; Dyn, Dynamic; EDI, Edinburgh Handedness Inventory; LBD, Left Brain Damage; MI, Motricity Index; MMSE, Mini Mental State Examination; NNPT, Nine Hole Peg Test; Stat, Static.

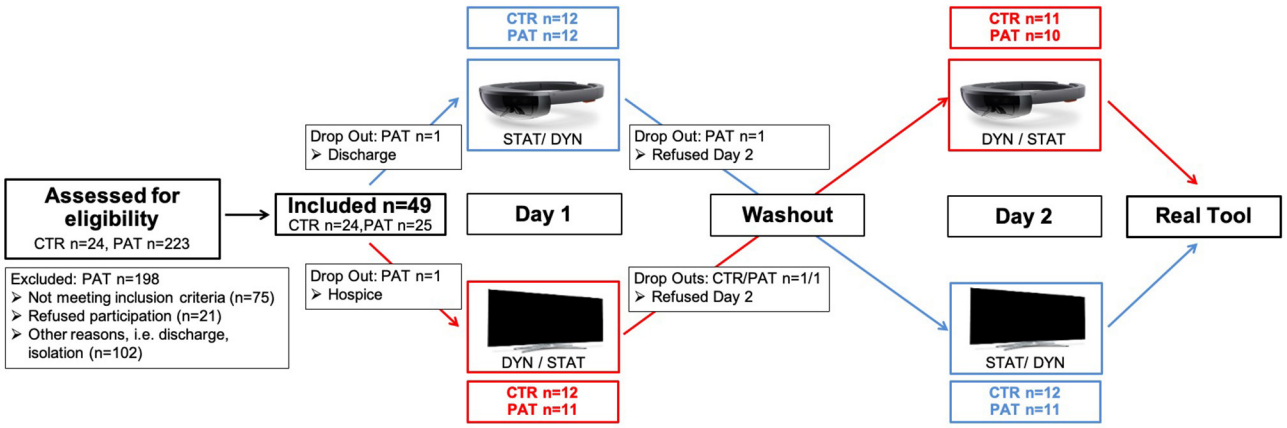

FIGURE 1 | Patients' flow through the study. All participants had to perform the pantomime task twice (Static/Dynamic) in each Environment (HMD/Screen), followed by the real tool condition. The washout time was set to >24 h and did not include any additional tasks. Three participants only completed Day 1 and were excluded from further analyses.

with LBD and 24 healthy age-matched control persons) who fulfilled the eligibility criteria: (1) stroke in the left hemisphere with signs of apraxia (or no stroke in controls), (2) normal or corrected-to-normal vision, (3) sufficient cognitive ability to understand and follow task instructions (tested prior to the study), (4) no other neurological, psychiatric diseases or poor general condition affecting testing (i.e., the patient had to be able to sit for the duration of the experiment). Healthy control participants were recruited via poster announcements distributed in the clinic and University and self-registration. The sample size was based on an estimate on earlier studies comparing different execution conditions for similar actions, in which significant effects were found in comparable samples (n = 23 per group) (15, 17). The study was approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich and all participants or their legal representatives provided written informed consent prior to testing, which was performed in accordance to the declaration of Helsinki. The protocol was prospectively registered with the German Clinical Trials Register (DRKS) on 22 September 2018 (TrialID = DRKS00015464, Universal Trial Number = U1111-1220-6410).

Trial Design

Within this randomized crossover study, we tested the influence of varying types of visual stimuli with different degrees of saliency to determine the most effective way of support. Participants had to mime the use of five common objects (hammer, flat-iron, watering can, key, electric bulb) with variable combinations of visual input. On the 1st day, they were randomized 1:1 via sealed envelopes to begin with one of the testing **Environments** (Screen vs. HMD), of which each testing environment was randomized 1:1 to start with one of the testing **Modes** (Static vs. Dynamic). After a 24 h "washout" period, the same task was performed starting with the other testing environment, ending up with four **different combinations**: $\text{Screen}^{\text{Stat}}$, $\text{Screen}^{\text{Dyn}}$, HMD^{Stat}, HMD^{Dyn} (**Figure 1**). Each object was presented four times in a row whereas the first presentation was designed as a familiarization where no action was required, to ensure that participants were able to see the images and minimize an influence of visuo-spatial deficits. The order of object presentation was balanced for these four combinations, and held constant for both testing days (i.e., one out of five predefined sequences of object presentations was assigned to each participant). In the screen environment, participants were supported by images of the objects presented on a laptop monitor (15.6-inch, 1,920 x 1,080-pixel resolution), whereby the viewing distance was held constant among all participants (i.e., in a reachable zone of 70 cm when leaning forwards). In the HMD environment, participants wore the Microsoft HoloLens device (1st generation) to view holographic images. In the dynamic mode, one could see the individual tool moving (e.g., striking hammer) while in the static mode the tool remained still (see **Supplementary Videos 2**, **3**). At the end of day 2 after all four conditions were completed, participants had to demonstrate the use of the real tool (in the absence of the target object) that was placed on the table in a standardized way (i.e., the tools were aligned in accordance with the other testing environments, i.e., oriented to promote an action with the left hand as shown in **Figure 2D**), not accompanied by any additional visual input ("Real Tool" condition).

Participants were seated in front of a table, either facing the screen or wearing the HMD (**Figure 2**). To familiarize with the HMD a practice holographic object, i.e., a red paper boat (see **Supplementary Video 1**), was presented accompanied by a standardized explanation of its main technical feature and current limitation of a limited field of view in HoloLens (1st generation). Practice items were included at the beginning of each day by showing printed objects to the participants (fork—corkscrew—saw), and task comprehension was assumed when participants at least attempted to produce a meaningful movement, based on the DILA-S pantomime task recommendations (13). In all conditions participants were

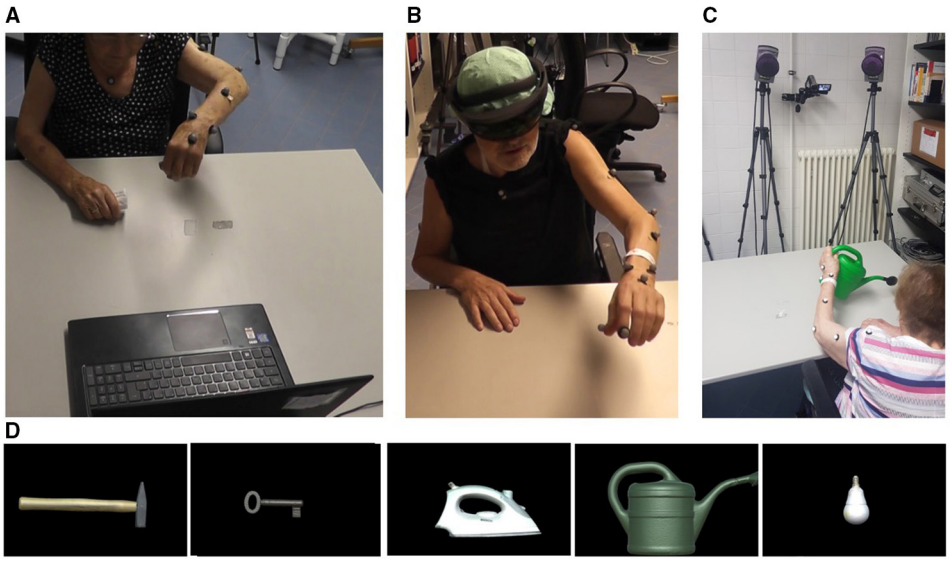

FIGURE 2 | Third person perspective of the experimental setup. **(A)** Screen condition, **(B)** HMD condition, **(C)** Real Tool condition; and **(D)** the first-person perspective of the five objects depicted as screen-based images. Only the tools and not the target items were shown (i.e., the hammer, but not a nail).

verbally instructed by the experimenter (e.g. "please show me how to pound in a nail with a hammer") as described in (13) and were allowed to start miming as soon as the picture of the object became visible. Their movements were videotaped for later observational evaluation. They used their left hand (non-paretic) in all conditions and were tested on consecutive days to reduce carryover effects and fatigue, on about the same time of the day, lasting a maximum of 1 h/day. For patients who still fatigued very fast, the additional clinical testing was postponed to a 3rd day. During testing participants were asked for any discomfort or motion sickness. Neither participants nor examiners were blinded due to the optical see-through device being used.

Software Development

The testing environments were designed using the game engine development tool, Unity 3D (Version 2017.4). The five objects were created by 3D-scanning their real-life counterparts in order to achieve high visual fidelity. Object selection was based on its movement characteristics to cover a variety of different movement components, movement planes and grip formations (e.g., repetitive hammering with elbow flexion/extension using a cylindrical grip in the longitudinal plane). Three of the five gestures involved non-repetitive movements (water a plant, iron a blouse, open a lock), while the other two were repetitive gestures (screw in an electric bulb, hammer a nail). For this study we chose gestures performed without body contact because of the complexity of holographic animations performed on the body. Only the tools and not their corresponding counterpart were shown (i.e., the hammer, but not a nail, see **Figure 2D**). The dynamic version is based on recordings of real tool use movements with the same physical objects (including the recipient object) using motion capturing (Qualisys Inc., Gothenburg, Sweden). The gathered kinematic data were post-processed to handle noise. In the screen environment, the objects had to be adjusted in size in order to be properly displayed on the screen. In the HMD environment, we adjusted the objects' position in space to maintain the objects' real sizes. Further, the objects were oriented in space in a way that the tools' handle functioned as an easy to graspable stimulus (38). The full project code is available at GitHub https://github.com/Ninarohrbach/panto-holo, and a visualization of the object presentations can be found in the supplements (**Supplementary Videos 2**, **3**).

Remote Control System

Generally interacting with the HoloLens device as an experimenter is inconvenient, because one would need to put on the device for each single interaction. We solved this problem by using a web application to remotely control the HoloLens application (see **Supplementary Video 1**). The advantage of a web application is that it can be run on almost any device that has a web browser, e.g., smartphones. The complete system consisted of three components: The web application, a webserver and the HoloLens application. The HoloLens application was implemented using Unity 2017.4 using C++. A Firebase application was used as a web server and Polymer 2.0 was used for the front-end of the web application. This way, the experimenter could easily change the values (i.e., object 1–5, and mode "static"/"dynamic") on the Firebase server in real-time. The same system was used for the screen environment, by running the Unity application on a laptop.

Clinical Tests and Questionnaires

Prior testing, participants were asked questions regarding their sociodemographic background and previous HMD experience. The Mini Mental State Examination (MMSE) (39) was conducted

to assess cognitive impairment. The Titmus Test (Stereo Optical Co., Chicago, IL) with its two sub-tests was administered to classify for the presence (i.e., House Fly test) and the quality of stereovision (i.e., Circles test). The Edinburgh Handedness Inventory (EDI) (40) was used to assess the dominance of a person's hand in everyday activities before the stroke. To evaluate manual dexterity, we conducted the Nine Hole Peg Test (NHPT) (41). For this purpose, the left (non-paretic) hand was tested twice using motion capture analysis and the mean time of two successful trials was computed (see "hand kinematics" in data analysis). Further, we examined the Motricity Index (MI) to evaluate the extent of the paralysis of the affected arm by assessing the strength (remaining force) of shoulder abduction, elbow flexion and finger griping (42). To diagnose for the presence of apraxia the Diagnostic Instrument for Limb Apraxia—Short Version (DILA-S) was used (13). Note, that the DILA-S was evaluated for patients with LBD and is applicable for patients with severe aphasia or neglect. At the end of each testing condition (i.e., four times), participants completed a slightly adapted presence questionnaire (43) (**Supplementary Table 1**).

DATA ANALYSIS

Scoring System

Supplementary Table 2 provides details on the scoring procedure. As the primary outcome parameter, a performance scoring was undertaken. For task evaluation we adapted the **Production scale** (PS) (13) in which four movement components were rated on a three-point scale resulting in a maximum score of 24 points per object and condition after three trials. Additionally, we applied the **Interaction scale** (IS) developed for the purpose of this study to investigate the participants' interaction with the different cues. With the standard pantomime procedure in clinical settings the examiner sometimes observes patients who seemingly try to interact with the presented item by reaching for and touching the depicted picture. One point per trial was given if participants actively tried to reach forward and grasp the virtual object or followed the movement, ending up with a maximum of three points per object and condition after three trials. Note that our experimental task and digital content do not require any interaction. Thus, the term "interaction" within this study does not reflect the overall accepted definition in the AR domain [for a recent review on immersive systems (44)].

Each participant's videotaped performance was viewed in its full length four times, once for each of the four movement parts. Two independent raters (NR, LL) scored the first 20 participants (10 patients, 10 controls) and critical aspects were discussed within the research team in a consensus meeting. Validating a certain percentage of the study sample by two independent evaluators is common and widely accepted practice e.g., 25% in (18) and (45). The inter-rater reliability of the pantomime scoring (400 data points for the Production and Interaction scale) and real tool scoring (50 data points) of the first ten healthy control subjects achieved large results for pantomiming (Kendall's Tau $\tau = 0.643$ for Production; $\tau = 0.602$ for Interaction) and real tool demo ($\tau = 0.862$). After further refinement of the system, all data were scored and uncertainties were collaboratively discussed until the two raters met consensus.

Statistical Analysis

All outcome variables were tested for normal distribution using Shapiro-Wilk's test. The statistical analysis included a *t*-test for age and non-parametric tests for sex, stereovision, MMSE and NHPT-time to determine if there were differences between the patient and the control group. For the pantomime performance (averaged score across all five objects for each of the four conditions) and the subjective experience of the presented objects (calculated mean score of presence data for each of the four conditions) a mixed repeated measures $2 \times 2 \times 2$ ANOVA was conducted to determine whether any changes in the dependent variables (Production Scale, Interaction Scale) were caused by the between-subject factor *Group* (Stroke, Control), the within-subject factors *Environment* (Screen, HMD) and *Mode* (Static, Dynamic), or their interactions. We dealt with missing values (Production: 2.06%, Interaction: 2.14%) by imputing the mean performance value for the respective object and condition (46). Significant interactions, simple effects and main effects were followed-up with Bonferroni-adjusted pairwise *post-hoc* tests comparing the performance scores of the different visual cues. The achieved real tool scores were compared separately between groups using independent *t*-tests. They were further analyzed within each group, by comparing them with the means of the four combinations of the pantomime task using *t*-tests for paired samples. We calculated the performance effects, i.e., the environmental (HMD-Effect), the conditional (DYN-Effect) and the combined effect (HOLO-Effect) for both scales, defined as the following:

- HMD-Effect = Mean (HMD^{Stat}, HMD^{Dyn}) – Mean ($Screen^{Stat}$, $Screen^{Dyn}$)
- DYN-Effect = Mean (HMD^{Dyn}, $Screen^{Dyn}$) – Mean (HMD^{Stat}, $Screen^{Stat}$)
- HOLO-Effect = Mean HMD^{Dyn} – Mean ($Screen^{Stat}$, $Screen^{Dyn}$, HMD^{Stat})

We assessed the relationship of the Production and Interaction scores within each group using Spearman's rank correlation (r_s). Further, the performance effects were correlated with the clinical data to test whether the timing of stroke onset, mental capacity, manual dexterity, stereovision or apraxia affect pantomime of tool use using Pearson's r or Spearman's correlation. The relationship between presence and pantomiming was analyzed for each condition within the patient group. For significant correlations, the magnitude was classified considering the following categories: $|r| \geq 0.10$ = small, $|r| \geq 0.30$ = medium and $|r| \geq 0.50$ = large (47). Data analysis was carried out in SPSS (version 26), and the level of significance was established at a 0.05 alpha-level (two-sided).

Hand Kinematics

In addition, we recorded hand movements (a spherical marker attached to the subject's left back of the hand) using motion capturing. Movements were recorded by three cameras (Oqus, Qualisys Inc., Gothenborg, Sweden) and a sample rate of 120 Hz.

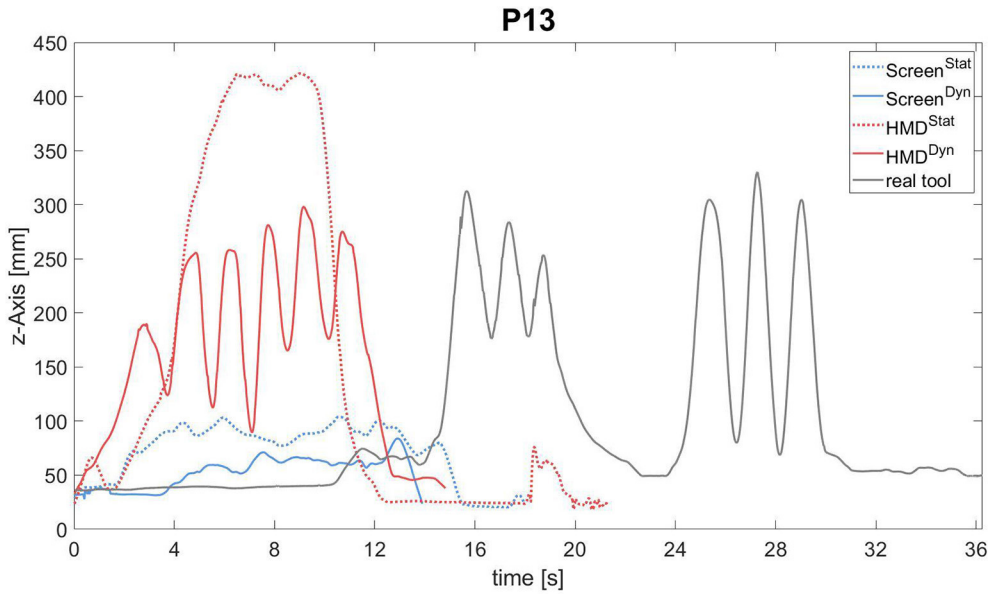

FIGURE 3 | Trajectories of hand movements in patient P13 attempting to pantomime the typical use of a hammer during the different experimental conditions is illustrated: Screen^{Stat} (blue line), Screen^{Dyn} (blue dotted line), HMD^{Stat} (red line), HMD^{Dyn} (red dotted line), real tool (gray line). The complete trajectory along the z-Axis in (mm) during the third of three trials is always shown.

TABLE 1 | Participant's demographics and clinical characteristics.

	LBD (*N* = *21*)	**Controls (*N* = 23)**	**Between-Group Comparisons**
Sex: male/female	10/11	10/13	$t_{(42)} = -0.988$, $p = 0.329$
Age: mean years (range)	69.81 (41–91)	65.87 (40–91)	$U = 231.5$, $Z = -0.272$, $p = 1.0$
Adverse events, side effects*: yes/no	0/21	0/23	
EDI: right/left/both	20/0/1	23/0/0	
Education level**: low/middle/high	8/8/4	6/7/10	
Experience with HMD: yes/no	0/21	0/23	
Etiology: Ischemic infarct/ICB	18/3	NA	
Aphasia***: yes/no	15/6	NA	
MMSE: mean (range)	21.25 (14–28), $N = 16$	28.83 (24–30)	$U = 8.500$, $Z = 34.6$, $p < 0.001$
MI: mean (range)	52.6 (0–100)	NA	
Neglect****: yes/no	6/15	NA	
NHPT: mean time in seconds (range)	47 (26–140)	24.5 (18.5–44)	$U = 445.00$, $Z = 42.5$, $p < 0.001$
Titmus Test			
House Fly: stereovision given (yes/no)	13/6	23/0	$U = 138.0$, $Z = -3.151$, $p = 0.002$
Circles: ≤/> 100 arc/sec	2/16	17/6	$U = 77.0$, $Z = -3.953$, $p < 0.001$
Time since event: mean duration in days (range)	250,7 (11–1,933)	NA	
Visual aids during testing: yes/no	12/9	21/3	

*EDI, Edinburgh Hand Inventory; HMD, Head Mounted Display; ICB, Intracranial bleeding; LBD, Left Brain Damage; MMSE, Mini Mental State Examination; MI, Motricity Index; NA, Not applicable; NHPT, Nine Hole Peg Test (left hand); t, t test for independent samples; U, Mann-Whitney-U-Test, * based on verbal reports, ** Education level: low = secondary school, middle = intermediate school =, high = high school or higher, ***based on Aachen Aphasia Test (AAT) analysis description, i.e., a combination of the subscales Token Test and written language, **** based on different severity levels assessed with different assessments; information provided by neuropsychologists out of a test battery including several paper-pencil tests.*

The kinematic approach served as an objective and sensitive analysis to evaluate the NHPT data and to provide an additional visual illustration to our qualitative findings. Based on the performance results, the patient with the strongest HOLO-Effect (see statistical analysis for further specification) was chosen for further kinematic analysis. Post-processing of the hammering

performance (repetitive up and down movement) of P13 was performed using MATLAB R2018b (MathWorks, Natick, MA, USA). We determined the starting and the ending time points by calculating the overall marker velocity in 3D space and thresholding it at $v_{th} = 0.012$ [m/s]. The vertical axis of the movement was extracted and plotted for visualization (**Figure 3**).

RESULTS

Participant Demographics

Participant characteristics and patient-specific information are provided in **Tables 1**, **2**. All but one patient (P23) showed signs of apraxia in at least one of the DILA-S sub-tests (**Supplementary Table 3**), with most patients being affected in the Imitation of gestures (meaningless: 95%, meaningful: 67%), in the Pantomime task (Production: 76%, Execution: 71%) and in the Naturalistic Action Task (NAT: 62%). While the majority of patients had at least mild problems in the Familiar Tools Task (FTT; Selection: 33%, Production: 67%, Execution: 62%) they were less frequently affected in the Novel Tools Task (NTT; Selection: 52%, Production: 29%, Execution: 29%).

Performance Results

Figure 4 displays the performance scores of both groups of the Production and Interaction scales, and **Table 3** shows the ANOVA results respectively. The individually achieved environmental (HMD-Effect), modal (DYN-Effect) and combined (HOLO-Effect) effects in patients are visualized in **Figure 5**. During HMD trials, the key was not visible for three patients (P1&P6: Key_HMD^{Stat}, P1&P16: Key_HMD^{Dyn}), and in another patient (P21) the Screen^{Stat} condition was not videotaped. Overall, we had a total of 26 missing data points out of 1,260 observations on the Production scale (2.06%) and 9 out of 420 on the Interaction scale (2.14%), respectively.

Production Scores

On the Production scale, a significant main effect of *Group* with overall higher scores in controls (**Figure 4A**) indicates that healthy subjects performed significantly better than patients ($MD = 6.5$; 95%-CI [4.1,8.9], $p < 0.001$). Further, we found significant main effects of *Environment, Mode* and significant interactions between *Environment* × *Group, Mode* × *Group*, and *Environment* × *Mode* × *Group*, but not between *Environment* × *Mode* (**Table 3**).

Next, we analyzed the different combinations within each group separately. Control participants reached almost maximum scores independent of the presented stimuli ($M = 23.2$, $SD = 0.64$ [21.4,23.9] with no significant effects or interactions ($p > 0.144$). In patients, we found a statistically significant effect of *Environment* and of *Mode*, but not between *Environment* × *Mode*. Bonferroni-adjusted pairwise comparisons indicate a better performance with the help of holographic (−1.2; 95%-CI [−2.1,−0.19], $p = 0.021$) or dynamic cues (−0.91; 95%-CI [−1.7,−0.16], $p = 0.019$).

Interaction Scores

We found a significant main effect of *Group* on the Interaction scale, suggesting that healthy subjects interacted significantly more with the presented stimuli (0.48; 95%-CI [0.10,0.86], $p = 0.014$; **Figure 4C**). Similar to the Production scores, we found significant main effects of *Environment* and of *Mode*, and a significant *Environment* × *Group* interaction which was driven by higher means in the HMD Environment in controls (Screen: 0.30; 95%-CI [0.13,0.47], HMD: 1.9; 95%-CI [1.4,2.4] compared to patients (Screen: 0.21; 95%-CI [0.11,0.32]; HMD: 1.0; 95%-CI [0.56,1.4]. All remaining interactions were non-significant ($p > 0.518$, **Table 3**).

In both groups, there was a significant effect of *Environment*, suggesting stronger effects of holographic than screen-based cues (Patients: −0.79; 95%-CI [−1.2,−0.39], $p < 0.001$; Controls: −1.6; 95%-CI [−2.1,−1.1], $p < 0.001$). A significant effect of *Mode* in patients and a borderline significant effect of *Mode* in controls ($p = 0.054$) point toward a higher effect of dynamic than static cues (Patients: −0.24; 95%-CI [−0.38,−0.11], $p = 0.001$; Controls: −0.27; 95%-CI [−0.54,0.005], $p = 0.054$).

Correlations Between Production and Interaction Scores

We found medium to large significant correlations between the Production and Interaction scores. In patients, higher interactions with animated screen-based objects were significantly associated with a better performance (Screen^{Dyn} $r_s = 0.699$, $p < 0.001$). In controls by contrast, when the interaction with static holographic items increased, the performance decreased (HMD^{Stat} $r_s = -0.537$, $p = 0.008$). All other correlations were non-significant (**Supplementary Table 4**).

Real Tool Comparison

Patients had significant problems demonstrating the real tool use ($M = 18.3$, $SD = 3.9$) compared to controls [$M = 23$, $SD = 0.74$, $t_{(42)} = 5.7$, $p < 0.001$]. In healthy subjects, all pairwise comparisons were non-significant ($p > 0.208$). In patients, there was a significant difference between real tool use ($M = 18.3$, $SD = 3.9$) and the Production scores achieved in Screen^{Stat} [$M = 15.9$, $SD = 5.8$, $t_{(20)} = 3.7$, $p = 0.001$], Screen^{Dyn} [$M = 16.3$, $SD = 6.0$, $t_{(20)} = 3.0$, $p = 0.007$], and HMD^{Stat} environments [$M = 16.5$, $SD = 6.6$, $t_{(20)} = 2.4$, $p = 0.027$]. In contrast, there was no difference between real tool use and the Production scores observed in the HMD^{Dyn} environment [$M = 17.9$, $SD = 5.6$, $t_{(20)} = 0.75$, $p = 0.461$), suggesting that the performance was best when either receiving dynamic holographic cues or when demonstrating real tool use (**Figure 4**).

Correlations Between Clinical Data and Pantomime Performance Effects

On the Production scale, a higher DYN-Effect was associated with a higher Circles score ($r_s = 0.524$, $p = 0.026$), a higher NHPT time ($r_s = -0.695$, $p < 0.001$), and a lower NTT Selection score ($r_s = -0.498$, $p = 0.021$). On the Interaction scale, a lower DYN-Effect goes along with a lower MMSE score ($r = 0.550$, $p = 0.027$), and with worse performances in object-interaction tasks (FTT Production $r_s = 0.510$, $p = 0.018$; NAT $r_s = 0.546$, $p = 0.013$).

TABLE 2 | Patient's characteristics.

ID	Sex	EDI	Age (y)	ICD-10	Etiology	Stage*	Neglect	Aphasia	MI	NHPT (t)	Stereovision	MMSE
P01	M	right	64	I61.2	ICB	sub-acute	no	Yes	76	42,44	intact	NA
P02	M	right	51	I61.0	ICB	sub-acute	yes	Yes	11	27,77	NA	19
P03	F	right	85	I63.4	Infarct	sub-acute	no	Yes	77	30,51	NA	25
P04	F	right	71	I63.5	Infarct	sub-acute	no	Yes	0	26,18	intact	21
P05	M	right	41	I63.3	Infarct	chronic	no	Yes	0	28,89	impaired	NA
P06	F	right	89	I63.4	Infarct	sub-acute	no	Yes	0	58,38	impaired	NA
P07	M	right	64	I63.4	Infarct	sub-acute	no	Yes	66	30,18	intact	23
P08	M	right	69	I63.2	Infarct	sub-acute	no	Yes	100	81,78	intact	24
P09	M	right	80	G82.29	Infarct	sub-acute	no	No	76	39,50	intact	24
P10	F	right	90	I63.4	Infarct	sub-acute	no	No	88	42,12	impaired	17
P11	M	both	74	I63.4	Infarct	sub-acute	no	Yes	77	39,04	intact	19
P13	F	right	61	I63.4	Infarct	chronic	yes	Yes	78	139,66	impaired	NA
P14	F	right	54	I63.0	Infarct	sub-acute	yes	No	39	59,01	impaired	26
P16	F	right	85	I.63.4	Infarct	chronic	no	Yes	0	61,05	intact	NA
P17	M	right	83	I.63.1	Infarct	sub-acute	no	Yes	100	42,78	intact	14
P18	F	right	72	I63.0	infarct	sub-acute	no	No	0	25,94	intact	19
P19	M	right	65	I63.4	Infarct	sub-acute	yes	Yes	100	68,68	impaired	16
P20	M	right	56	I61.1	ICB	sub-acute	no	Yes	83	28,79	intact	28
P21	F	right	91	I63.5	Infarct	chronic	no	No	100	37,87	intact	21
P22	F	right	79	I67.88	Infarct	sub-acute	yes	Yes	34	52,03	intact	25
P23	F	right	42	I63.5	Infarct	chronic	yes	No	0	26,62	intact	19

Due to communication problems, not all patients could be tested for stereovision and cognition, but comprehension was sufficient to follow task instructions and all patients were able to complete the AR-testing.

*EDI, Edinburgh Hand Inventory; F, Female; ICB, Intracranial bleeding; ICD-10, International Classification of Diseases-Tenth Revision; M, Male; MMSE, Mini Mental State Examination; MI, Motricity Index; NA, Not applicable; NHPT(t), Nine Hole Peg Test (time in seconds, with left hand). *Stage: Sub-acute= <6 months, chronic: >6 months.*

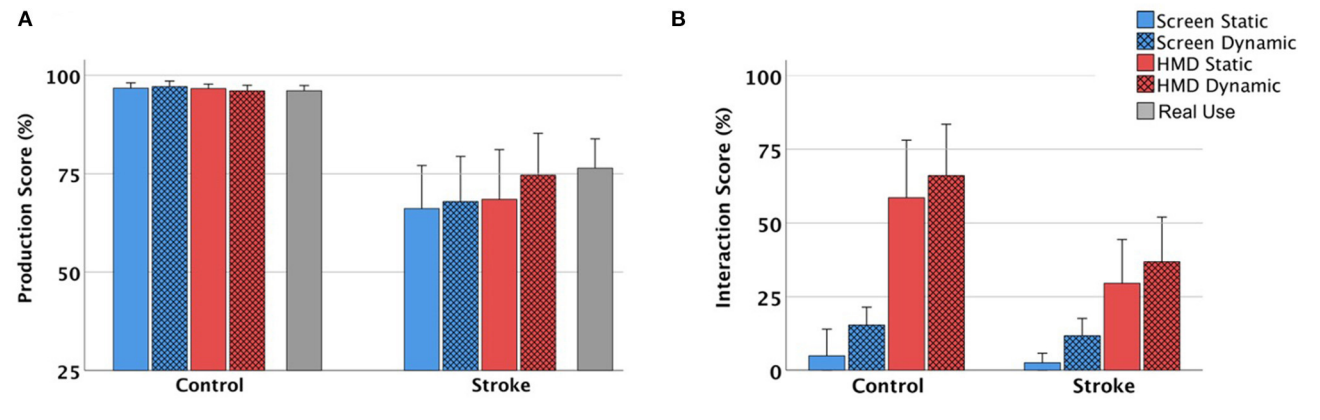

FIGURE 4 | (A,B) Results of the pantomime performance of the control group (left) and stroke group (right); Mean and 95% confidence interval values for the interactions of Environment (HMD/Screen) and Mode (static/dynamic) in **(A)** Production scale and **(B)** Interaction scale are reported.

Further, a non-significant trend between stereovision and the HOLO-Effect^{IS} points toward more frequent interactions with animated holographic items when a higher quality in stereovision is given ($r_s = 0.449$, $p = 0.061$). All other correlations between any of the calculated effects and the clinical tests failed to reveal statistical significance. See **Supplementary Tables 5**, **6** for correlations with clinical data and DILA-S results.

Kinematic Analysis

Kinematic analyses were run in order to visualize the qualitative findings. **Figure 3** exemplarily depicts the kinematic analysis for patient 13 who experienced the strongest "HOLO-Effect" based on the results of the performance scoring (**Figure 5**). The complete trajectory along the z-Axis in (mm) of the most successful version of each condition is always shown

TABLE 3 | ANOVA summary for production scale, interaction scale and sense of presence.

Production Scale	**Statistical parameters**		
	***F*(df)**	***p***	**Effect size η_p^2**
Group	$F_{(1,42)} = 28.6$	<0.001	0.405
Environment	$F_{(1,42)} = 4.9$	0.031	0.106
Mode	$F_{(1,42)} = 6.2$	0.017	0.129
Group × Environment	$F_{(1,42)} = 8.2$	0.007	0.163
Group × Mode	$F_{(1,42)} = 6.8$	0.012	0.140
Environment × Mode	$F_{(1,42)} = 1.7$	0.203	0.038
Group × Environment × Mode	$F_{(1,42)} = 4.5$	0.039	0.097

	Healthy subjects		**Patients**			
	***F*(df)**	***p***	**Effect size η_p^2**	***F*(df)**	***p***	**Effect size η_p^2**
Environment	$F_{(1,22)} = 1.9$	0.176	0.082	$F_{(1,20)} = 6.2$	0.021	0.238
Mode	$F_{(1,22)} = 0.05$	0.826	0.002	$F_{(1,20)} = 6.5$	0.019	0.244
Environment × Mode	$F_{(1,22)} = 2.3$	0.144	0.095	$F_{(1,20)} = 2.9$	0.103	0.127

Interaction Scale			
	***F*(df)**	***p***	**Effect size η_p^2**
Group	$F_{(1,42)} = 6.5$	0.014	0.135
Environment	$F_{(1,42)} = 55.8$	<0.001	0.570
Mode	$F_{(1,42)} = 11.3$	0.002	0.213
Group × Environment	$F_{(1,42)} = 6.1$	0.017	0.127
Group × Mode	$F_{(1,42)} = 0.03$	0.862	0.518
Environment × Mode	$F_{(1,42)} = 0.43$	0.518	0.010
Group × Environment × Mode	$F_{(1,42)} = 0.01$	0.932	0.000

	Healthy subjects		**Patients**			
	***F*(df)**	***p***	**Effect size η_p^2**	***F*(df)**	***p***	**Effect size η_p^2**
Environment	$F_{(1,22)} = 39.9$	<0.001	0.645	$F_{(1,20)} = 17.7$	<0.001	0.470
Mode	$F_{(1,22)} = 4.16$	0.052	0.159	$F_{(1,20)} = 13.5$	0.001	0.403
Environment × Mode	$F_{(1,22)} = 0.20$	0.657	0.009	$F_{(1,20)} = 0.277$	0.605	0.014

SENSE OF PRESENCE*			
	***F*(df)**	***p***	**Effect size η_p^2**
Group	$F_{(1,34)} = 0.120$	0.731	0.004
Environment	$F_{(1,34)} = 27.9$	<0.001	0.450
Mode	$F_{(1,34)} = 0.28$	0.601	0.008
Group × Environment	$F_{(1,34)} = 5.5$	0.025	0.139
Group × Mode	$F_{(1,34)} = 0.48$	0.494	0.014
Environment × Mode	$F_{(1,34)} = 0.02$	0.886	0.001
Group × Environment × Mode	$F_{(1,34)} = 0.27$	0.605	0.008

**A few participants did not answer Q3 (HMD^{Stat}: C8, C9, P20; HMD^{Dyn}: C9, P20), herein, we imputed the mean within each group. Eight patients did not or only partially fill in the presence questionnaire (P4, P6, P10, P12, P13, P14, P15, P16), thus, we included 36 data sets in the mrANOVA (Controls n = 23, Patients n = 13).*

(here, the third of the three trials, respectively). In real tool demonstration she failed during the first (Production: 0 points) and second attempt (Production: two points for grip formation when grasping the hammer), but she managed to perform a nice hammering movement (Production: seven points, −1 because of a distorted movement orientation) after some hesitation in her last trial ("conduite d'approche," after all it still took her 10 s to initiate the action). All her attempts to pantomime hammering

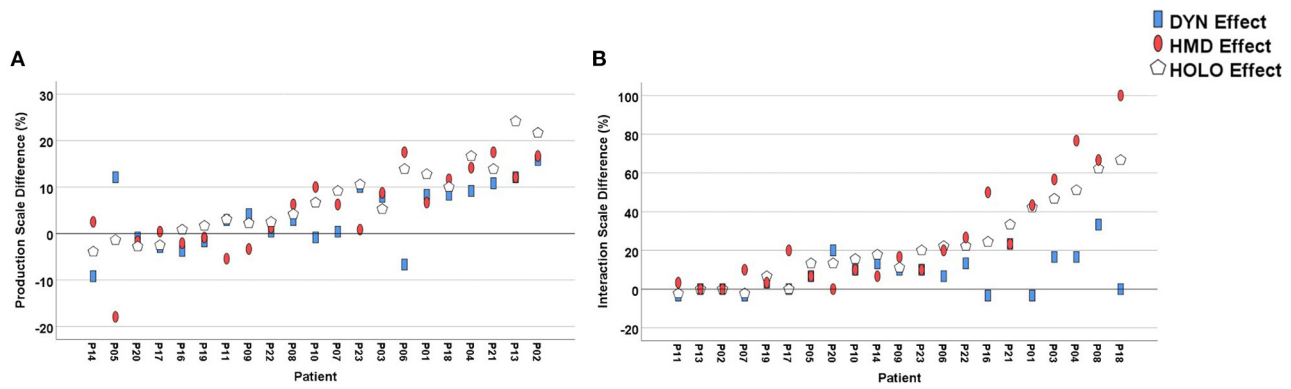

FIGURE 5 | Conditional (DYN), environmental (HMD) and combined (HOLO) effects of individual patients displayed in **(A)** Production Scale and **(B)** Interaction Scale.

in Screen^{Stat}, Screen^{Dyn}, and HMD^{Stat} were characterized by "toying" (Production: zero points in all conditions, respectively). In the HMD^{Dyn} condition by contrast, she presented clear up- and downwards hits with the support of the animated holographic hammer during her second and third attempts (Production: seven points in both attempts; −1 because of distorted grip formation). Note, P13 was randomized to receive HMD-based cues first, followed by screen-based cues on day 2. The corresponding video can be found in the supplements (**Supplementary Video 4**). The analyses demonstrated that the qualitative findings can be verified by kinematic trajectories showing a clear improvement with HMD^{Dyn} support (HOLO-Effect).

Sense of Presence

The statistics is shown in **Table 3**. The two groups did not differ significantly ($p = 0.731$). We found a significant main effect of *Environment* and a significant *Environment* × *Group* interaction, which was driven by a higher sense of presence in the HMD than in the screen environment (Controls^{Screen}: 2.9, 95%-CI [2.4,3.4], Controls^{HMD}: 4.7, 95%-CI [4.4,4.9], Patients^{Screen}: 3.3, 95%-CI [2.7,4.1], Patients^{HMD}: 4.1, 95%-CI [3.7,4.3]). Realness of the presented objects was rated as high in the screen environment ($M = 3.4$, $SD = 1.8$) and very high in the HMD environment ($M = 4.8$, $SD = 1$). While spatial presence was judged low in the screen environment ($M = 2.4$, $SD = 1.9$) it was rated as very high in the HMD environment ($M = 5.1$, $SD = 1$). Perceptual stress was perceived as moderate in both environments (Screen $M = 3.4$, $SD = 1.2$; HMD $M = 3.4$, $SD = 1.4$). All other effects and interactions were non-significant ($p > 0.494$).

Correlations Between Presence and Pantomiming

We found a significant correlation between presence and HMD^{Dyn} Production results ($r = 0.534$, $p = 0.049$), suggesting that as the sense of presence increases with animated holograms, so does the performance. All other correlations were non-significant (**Supplementary Table 7**).

DISCUSSION

In this study the effects of pantomiming with visual feedback provided in different environments (Screen vs. HMD) and different modes (static vs. dynamic) and the impact of presence in each condition were compared. Age-matched control participants performed as expected, close to ceiling in all conditions and significantly better than patients. In contrast, the patients' performances were dependent upon the type of visual feedback given. As hypothesized, patients achieved significantly higher scores when they received holographic (HMD-Effect) or dynamic cues (DYN-Effect). Despite not reaching the level of significance, best results were observed with dynamic holograms (HOLO-Effect, **Figure 5A**). Impressively, single patients improved their overall performance of up to 24% with this form of visual support. The kinematic analysis of one particularly impressive patient (P13), who failed in all conditions except when cued with animated holograms, is shown in **Figure 3** and **Supplementary Video 4**.

A key finding within this study is that pantomiming tended toward the real tool demonstration performance with the support of visual stimuli of increasing salience (**Figure 4A**). It has been hypothesized that different representations underline pantomimed actions and real tool use, with pantomimes serving communication (when trying to enable others to recognize the pretended actions) while real tool actions being instrumental (10, 17, 21, 48). One possible explanation for behavioral improvement when presented with salient stimuli is that the provided holographic cues facilitated compensatory action simulation processes by triggering activities in relevant cortical areas for pantomime of tool use (49). Lesion symptom mapping studies show that defective pantomime of tool use is associated with damage in left ventro-dorsal regions (14, 50, 51), with communicative aspects being related to rather anterior regions in the inferior frontal cortex, and aspects related to motor cognitive movement production being rather associated with posterior regions in the network (5). The latter lesion correlates in left parietal regions are in line with those reported to go along with deficient demonstration of tool use (52). Given the salient nature of holographic presentations of familiar objects

one may hypothesize that more specific neural responses in ventral visual streams have been elicited by object recognition processes. Present information about the object may help to specify potential actions by narrowing down action opportunities supported by rather posterior and dorsal regions. Perhaps these processes elicited by the salient cues may help channeling higher-order functions such as attention and reduce the load on action simulation processes in a left fronto-temporo-parietal network. In line with this idea, the visual streams in the ventral and dorsal cortex, that are responsible for perceiving and interacting with common objects in the three-dimensional space, have been shown to respond similarly in AR tasks as compared to real-world tasks (53). Thus, one reason for improved pantomiming might be that the increased saliency in visual input has shifted the pantomime actions from communicative gestures to rather instrumental actions.

Clearly, a strength of this study lies in the design of holograms by 3D-scanning the original tools and recording its real use. The induced sense of presence was significantly higher in HMD than in screen environments, and in the HMD^{Dyn} environment pantomiming improved significantly with higher presence ratings. The realness and high spatial presence evoked by our holograms may have made pantomiming less symbolic as it was rather influenced by the strong external cues. Further, it has been shown that apraxics have deficits in intrinsic coordinate control (11, 22). In such, participants might have extrinsically coordinated their movements in reference to the dynamic or holographic objects. The context factors in the HMD environment, e.g., the orientation in space (designed in a way to invite the participant to reach for it) and the real-sized holograms might have reduced the opportunities of grip formation and movement orientation, thereby limiting the degrees of freedom. Moreover, the structural and texture information, including light reflections, given in our holograms could have helped patients (37). These details became even more extensive in HMD^{Dyn} conditions, offering different perspectives, such as the view of the bottom of the watering can when it is moved. For instance, some patients showed clear difficulties in spatial orientation in screen conditions, but the holographic presentations helped them orientating in space correctly.

Lastly, the dynamic presentation in both environments might have attracted more attention and have had a more prompting character stimulating the correct movement content (20). In this regard, we observed individual patients trying to copy the shown movements, e.g., by following the rhythmic beat of hammering. In neuroimaging studies investigating healthy people, a larger response in the lateral temporal cortex relative to the ventral cortex has been shown when dynamic compared to static humans and tools are viewed, suggesting the lateral temporal cortex to be responsible for complex motion processing (54). Potentially, the moving cues enhanced the activity in the lateral temporal cortex which may have been integrated into the perception-action network processing pantomimes.

This can be partially supported by the Interaction scores, showing significant higher object interactions in HMD or DYN conditions. In patients, higher interactions during the $Screen^{Dyn}$ condition even significantly correlated with increased Production scores, which indicates an added value of dynamic cues in screen-based systems. In addition, patients with a higher quality in stereovision, a better manual dexterity and worse mechanical problem solving benefit more from dynamic cues. One possible explanation is that patients with mechanical problem solving deficits may profit from the increasing visual and semantic information consistent with the task provided by the three-dimensional cues from the HoloLens (e.g., when focusing perception on the best suited affordances to solve the task, here the correct representation of the moving tool). Indirectly, this could be taken as an indicator of an important role of mechanical problem solving in tool use behavior and would therefore be in line with the reasoning-based approach to human tool use (23, 55, 56).

Nevertheless, correlations between Interaction and Production scores during HMD conditions did not become significant ($p > 0.22$). In contrast, and probably even more striking, the patients who experienced the strongest HOLO-Effects on the Production scores (P13, P02) did not interact with the given cues at all (**Figure 5**). Moreover, in healthy subjects the interactions with static holograms even negatively influenced performance, in a way that they changed their motor behavior resulting in unnatural, error-loaded movements when trying to reach for holograms. Potentially, these participants got distracted from the actual task by volitionally directing their attentional focus on the salient cues (36), resulting in more errors. That is, consistent with the results of a feasibility study on AR-based ADL support, the unnatural interaction with holographic animations that impaired the performance by requesting its own resources (57). We would have expected higher presence to result in more interactions with the virtual objects. However, we did not find a significant correlation which can be explained by the experimental task design not *requiring* any real interaction. Still, at this point it remains unclear why some participants were very responsive to the stimuli (such as P18, who interacted with holograms in 100% of the HMD conditions), while others seemed not to respond at all (**Figure 5**). The interaction with dynamic objects was higher in controls as well as in patients with a higher mental state, a better FTT Selection and NAT score. Possibly, unimpaired people are more prone to interacting with holograms because they have more cognitive resources to focus on the augmented information, but this hypothesis has to be further investigated.

Another likely explanation for the improvements is that both the dynamic and holographic information provided error signals for the perceptual-motor system as suggested by Jax et al. (11). While patients with apraxia often struggle in movement preparation (i.e., planning) the adjustment of the movement plan (i.e., online correction) is often intact (22). Similar to reports of Jax and colleagues (11) about the observed "conduit d'approche" in some patients, we also noted an increase in accuracy after multiple repetitions. Patients might have visually recognized their incorrect movements and tried to more closely approximate the correct action represented by the animated holograms.

Limitations

The psychometric properties of the applied Presence questionnaire (43) have not yet been validated in the stroke population or in patients with cognitive limitations. Unfortunately, eight patients failed to fill in the questionnaire, which indicates that it may not be the best measure to assess presence in this population. Besides a need of alternative questionnaires, the integration of objective measures (e.g., eye movements) is worth further investigation. In HoloLens 2nd generation, the feature of eye-tracking is incorporated offering an easy way to analyse visual attention based on eye movements, to assess salience and to identify the user's intention (35) and areas of interests (23). Indeed, while spatial attention is a major mechanism for saliency detection, patients with visuo-spatial or attentional deficits might not be able to focus their limited perceptual resources on the holograms. In this study, patients with a higher quality in stereovision had a higher DYN-Effect on the Production scale and a trend points toward an association of higher stereovision and interactions with animated holograms. We cannot rule out that some patients have been unable to see the holograms as intended and thus, have not benefited from its salient contextual information.

The technical presentation of realistic holograms also had its short-comings. In particular, some patients were unable to detect the key, possibly because it was displayed too close to the user and might have been overlooked because of not being visually distinct enough from its surrounding. On the other hand, participants criticized the holographic watering can appearing too far away in order to grasp for it, which was necessary to enable real-size presentations in the HoloLens. This illustrates the difficulty in finding the optimal zone for hologram positioning in experimental research, especially with the current technological limitations (e.g., limited field of view). The fact that the dynamic features had no significant impact on presence ratings may be due to these technological constraints (28).

The predefined eligibility criteria within the present study were quite broad. Consequently, we included patients in the subacute as well as in the chronic stage, patients with and without a diagnose of neglect, aphasia or cognitive decline, but did not adjust for these possible confounding factors. At the moment we are therefore not able to give differential recommendations to patients early and late after stroke. In addition, the effect of cues may have been underestimated in some patients if aphasia, neglect or attention deficits had deteriorated task understanding or stimulus perception. Further and in line with recent recommendations on post-stroke rehabilitation trials (58), we ensured an aphasia and neglect friendly testing (by following the DILA-S recommendations), which improved our recruitment rate and increases the generalizability of our results.

Outlook

Apraxia is a major predictor of poor functional performance in ADL and of increased dependence on caregivers. To date, effective rehabilitation strategies are still limited (9, 59) and mainly include compensatory approaches, such as strategy training (8, 60), errorless learning (61), behavioral training (62) or task-specific and meaningful training (63). In recent years, technology-based approaches facilitating single-tool use and multistep actions have been proposed as promising strategies (9, 64). AR technology has already found its way into a large field of applications, where holographic elements enrich the perception of the real environment, e.g., by providing cognitive support during different tasks (65). In the wide field of rehabilitation, AR will introduce new pathways for therapeutic or assistive approaches with the potential of providing an engaging and motivating training environment (31), improving physical outcomes when applied as an adjunct therapy (29), supporting mental rehabilitation (44) or cognitive rehabilitation (57, 66). Based on our findings, we envision HMD-based AR systems to assist patients in their ADLs in the future, thus maintaining autonomy. The advantages of wearable cognitive support systems over existing screen-based approaches (66, 67) are having both hands available for interactions with the physical environment while still being able to move flexibly from one place to another. In this regard, we see two main application areas where AR can be used: (1) as a supportive training tool to facilitate performance improvement and (2) as a (well-controllable) diagnostic research tool to further examine the role and importance of different modes and types of visual cues and to identify predicting variables.

While we showed that holograms can attract attention (e.g., by being visually salient) and improve performance, they can potentially also distract from the real activity and may require voluntary effort to redirect the attention to the physical objects (36). The objects within this study were displayed in a left handed setting (**Figure 2D**) and the holographic cues were aligned in space to invite the participant to reach for it as it was shown that the perception of affordances (here the orientation of the tools in space) influences the motor response that is best suited for interacting with the target object (23, 56, 68). In future trials on real tool support however, we recommend to place cues in a non-reachable zone because no interaction with holographic but rather real objects is desired. Besides, AR supported manual task guidance inside the peripersonal space is associated with vergence-accomodation-conflict (e.g., when the virtual content is inconsistent with the real world) and focus-rivalry (e.g., when simultaneously focusing on real and virtual content). These common perceptual conflicts experienced in artificial environments may impair the performance due to visual fatigue and mental workload, especially with increased task difficulty as recently suggested by preliminary data on EEG recordings during AR use (69).

Future experiments should investigate whether a further increase in visual fidelity and contextual information will lead to even better results (e.g., by adding the target item or illustrating a holographic hand correctly performing the action). Indeed, findings from a recent eye-tracking study analyzing the visuo-perceptual context within a virtual scene show that thematically consistent object-tool pairs (e.g., hammer and nail) can have a facilitating influence on visual attention (23). In addition, audio-visual complexity does provide opportunities to enhance individual meaning, salience and authenticity (70–72).

CONCLUSION

This study was the first to explore the effect of dynamic holographic cues on pantomiming in LBD patients. We provide first knowledge about which type of AR cue might be most beneficial in supporting patients with apraxia, present current limitations and give suggestions for further research. Specifically, studies are necessary to characterize the conditions that lead to optimal motor behavior in augmented environments, and to identify responders and factors that increase the potential effects of this new form of support. With further technological achievements (65) we believe this new approach to positively impact the rehabilitation process of patients with apraxia.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Center for Open Science (COS) Open Science Framework (OSF), https://osf.io/uakw2/?view_only=a55698fafb6541f7878284bab64e940c.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich (reference number 175/17S). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NR and JH: conceptualization, methodology, and formal analysis. NR and AT: software and visualization. NR and LL: validation. NR, LL, and KJ: investigation. NR: data curation and writing – original draft preparation. CK, JR, KJ, and JH: writing – review & editing. CK: project administration. CK and JH: supervision. JR, KJ, and JH: resources. NR, CK, and JH: funding acquisition. All authors contributed to the final draft of the manuscript, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.711900/full#supplementary-material

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Autonomic Modulation in Duchenne Muscular Dystrophy During a Computer Task: A Prospective Transversal Controlled Trial Assessment by Non-linear Techniques

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Introduction: Due to functional and autonomic difficulties faced by individuals with Duchenne Muscular Dystrophy (DMD), the use of assistive technology is critical to provide or facilitate functional abilities. The key objective was to investigate acute cardiac autonomic responses, by application of Heart Rate Variability (HRV), during computer tasks in subjects with DMD via techniques based on non-linear dynamics.

Method: HRV was attained via a Polar RS800CX. Then, was evaluated by Chaotic Global Techniques (CGT). Forty-five male subjects were included in the DMD group and age-matched with 45 in the healthy Typical Development (TD) control group. They were assessed for 20 min at rest sitting, and then 5 min whilst performing the maze task on a computer.

Results: Both TD and DMD subjects exhibited a significantly reduced HRV measured by chaotic global combinations when undertaking the computer maze paradigm tests. DMD subjects presented decreased HRV during rest and computer task than TD subjects.

Conclusion: While there is an impaired HRV in subjects with DMD, there remains an adaptation of the ANS during the computer tasks. The identification of autonomic impairment is critical, considering that the computer tasks in the DMD community may elevate their level of social inclusion, participation and independence.

Keywords: heart rate variability, Duchenne Muscular Dystrophy, autonomic nervous system, Chaotic Global Techniques, health care technology

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INTRODUCTION

Duchenne Muscular Dystrophy (DMD), is the most prevalent form of muscular dystrophy (1). It is a terminal illness characterized by progressive muscular weakness with proximal onset in the lower limbs spreading later to the rest of the body, which leads the individual to become confined to a wheelchair (2). In addition, cardiorespiratory (3), and autonomic (4) changes are observed and death in early adulthood, at around 20 years old (2).

In consideration of the progressive functional difficulties presented by people with DMD, the use of assistive technology by rehabilitation programs is important as it promotes greater functional independence and improves the social performance of these disabled persons (5). With computational advances in assistive technology, rehabilitation programs via computing situations during treatment allow the persons with DMD to practice tasks in a different environment using an informal interface and rapid responses. It is similarly capable of providing a dynamic interaction and vivacity with elements and goals, by means of logical reasoning and reaction times associated with the movement, permitting the repetition of muscle contractions and improved performance (6). In this manner, studying the acute and chronic responses of altered physiological systems in DMD individuals despite this technology is fundamental and could support a better understanding of these changes induced by DMD and, an improved guide as to it becoming a therapeutic procedure.

As described previously, an important physiological system modified by DMD is the autonomic nervous system (ANS) (7). Studies including the acute cardiac autonomic responses during computer tasks in DMD are rare. Yet, by implying the linear methods for analysis of heart rate variability (HRV) to evaluate cardiac autonomic responses in DMD subjects during computer tasks, Alvarez et al. (8) detected that DMD subjects responded with a reduced HRV. But then, those during computer tasks exhibited greater intensity of cardiac autonomic responses when compared to the Typical Developed (TD) subjects which were the control group.

Nevertheless, Sassi et al. (9) stated that non-linear techniques of HRV may provide new evidence for the understanding of cardiac control, as it provides information on the complexity of the underlying physiological mechanisms. An innovative group of procedures sensitive non-linearly for the detection of HRV fluctuations that allows us to understand the irregularity, unpredictability, extent of fractal self-similarity, and complexity of the signals are the Chaotic Global Techniques (CGT) (10). These metrics have been effectively applied to assess cardiac autonomic modulation in physiological and pathological conditions (11–15), once non-linear methods describe complex rhythm fluctuations more appropriately than linear methods (16), as "chaos theory" exhibits characteristics that are consistent with those found physiologically in the human organism.

The human organism exhibits chaotic properties, specifically, it is composed of several systems, which are dynamic, deterministic, and sensitive to initial circumstances. All these factors are capable of producing non-linear, non-proportional, or direct responses to stimuli in these systems, hence, trivial dysfunctions in one organ can engender different levels of dysfunction in the others (17, 18). Thus, the human body is better understood as a complex and non-linear system, hence assessments of HRV via non-linear techniques have gained recognition (19).

Accordingly, we proposed to study acute cardiac autonomic responses during computer tasks in individuals with DMD vs. TD people using CGT. The CGT may complement important information in the research literature on the complexity of the cardiac autonomic response during the execution of computer games. We hypothesized that during computer tasks the HRV responses *via* CGT demonstrated a lesser response to complexity. Subsequently, it should have a greater response in the DMD subjects.

MATERIALS AND METHODS

This trial was completed using the data analyzed and published by Alvarez et al. (8), yet, for this study the data were evaluated through CGT. The present study was performed in accordance to the Declaration of Helsinki.

This study conforms to the Consolidated Standards of Reporting Trials (CONSORT) statement (20).

Ethical Approval and Informed Consent

The study protocol was approved by the research ethics committee of the University of São Paulo, reference number 236/13 was attached. Written consent terms were obtained from participants (or guardians) over 18 years old. Acceptance terms were obtained from participants younger than 17 and also written consent terms from the legally authorized representative/parents of those participants under 17 years old.

Participants

Forty-five individuals with DMD and 45 age-matched healthy TD individuals participated in the trial. DMD diagnoses was based on molecular methods and/or muscular protein expression. Exclusion criteria comprised subjects with severely dilated myocardium, other associated diseases and individuals with inability to understand task instructions. DMD severity was classified according to the Vignos scale (21). See **Table 1**.

Data Collection

The protocol was identical to that used in Alvarez et al. (8) where HR was recorded beat-to-beat (RR intervals) using the portable Polar RS800CX eletrocardiographic monitor (Polar Electro, Finland). HR was recorded prior to the onset and at the end of the 5 min of the computer maze paradigm task.

The subjects were seated in a standard chair (walkers, TD group, and DMD) or in their own wheelchair (non-walkers, DMD group), the Polar watch was situated on their wrist. The analysis of HRV was possible via the recording of RR interval in two periods: the period of 20 min at rest seated, and then during the computer task for 5 min, as demonstrated in **Figure 1**.

TABLE 1 | Disease status according to Vignos scale.

Vignos scale	Description of DMD patients mobility at the specified Vignos scale level. The Vignos scales from zero to ten (0–10)	No of patients
1	Walks and climbs stairs without assistance	4
2	Walks and climbs stairs with aid of railing	4
3	Walks and climbs stairs slowly with aid of railing (more than 25 s for eight standard steps)	1
4	Walks unassisted and rises from chair; cannot climb stairs	1
5	Walks unassisted; cannot rise from chair; cannot climb stairs	0
6	Walks only with assistance or walks independently with leg braces	0
7	Walks in leg braces but requires assistance for balance	19
8	Maintains standing with leg braces but is unable to walk even with assistance	14
9	In wheelchair	2
10	Confined to bed	0

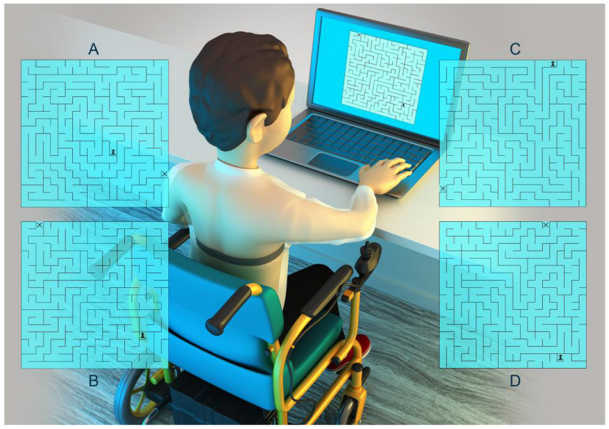

FIGURE 1 | Visualization of experimental set up. Mazes **(A–D)** represent the four mazes used in this study. The range was of one to four mazes performed for the participants during 5 minutes.

The computer task used a maze paradigm with one correct pathway that could be negotiated and ultimately solved; the paradigm was adapted by Souza et al. (22). All participants were positioned comfortably with an evaluator responsible for instruction and data annotation.

Each individual was instructed to walk the correct path with the digital character pawn (pointed on the screen by the evaluator) to the exit of the maze identified by an "x" (pointed on the screen by the evaluator). It was provided for the subjects, who used the arrow buttons on the keyboard, identified by up, down, right and left, using the dominant hand, with the arrows moving through a 20 cm × 20 cm maze. Participants were told to complete the maze as quickly as possible.

HRV Analysis

HRV analysis followed the guidelines published by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (23). The RR intervals were recorded, and then were downloaded to the Polar Precision Performance program (v.3.0). This software enabled the visualization of HR and the extraction of a cardiac period (RR intervals series; the variation of beat-to-beat interval in milliseconds) file in ".txt" format. For analysis of HRV data at rest, we evaluated 1,000 consecutive RR intervals, and for HRV analysis for the computational task, the number of consecutive RR intervals obtained was exactly 256 RR intervals. Digital filtering complemented by manual filtering was performed to eliminate artifacts and only series with >95% of sinus beats were included in the study (19). HRV analysis was undertaken through CGT.

CGT Analysis

As stated in 2016 by Wajnsztejn et al. (12) and, later by Alves et al. (24), these techniques encompass of a variety of mathematical and signal processing events. In this study, we enforced the Multi-Taper Method (MTM) power spectral technique (12, 24) to generate *high spectral* Entropy (*hs*Entropy) (24), *high spectral* Detrended Fluctuation Analysis (*hs*DFA) (25), and the Spectral Multi-Taper Method (sMTM) (10). From these three chaotic global values we computed seven non-trivial combinations which we termed the Chaotic Forward Parameters (CFP1 to CFP7) (26–29). For further information regarding the MTM techniques it is suggested to refer to Percival and Walden (30) or Thomson (31).

Normality and Levene's Test

The dependent variables (CFP1 to CFP7), and the independent variables "group" (DMD and TD) and "task," at (rest or computer task through maze paradigm). Parametric statistics assume the datasets are normally distributed, so the use of the mean as a measure of central tendancy. Consequently, the first assumption for the two-way analysis of variance test is normality. We applied the Anderson-Darling (26) and the Lilliefors (27) tests. The Anderson-Darling test for normality applies an empirical cumulative distribution function. The Lilliefors test is useful in studies with small sample sizes ($n < 20$). The results of the tests for normality were borderline. Nonetheless, as there is no non-parametric alternative to the two-way analysis of variance test we proceed aware that the accuracy could be flawed. For this reason we raise the level of significances to $p < 0.01$ (or <1%), rather than the usual $p < 0.05$ (or <5%). The second assumption was that of the equality of variances by Levene's test (32, 33). Hence, the dependent variables were submitted to a 2 (group: DMD, TD) by 2 (Task: Rest, Computer) Multiple Analysis of Variance (MANOVA) with Repeated Measures (RM) on the last factor for each CFP index. *Post-hoc* comparisons were undertaken by Tukey-LSD (Least Significant Difference) test. Partial eta-squared (η_p^2) was reported to measure the effect sizes and were interpreted as small (effect size >0.01), medium (effect size >0.06), or large (effect size >0.14) (34, 35); additionally we reported the observed power (OP). The software package operated was SPSS, version 26.0 (Chicago, Illinois, USA).

TABLE 2 | Values (mean ± standard deviation) of age, height, mass, and body mass index (BMI) for both TD and DMD groups.

Variable	TD-group	DMD-group	*p*-value
Age (years)	15.4 ± 2.8	15.4 ± 2.9	0.455
Height (m)	1.68 ± 0.12	1.56 ± 0.17	<0.001
Mass (kg)	63.2 ± 15.5	55.84 ± 17.9	0.013
BMI (kg/m^2)	20.04 ± 3.72	22.42 ± 4.71	0.331

TD, Typical Development; DMD, Duchenne Muscular Dystrophy; BMI, body mass index; m, meters; kg, kilograms; kg/m^2, kilograms per square meter.

TABLE 3 | The cardiac medications for DMD-group.

Medication on DMD-group	Number of patients (%)
Beta-blockers	13 (28.89)
ACE-inhibitor	5 (11.11)
Beta-blockers + ACE-inhibitors	20 (44.44)
Corticosteroids	44 (97.77)
No medication	7 (15.56)

ACE-inhibitors, angiotensin-converting enzyme inhibitors.

TABLE 4 | Levene's test of equality of error variances: *F*-value and significances of the seven permutations of chaotic global parameters (CFP1 to CFP7).

CFPx	*F*	Sig.
CFP1	1.221	0.304
CFP2	0.806	0.492
CFP3	0.410	0.746
CFP4	0.606	0.612
CFP5	1.572	0.198
CFP6	0.707	0.549
CFP7	4.159	0.007

This tests the null hypothesis that the error variances of the dependant variable is equal across groups.

RESULTS

Anthropometric Data and Medications

Table 2 presents the anthropometric data and **Table 3** lists the medications taken by the DMD group. The TD group did not take any medications.

Normality and Levene's Test

The results of the Levene's test of equality, are illustrated in **Table 4**. A significant *p*-value is set at >0.05 ($p > 0.05$, >5%). This ensures that similar variances can be assumed or else the ANOVA test is invalid. This was achieved by the all of the chaotic global combinations applied with the exception of CFP7.

Repeated Measures-Multiple Analysis of Variance

Significant effects for Group [Wilks Lambda = 0.006; $F_{(7, 82)} = 1897.1$; $p < 0.001$; $\eta_p^2 = 0.99$: OP: 1.00], Task [Wilks Lambda = 0.004; $F_{(7, 82)} = 2739.2$; $p < 0.001$; $\eta_p^2 = 0.99$: OP: 1.00] and significant interaction between Group and Task [Wilks Lambda = 0.032; $F_{(7, 82)} = 352.1$; $p < 0.001$; $\eta_p^2 = 0.97$: OP: 1.00]. The separate ANOVAs that established differences between Groups and Tasks in each CFP, besides their Mean, Standard Deviation, Confidence Interval, and *post-hoc* values are described in **Table 5**.

Mean and Standard Deviation

Regarding **Figure 2**, the boxplot (left) for CFP1 to CFP7 of TD subjects RR intervals' in TD control subjects "at rest" (CCFPx: RR intervals of length 1,000) and TD control computer task subjects (TCFPx: RR intervals of length 256). Next, the boxplot (right) for CFP1 to CFP7 of DMD subjects' RR intervals in DMD control subjects "at rest" (CCFPx: RR intervals of length 1,000) and computer task subjects with DMD (TCFPx: RR intervals of length 256).

The output of the RM-MANOVA can be defined as follows. Initially, deviations in the chaotic global responses in the computer task mode (**Table 5**). There are significant reductions from rest to computer task CFP1, CFP3, CFP4, CFP6, and CFP7, and an increase for CFP5. Next, we revealed that there are significantly lower responses in DMD group (in both rest and computer task) compared to TD group for CFP3, CFP4, CFP5, and CFP7. Finally, while the interaction term for the computer task and DMD is statistically significant for CFP2, CFP3, and CFP6, the *post-hoc* results are non-significant at a level of significance of $p < 0.01$ (or <1%).

Regression Analysis

To understand which factors may influence the HRV response in DMD subjects, three regression analysis were completed between the dependent variables [(1) use of beta-blockers (yes/no), (2) use of ACE inhibitors (yes/no), and (3) use of corticoids (yes/no)] and independent variables [the differences between values of CFP1 to CFP7 on computer task and at rest, namely Δ of computer task and rest]. The analysis revealed no significant regression models for any of the three dependent variables (see **Table 6**).

DISCUSSION

We evaluated HRV responses induced by a computer task in people with DMD and TD. As an important outcome, we established that, while the DMD group offered significantly lower autonomic responses when compared to the TD group in both rest and computer task, DMD and TD groups presented similar patterns of response from rest to computer task; explicitly, intense autonomic responses induced by the task, as established in **Table 5**. We can postulate that this similar pattern of responses could be due to the condition that it was a task that required more distal muscular effort, with only the need of finger movement (which is mostly maintained in adolescents with DMD), and became more of a cognitive task.

This response of both DMD and TD groups has been previously revealed in the study of Luque-Casado et al. (36), which concluded that cardiac autonomic modulation is highly sensitive to overall demands of sustained attention under the influence of cognitive processes, leading to a decrease of heart rate variability (HRV); then this is the case of the task used

TABLE 5 | The table below demonstrates the results of a Repeated Measures-Multiple Analysis of Variance (RM-MANOVA), between Groups, within Tasks and its interactions, in addition to mean, stardard deviation, and confidence intervals for each CFP.

		Rest	Computer task		Main effect task (*df*: 1, 88)	Main effect group (*df*: 1, 88)	Interaction taks × group (*df*: 1, 88)
	Groups	**Mean ± SD [95% CI]**	**Mean ± SD [95% CI]**	***p*-value[§] (Rest × Computer)**	***F*; *p*-value; η_p^2; O.P.**	***F*; *p*-value; η_p^2; O.P.**	***F*; *p*-value; η_p^2; O.P.**
CFP1	DMD	0.8371 ± 0.1270 [0.798; 0.877]	0.7817 ± 0.1189 [0.745; 0.819]	**<0.001**↓	57.1; ***<0.001;*** 0.39; 1.00	1.13; 0.289; 0.01; 0.18	1.14; 0.288; 0.01; 0.19
	TD	0.8739 ± 0.1399 [0.834; 0.914]	0.8003 ± 0.1318 [0.763; 0.837]	**<0.001**↓			
	p-value[§] (DMD × TD)	0.194	0.484				
CFP2	DMD	0.6116 ± 0.1106 [0.583; 0.640]	0.5942 ± 0.0988 [0.567; 0.621]	**<0.001**↓	1.70; *0.196;* 0.02; 0.25	0.62; 0.434; 0.01; 0.12	15.4; ***<0.001;*** 0.16; 0.97
	TD	0.6003 ± 0.0811 [0.572; 0.629]	0.6349 ± 0.0829 [0.608; 0.662]	0.067			
	p-value[§] (DMD × TD)	0.580	0.037*				
CFP3	DMD	0.7463 ± 0.1128 [0.712; 0.781]	0.6655 ± 0.1131 [0.630; 0.701]	**<0.001**↓	185.8; ***<0.001;*** 0.68; 1.00	15.6; ***<0.001;*** 0.15; 0.97	16.9; ***<0.001;*** 0.16; 0.98
	TD	0.6889 ± 0.1201 [0.654; 0.723]	0.5383 ± 0.1252 [0.503; 0.574]	**<0.001**↓			
	p-value[§] (DMD × TD)	0.022*	**<0.001**				
CFP4	DMD	0.6586 ± 0.2118 [0.600; 0.717]	0.6279 ± 0.1960 [0.572; 0.683]	**<0.001**↓	18.1; ***<0.001;*** 0.17; 0.99	13.9; ***<0.001;*** 0.14; 0.96	2.65; 0.107; 0.03; 0.36
	TD	0.8231 ± 0.1831 [0.764; 0.882]	0.7541 ± 0.1789 [0.669; 0.810]	0.067			
	p-value[§] (DMD × TD)	**<0.001**	**0.002**				
CFP5	DMD	0.3500 ± 0.1589 [0.308; 0.392]	0.3832 ± 0.1524 [0.341; 0.426]	**<0.001**↑	22.3; ***<0.001;*** 0.20; 1.00	42.6; ***<0.001;*** 0.33; 1.00	0.90; 0.345; 0.01; 0.16
	TD	0.5289 ± 0.1216 [0.487; 0.571]	0.5789 ± 0.1331 [0.536; 0.621]	**0.009**↑			
	p-value[§] (DMD × TD)	**<0.001**	**<0.001**				
CFP6	DMD	0.5530 ± 0.1591 [0.508; 0.598]	0.4929 ± 0.1407 [0.452; 0.534]	**<0.001**↓	135.8; ***<0.001;*** 0.61; 1.00	1.10; 0.296; 0.01; 0.18	24.6; ***<0.001;*** 0.22; 1.00
	TD	0.6284 ± 0.1475 [0.583; 0.674]	0.4793 ± 0.1353 [0.438; 520]	**<0.001**↓			
	p-value[§] (DMD × TD)	0.022*	0.641				
CFP7	DMD	0.4413 ± 0.2124 [0.388; 0.495]	0.3932 ± 0.1984 [0.341; 0.446]	**0.009**↓	16.1; ***<0.001;*** 0.15; 0.98	33.9; ***<0.001;*** 0.28; 1.00	0.06; 0.814; 0.00; 0.06
	TD	0.2287 ± 0.1439 [0.175; 0.282]	0.1860 ± 0.1530 [0.134; 0.238]	**0.004**↓			
	p-value[§] (DMD × TD)	**<0.001**	**<0.001**				

*The significant p-values (<0.01) are exemplified in bold, and the marginally significant results are followed by an *. DMD, Duchenne Muscular Dystrophy group; TD, Typically Developed group; CFP, Chaotic Forward Parameters; SD, standard deviation; CI, confidence interval; df, degrees of freedom; O.P., observed power. [§]p-value from post-hoc (Tukey-LSD) comparisons; arrows indicate whether the values represent significant decrease (↓) or increase (↑) of the indices from rest to computer task.*

in our study that requires sustained attention and cognitive effort (besides the distal muscular effort) to attain the target. This process appears to be the role of the prefrontal cortex in the modulation of subcortical cardio-acceleratory circuits via an inhibitory pathway that is associated with vagal function and that can be indexed by HRV (*via* the baroreceptor system, namely, the negative feedback loop adjusting heart activity to the blood pressure fluctuations) (37, 38).

Considering the general lower autonomic response from DMD here, in this study; in a previous study, Silva et al. (4) through a systematic review about the HRV of subjects with DMD, confirmed that these subjects presented an impaired autonomic modulation with a decreased parasympathetic modulation and, occasionally, increased sympathetic control. Vanderlei et al. (39) revealed in obese young individuals an increase in the chaotic global response, but this is unusual since

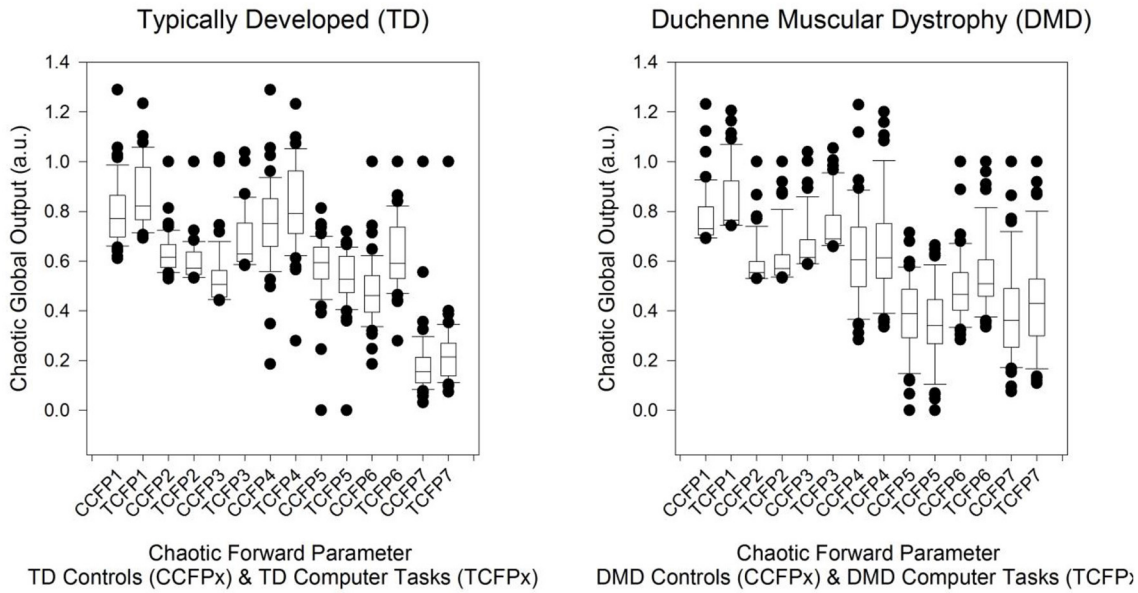

FIGURE 2 | Boxplot (left) for CFP1 to CFP7 of TD subjects RR intervals in TD control subjects' "at rest" and TD control computer task subjects. Boxplot (right) for CFP1 to CFP7 of DMD subjects' RR intervals in DMD control subjects "at rest" and computer task subjects with DMD. The point nearest to the zero is the minimum and the point furthermost away is the maximum. The point next nearest to the zero is the 5th percentile and next furthest away is the 95th percentile. The edge of the box nearest to zero specifies the 25th percentile, and the edge of the box furthest from zero specifies the 75th percentile. The line within the box is the median. Error bars are the 10th and 90th percentiles.

TABLE 6 | The table illustrates the regression models and three dependent variables.

Dependent variables:	**Beta-blockers**		**ACEi**		**Corticosteroids**	
Model summary and ANOVA:	$F_{(7, 37)} = 1.96$; $p = 0.088$; $r^2 = 0.27$		$F_{(7, 37)} = 0.33$; $p = 0.935$; $r^2 = 0.06$		$F_{(7, 37)} = 0.81$; $p = 0.582$; $r^2 = 0.13$	
Coefficients:	***ß***	***p*-value**	***ß***	***p*-value**	***ß***	***p*-value**
CFP1	1.44	0.768	−1.789	0.748	−6.644	0.218
CFP2	−4.48	0.127	0.121	0.971	3.539	0.266
CFP3	1.03	0.880	1.959	0.800	8.933	0.234
CFP4	1.26	0.842	−0.152	0.983	6.786	0.331
CFP5	13.48	0.167	5.811	0.596	−6.131	0.560
CFP6	−4.21	0.544	−1.266	0.872	−7.540	0.322
CFP7	13.70	0.104	3.618	0.701	−13.557	0.139

CFP, Chaotic Forward Parameters; ACEi, angiotensin converting enzyme inhibitors.

typically the pathological or disease state reduces HRV through a decreased chaotic global response.

Regarding autonomic responses during the computer task in subjects with DMD, Alvarez et al. (8) suggested the computational tasks can support the functional capacities through training and competence of the ANS, and that cardiac autonomic modulation data is useful for clinical practice. Thus, computer tasks must be performed under supervision and care taken to avoid psychological overload and exacerbation to the ANS, as previous studies have achieved reduced HRV from an early stage of disease in DMD (4, 32, 33), conceivably leading to cardiac (40, 41), or respiratory (42) failure.

Even so, Alvarez et al. (8) evaluated only linear approaches and previous studies have demonstrated that non-linear methods are clinically important for the interpretation of pathological mechanisms related to HRV, providing extra information to using linear methods alone (43). de Godoy (43) concluded, via a review study on patients with cardiovascular disease, that the non-linear analysis of HRV is valuable to characterize autonomic balance, which is a reliable marker of complications and subsequent mortality.

The HRV analysis techniques with linear methods, in the time and frequency domains are not sufficient to characterize a cardiac dynamical balance. Instead, the mechanisms involved in cardiovascular regulation interact with each other in complex and chaotic ways (43). Therefore, HRV analysis using CGT should be able to characterize the HRV in a more reliable manner and, afterwards, autonomic cardiac modulation.

In this study, we have revealed that the computer task reduces the HRV as measured by CGT in the CFP1, CFP3, CFP4, CFP5, CFP6, and CFP7 combinations. This is the case for TD and the DMD groups. It was expected that CFP1 and CFP3 would be two of the most significant parameters. CFP1 applies all three chaotic global parameters. There is evidence to enforce CFP1 as the most robust function as with the optimization study by Garner and Ling (10). Intrinsically, it is generally the most robust combination overall. Moreover, it is the most robust in the forward problems in youth and childhood obesity (44), type I diabetes mellitus (13), and COPD (11). CFP3 is frequently the most statistically significant combination, based on statistical significance alone.

This has been demonstrated for both forward (11, 13, 39) and inverse (10) problems. The critical factor regarding the significance of the results is data length. We would advise a data length of at least 900 RR intervals. This is pertinent here as in some datasets the number of RR intervals was exactly 256 hence about 5 min of time-series when undergoing the task. Despite a potential sparse data hazard the correct levels of significance were achieved ($p < 0.01$; <1%). There is a difference between number of RR intervals in both groups for rest and task. Task time was reduced compared to rest time owing to muscle fatigue that could be caused in the DMD group, as this is a characteristic of the disease.

Future algorithmic manipulations could involve varying the DPSS (45) settings or adjusting Thomson's non-linear combination methods (31) to maximize discrimination. Lastly, weightings of these CGT could be modified as here they are set at unity. This is particularly appropriate for the CFP1 and CFP3 combinations.

Given that DMD subjects benefit from assistive technology; social inclusion, participation, and development—the necessary physiological responses from the technology must be assessed with the possible risk of cardiac, respiratory, dynamical disease (46, 47) states, and general physiological decline. Yet, we understand that future studies should evaluate the HRV recovery from computer tasks so as to state if ANS recovers (or not) from activity, and also to measure if there are positive posterior effects on HRV, as occurs with chronic response of blood pressure after exercises. So, our results support the detection of autonomic responses in DMD during a computer task, to permit the planning of an advantageous clinical management of this group of patients.

Some limitations from this study should be highlighted:

(1) The use of pharmacotherapies could influence our results; beta-blockers and angiotensin-converting enzyme (ACE) inhibitors could interfere in autonomic functions, but these medications are often prescribed and their cessation is not medically or ethically possible, so patients included in the study continued to take these medications. Similarly, we performed a regression analysis so as to study if these medications interfered with our outcomes and did not find any significant results. Besides, we encourage additional studies to evaluate the early effects of autonomic dysfunction in DMD children during the computer tasks; especially those without medication.
(2) To obtain HRV data at different stages of the disease and to better characterize the population; various degrees of pathology (Vignos scale 1–9) were included;
(3) We did not enforce any breathing rhythm and/or emotional analysis; those data in DMD and control group provided useful information and could be important for future studies.

CONCLUSION

DMD subjects presented a lower non-linear HRV compared to TD subjects at rest and during a computer task. Both groups exhibited a similar pattern of reduced non-linear HRV during computer tasks with sustained attention demand when measured by the CGT. It demonstrates that although there is an impaired HRV in subjects with DMD, there remains an adaptation of the ANS throughout the computer task. The identification of autonomic impairment is critical when considering the patients' ANS responses, taking into consideration that the computer tasks in the DMD community may elevate their level of social inclusion, participation, and independence. Hence, assistive technologies should be organized in combination with continuous physiological monitoring to lessen serious and possibly hazardous effects.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. The Matlab code is unavailable due to commercial reasons.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of São Paulo, reference number 236/13. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MA and TS collected data and performed conduction of experiments. MA, CM, TS, VV, CF-F, LV, CF, and DG drafted the manuscript. MA followed the journal guidelines. DG and TS performed statistical analysis. CM supervised the study. MA and CM gave final approval for the version submitted for publication. DG and AS extensively reviewed the manuscript, English Grammar, and spelling. All authors reviewed and approved the manuscript.

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Efficacy of Virtual Reality and Exergaming in Improving Balance in Patients With Multiple Sclerosis: A Systematic Review and Meta-Analysis

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Multiple sclerosis (MS) is one of the most common causes of neurological progressive disease and can lead to loss of mobility, walk impairment, and balance disturbance. Among several rehabilitative approaches proposed, exergaming and virtual reality (VR) have been studied in the recent years. Active video game therapy could reduce the boredom of the rehabilitation process, increasing patient motivation, providing direct feedback, and enabling dual-task training. Aim of this systematic review was to assess the efficacy of exergaming and VR for balance recovery in patients with MS. PubMed, Scopus, and Web of Science were systematically searched from the inception until May 14, 2021 to identify randomized controlled trials (RCTs) presenting: patients with MS as participants, exergaming and VR as intervention, conventional rehabilitation as comparator, and balance assessment [Berg Balance Scale (BBS)] as outcome measure. We also performed a meta-analysis of the mean difference in the BBS via the random-effects method. Out of 93 records, this systematic review included and analyzed 7 RCTs, involving a total of 209 patients affected by MS, of which 97 patients performed exergaming or VR and 112 patients underwent conventional rehabilitation. The meta-analysis reported a significant overall ES of 4.25 ($p < 0.0001$), showing in the subgroup analysis a non-significant ES of 1.85 ($p = 0.39$) for the VR and a significant ES of 4.49 ($p < 0.0001$) for the exergames in terms of the BBS improvement. Taken together, these findings suggested that balance rehabilitation using exergames appears to be more effective than conventional rehabilitation in patients affected by MS.

Keywords: virtual reality, exergames, multiple sclerosis, balance, rehabilitation, meta-analysis

INTRODUCTION

Multiple sclerosis (MS) is one of the most common causes of progressive neurological disability among young adults (1). Upper limb impairments, muscle weakness, spasticity, reduced functional performance, and fatigue are common clinical manifestations in patients with MS (2–6). A crucial impairment that might be often showed by patients with MS is balance disturbance, which could result in a higher risk of falling and reduced independence in the activities of daily living (ADLs) (7–10). To overcome these highly disabling issues, different rehabilitative approaches have been proposed so far in the literature (11, 12). In addition to conventional physiotherapy and rehabilitation interventions, technological devices are a promising therapeutic intervention in the complex framework of MS treatment. In this scenario, virtual reality (VR) approaches are suggested as potentially useful tools in several rehabilitative pathological conditions (13). Indeed, VR might enhance the interaction with surrounding artificial environment created to appear similar to the original one, allowing a multisensorial feedback training that might further increase the rehabilitation efficacy. Indeed, human balance control is the results of multiple sensory system inputs, integrated into a complex mechanism of constant reweight and adjustments, as visual, vestibular, and proprioception signals are continuously converted to corrective motor actions (14). Hence, a multisensorial augmented reality might be a particularly effective rehabilitation approach in MS balance impairments.

Moreover, it is provided though a display that can be also head-mounted, with complementary motion tracking devices, sound effects, and eventually end-effectors such as joysticks or sensors able to capture even muscle and brain signals (15). VR has been integrated in several neurological diseases rehabilitative protocols, including patients affected by MS, with promising results (13, 16–18). As a complementary tool of VR in rehabilitation programs (19), patients could also perform exergames, defined as the activity of playing video games that involve physical exertion (20). In the recent years, exergaming has been widely used in several rehabilitative programs and clinical study (21–23). Active video game therapy could reduce the boredom of the rehabilitation process, increasing patient motivation, providing direct feedback, and enabling dual-task training. In this study, commercially available exergames (e.g., Nintendo Wii and Microsoft Kinect) have successfully transformed living rooms into playful training environments for about 10 years (24). Clinical and home trials have been conducted to investigate the effectiveness of Nintendo Wii Fit in patients with MS, focusing on balance and gait improvement, but the results are controversial (25). In the recent years, researchers started to evaluate exergames as a rehabilitation tool for patients with MS (26). Exergaming has proved to be an acceptable, feasible, safe, fun, stimulating, and self-motivating tool (27). However, there is limited evidence of its efficacy among neurological pathologies, in particular, in patients with Parkinson's disease, stroke, and hereditary sensory motor neuropathy (28–30). To the best of our knowledge, few randomized controlled trials (RCTs) investigated the efficacy of exergaming in MS. Therefore, in systematic review and meta-analysis, we sought to evaluate the efficacy of exergames and VR compared with conventional rehabilitation treatment in terms of balance improvement in patients affected by MS.

METHODS

Search Strategy

PubMed, Scopus, and Web of Science databases were systematically searched for English language articles published from the inception until May 14, 2021, according to each specific thesaurus, following the strategy depicted by **Supplementary Table 1**. This systematic review with meta-analysis was conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (31) and the Cochrane Handbook for Systematic Reviews of Interventions (32). Systematic review protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) (number: CRD42021257449).

Selection Criteria

After removing duplicates, two reviewers independently screened all the articles for eligibility. In case of disagreement, a consensus was reached with the opinion of a third reviewer. RCTs were considered eligible, if responding to the questions defined by the following the participants, intervention, comparator and outcome (PICO) model:

P) Participants: patients with MS.
I) Intervention: Exergames and/or VR.
C) Comparator: Conventional rehabilitation.
O) Outcome measure: Balance assessed by the Berg Balance Scale (BBS).

We included only RCTs with two groups (study group and control group) providing data at the end of the intervention (after 1 week later as maximum). We excluded: (1) studies including patients with MS aged <18 years; (2) studies including patients with MS with the Expanded Disability Status Scale (EDSS) score > 6; (3) cross-over study design; (4) studies written in a language different from English; (5) full-text unavailability (i.e., posters and conference abstracts); and (6) studies involving animals.

Data Extraction

Two reviewers independently extracted main data from the included RCTs through a customized data extraction model on a Microsoft Excel sheet. In case of disagreement, a consensus was obtained asking the opinion of another reviewer.

We extracted the following data: (1) First author; (2) Publication year; (3) Nationality; (4) Age of study participants; (5) Type of exergames and/or VR as intervention; (6) Type of control (placebo or sham treatment); (7) Population and number of patients included in the RCTs; (8) the BBS values as outcome measure; and (9) Main findings.

Data Synthesis

The RCTs were synthesized describing extracted data and the study quality was independently assessed by two authors

TABLE 1 | Reasons for article exclusion by the present systematic review.

Articles excluded after title and abstract screening phase ($n = 34$)*	
Not population of interest	0 (0.0)
Not intervention of interest	0 (0.0)
Not comparison of interest	2 (5.8)
Not outcome of interest	1 (2.9)
Study design different from RCTs	30 (88.2)
Language different than English	1 (2.9)
Articles excluded after full-text screening phase ($n = 20$)	
Not population of interest	0 (0.0)
Not intervention of interest	3 (15.0)
Not comparison of interest	6 (30.0)
Not outcome of interest	11 (55.0)
Full-text unavailability	0 (0.0)
Language different than English	0 (0.0)
Simultaneous publication in two scientific Journals	0 (0.0)

*The exclusion of the articles followed the PICO model defined in the Methods Section. Data are expressed as counts (percentages). *Papers were excluded also for more than one reason during the title and abstract screening phase.*

according to the PEDro scale (33). In case of disagreement, a third reviewer was asked to obtain a consensus. RCTs included were classified, according to the PEDro scale (33), as excellent (9–10 points), good (6–8 points), fair (4–5 points), or poor (<4 points) quality studies. Additionally, two authors assessed the risk-of-bias using the revised Cochrane risk-of-bias 2 (RoB 2) tool for randomized trials (34) and discussed any disagreements until consensus was reached with a third reviewer.

Statistical Analysis

The statistical analysis was performed on Stata version 15.0 (Stata, College Station, Texas, USA) and RevMan version 5.3. The heterogeneity among comparisons was estimated by the chi-squared and I^2 statistic tests. An $I^2 > 50\%$ determined significant heterogeneity across the articles. Effect size (ES) measure and a random-effects model were obtained to determine the pooled estimates with 95% CIs. Missing means and SDs were estimated from medians, ranges, and interquartile ranges (IQRs) using the method introduced by Hozo et al. (35). Then, we carried out a sensitivity analysis on the stability of the combined results. Lastly, we also performed a subgroup analysis on the intervention type to investigate the source of heterogeneity. The potential publication bias was assessed using a contour-enhanced funnel plot of effect size against its SE.

RESULTS

Study Characteristics

At the end of the search, 93 studies were identified, 61 of which were considered suitable for title and abstract screening, after the removal of duplicates. Out of these, 34 studies were excluded after the title and abstract screening, according to the PICO model. Thus, the selected articles were assessed for eligibility and 20 of them were excluded according to the following reasons: not intervention of interest ($n = 3$), not comparison of interest ($n = 6$), and not outcome of interest ($n = 11$) (see **Table 1** for further details). Therefore, 7 RCTs (26, 36–41) were included in this systematic review, as shown by the PRISMA flowchart in **Figure 1**. The main characteristics of these studies are given in detail in **Table 2**. The included studies (26, 36–41) have been published in the last 7 years (from 2003 to 2020). Five (36, 37, 39–41) (71.4%) studies were conducted in Europe [one (36) study from Italy, two (37, 41) study from Spain, one (39) study from Hungary, one (40) study from Israel] and two (26, 38) (28.6%) studies were conducted in Eastern Mediterranean [one (26) study from Jordan, one (38) study from Iran]. A total of 209 subjects were analyzed and 97 subjects performed VR or exergaming as balance training, whereas 112 subjects were included in the control group (undergoing conventional balance training). Study cohorts of the RCTs included ranged from 11 (41) to 47 (37) patients, with a mean age ranging from 34.9 ± 8.9 (26) to 48.3 ± 10.8 years (41). Concerning the follow-up evaluations, only one RCT (38) performed a follow-up at 12 weeks from baseline. Five RCTs (26, 36–39) investigated the effectiveness of exergaming and two RCTs (40, 41) investigated the effectiveness of VR.

Exergaming

Five RCTs (26, 36–39) assessed exergames as intervention compared with conventional balance training. Brichetto et al. (36) showed a significant improvement in the BBS in the experimental group after therapy (54.6 ± 2.2 vs. 49.7 ± 3.9; time × treatment: $p < 0.05$). Gutierrez et al. (37) reported a significant improvement in the BBS in the experimental group when comparing with control group at the end of the balance training (89.4 ± 6.6 vs. 81.9 ± 10.1; $F = 29.896$, $p < 0.001$). Similar results were found by Khalil et al. (26). They showed a significant difference between groups according to the balance score in favor of the experimental group (EG) (50.4 ± 3.7 vs. 45.1 ± 8.64; $p = 0.012$). On the other hand, Mohlemi et al. (38) investigated the efficacy of Xbox360® plus conventional balance training vs. conventional rehabilitation, showing an improvement in the BBS in both the groups at the end of the treatment (EG: 46.6 ± 3.9 vs. 52.4 ± 2.1; $p < 0.001$; control group (CG) 45.5 ± 7.2 vs. 49.9 ± 5.5; $p < 0.001$) and at follow-up (52.0 ± 2.7; $p < 0.001$; 49.0 ± 5.7; $p = 0.01$, respectively). However, no differences between group were showed ($p = 0.32$ at the end; $p = 0.10$ at the follow-up). Similar results were found by Tollar et al. (39). The authors showed significant differences within groups in terms of balance activity after exergaming training (study group: 6.1 ± 3.5; $p < 0.005$ vs. control group: 3.9 ± 2.3; $p < 0.005$), but improvements in the BBS did not differ between groups.

Virtual Reality

Two studies (40, 41) have investigated the effectiveness of VR vs. conventional balance training. Karlon et al. (40) in 2016 reported non-statistically significant differences between groups in the BBS score after treatment (47.9 ± 6.4 vs. 44.6 ± 4.9; F (p-value) = 1.794 (0.561)]. On the other hand, Lozano-Quilis et al. (41) used a kinect-based VR plus conventional balance training as intervention. A significant improvement in

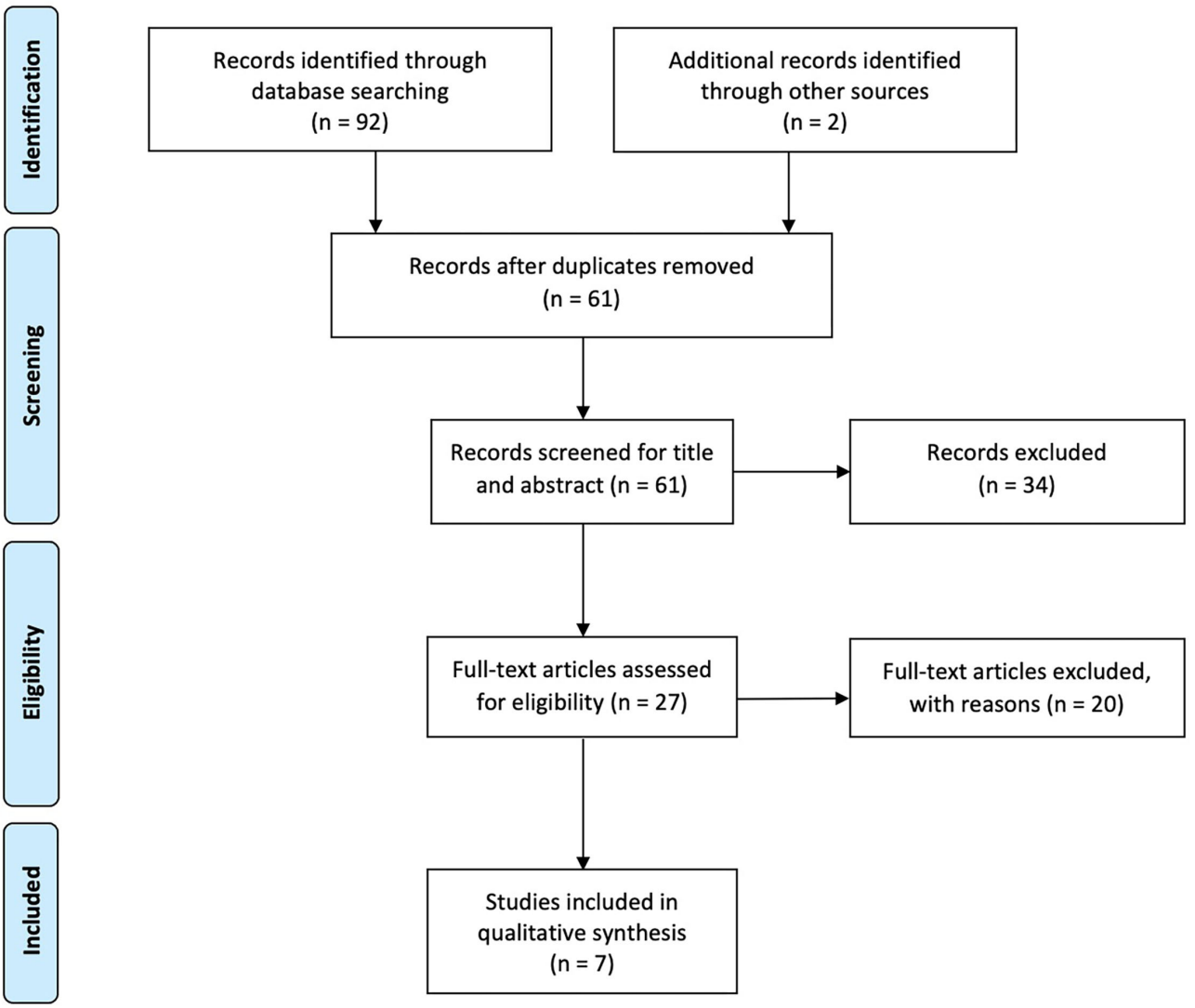

FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

the BBS was found between groups in favor of the experimental group (50.3 ± 5.6 vs. 51.6 ± 5.8; $p < 0.030$).

Meta-Analysis

A meta-analysis was performed to highlight the efficacy of exergames and VR in improving balance (measured by the BBS) in patients affected by MS, showing an overall ES of 4.25 (95% CI = 3.14–5.36, $p = 0.00001$). The subgroup analysis reported a non-significant ES of VR in terms of the BBS improvement [1.85 (95% CI = 2.33–6.04), $p = 0.39$], whereas there was a significant improvement in the ES of the exergaming [4.49 (95% CI = 3.32–5.66), $p = 0.00001$], as shown by **Figure 2**. Given the low number of RCTs, a random-effects model was adopted. Moreover, the Begg's funnel plot analysis of publishing bias reported qualitatively symmetry in the RCTs included in this study, as shown in **Figure 3**.

Risk-of-Bias

The risk-of-bias among the RCTs analyzed was estimated using the RoB 2 (42) (see **Figure 4** for further details). With respect to the selection bias, six studies (85.7%) ensured a correct randomization (26, 36–40). Five RCTs (71.4%) (26, 36–39) excluded performance bias. On the other hand, six studies (85.7%) (26, 36, 38–41) provided guarantees on blinding of outcome assessment and six studies (85.7%) (26, 36–40) adequately assessed attrition bias.

DISCUSSION

Virtual reality has recently emerged as a promising intervention in the rehabilitation of several neurological diseases (28–30, 43). This intriguing and complex technique can evoke brain behavioral responses that mimic real-world interaction, acting

TABLE 2 | Main characteristics of the randomized controlled trials included in the present systematic review.

Article	Nationality	Study group	Control group	EDSS	Intervention	Comparison	Outcome measure and time-point assessments	Main findings
Brichetto et al. (36) Mult Scler 2013	Italy	$n = 18$; 8 M/10 F Age: 40.7 ± 11.5 years	$n = 18$; 6 M/12 F Age: 43.2 ± 10.6 years	≤6	Wii® balance board, 12 sessions, 3 times/week	Conventional balance training, 12 sessions, 60 min, 3 time/week	BBS at baseline and at the end of treatment	Significant differences in BBS between groups in favor of experimental group ($p < 0.05$)
Gutierrez et al. (37) NeuroRehabilitation 2013	Spain	$n = 24$; 11 M/13 F Age: 39.7 ± 8.1 years	$n = 23$; 9 M/14 F Age: 42.8 ± 7.4 years	Ranging from 3 to 5	Xbox360® console with Microsoft® Kinect, 40 sessions, 4 time/week	Conventional balance training, 2 times/week, 40 min	BBS at baseline and at the end of treatment	Significant differences in BBS between groups in favor of experimental group ($p < 0.001$)
Khalil et al. (26) NeuroRehabilitation 2018	Jordan	$n = 16$; 4 M/12 F Age: 39.9 ± 12.8 years	$n = 16$; 6 M/10 F Age: 34.9 ± 8.9 years	Ranging from 3 to 6.5	Wii ® balance board, 12 sessions + 6 session at home, 3 times/week	Conventional home balance training, 18 sessions, 3 times/week	BBS at baseline and at the end of treatment	Significant differences in BBS between groups in favor of experimental group ($p < 0.012$)
Mohlemi F et al. (38) Arch Phys Med Rehabil 2020	Iran	$n = 19$; 7 M/12 F Age: 36.8 ± 8.4 years	$n = 20$; 8 M/12 F Age: 41.6 ± 8.4years	<6	Xbox360® with Microsoft's Kinect + conventional balance training, 18 sessions, 3 time/week	Conventional balance training, 18 sessions, 3 time/week	BBS at baseline, at the end of treatment and after 3 months	No significant differences in BBS between groups were found
Tollar et al. (39) Med Sci Sport Exerc. 2020	Hungary	$n = 14$; 7 M/7 F Age: 48.2 ± 5.9 years	$n = 14$; 7 M/7 F Age: 46.9 ± 6.4 years	Ranging from 4 to 6	Xbox360 ® with Microsoft's Kinect, 25 sessions, 5 times/week	Conventional balance training, 25 sessions, 5 time/week	BBS at baseline and at the end of treatment	No significant differences in BBS between groups were found
Karlon et al. (40) J Neuroeng Rehabil 2016	Israel	$n = 15$; 5 M/10 F Age: 47.3 ± 9.6 years	$n = 15$; 6 M/9 F Age: 43.9 ± 10.6 years	Ranging from 3 to 6	Immersive VR, CAREN system, 12 sessions, 30 minutes, 2 times/week	Conventional balance training, 12 sessions, 30 minutes, 2 times/week	BBS at baseline and at the end of treatment	No significant differences in BBS between groups were found
Lozano-Quilis et al. (41) JMIR Serious Games 2014	Spain	$n = 5$; 4 M/1 F Age: 40.6 ± 9.1 years	$n = 6$; 3 M/3 F Age: 48.3 ± 10.8 years	Not provided	Immersive VR, RemoviEM system, 10 sessions, 15 min, 1 time/week + Conventional balance training, 45 min	Conventional balance training 10 sessions, 60 min, 1 time/week	BBS at baseline and at the end of treatment	Significant differences in BBS between groups in favor of experimental group ($p < 0.030$)

Values are presented as mean ± SD and mean (range).
M, male; F, female; EDSS, Expanded Disability Status Scale; BBS, Berg Balance Scale.

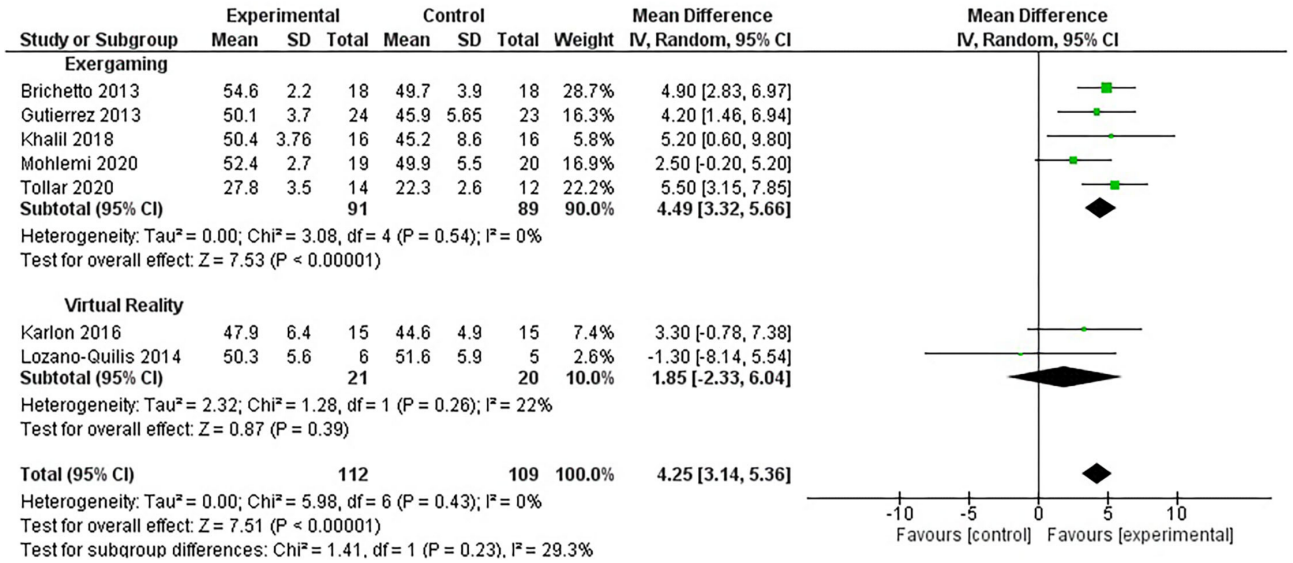

FIGURE 2 | Forest plot illustrating the comparison between exergaming and virtual reality interventions vs. conventional rehabilitation through a meta-analysis.

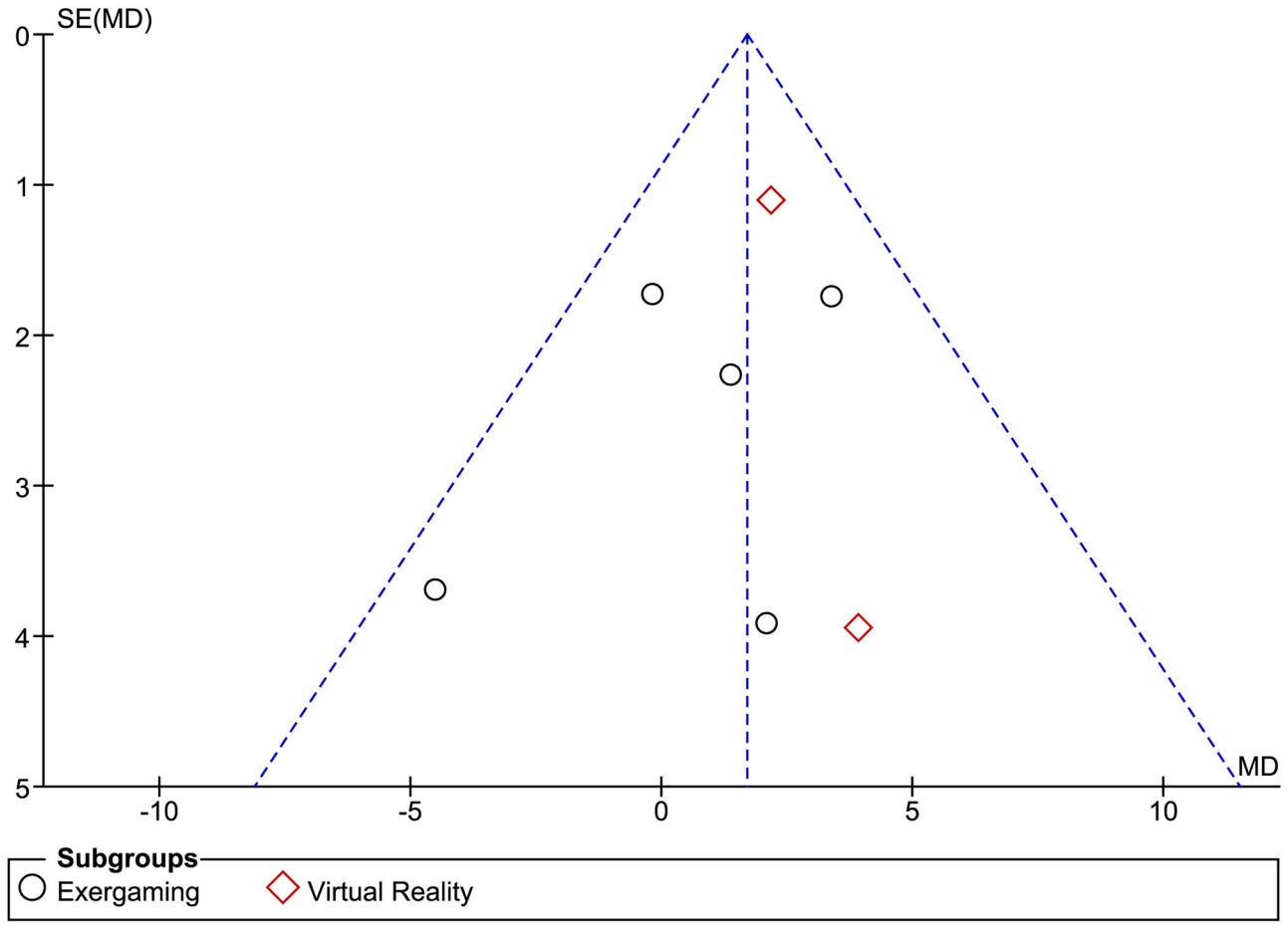

FIGURE 3 | Begg's funnel plot analysis of publishing bias in the studies included in the present systematic review.

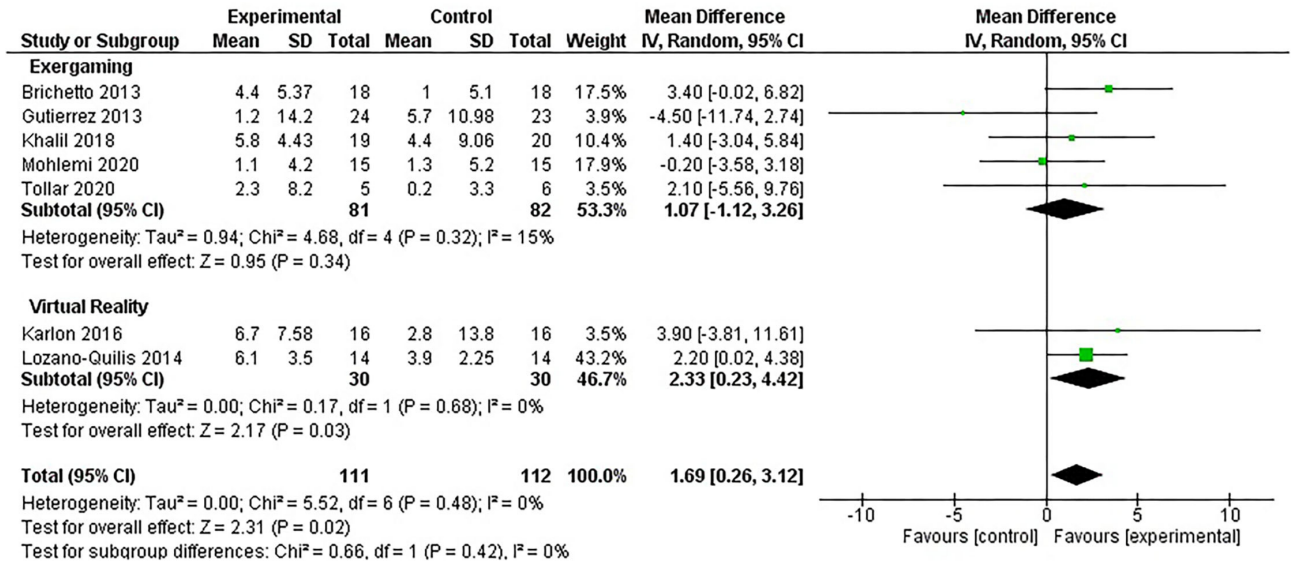

FIGURE 4 | Risk-of-bias assessed by the version 2 of the Cochrane risk-of-bias 2 (RoB 2) tool for randomized trials.

in real-time but in a safe environment. Exergaming consists of whole-body physical exercises comparable to a moderate intensity training, performed through active video games (44). It has been used in the rehabilitation of several neurological diseases to enhance both the cognitive and physical function and improve balance (45–47), as it offers task-oriented exercises enhancing motor learning and neural plasticity (48). Our findings are in line with previous evidence in the neurorehabilitation field, reporting that VR and exergaming are cumulatively effective on gait and balance in Parkinson's disease (49, 50), patients with poststroke (51), traumatic brain injury (52), and cerebral palsy (53). Despite the overall significance demonstrated for these two rehabilitation approaches ($p = 0.00001$), it should be noted that in the subgroup analysis, only exergames reported a significant effect size ($p = 0.00001$) compared to VR ($p = 0.39$).

Although robotic rehabilitation effects on balance and gait have been recently investigated with positive results in patients with MS (54), few studies in literature addressed the effectiveness of VR and exergames compared with conventional treatment in patients with MS and in most cases only considering VR as a complementary tool in MS rehabilitation concerning balance. This could be related to the relative novelty of these devices and the difficult implementation in the clinical setting.

Firstly, Casuso-Holgado et al. (55), analyzed in a systematic review the effectiveness of VR on gait and balance in patients affected by MS, showing significant differences in comparison with no interventions and inconclusive evidence compared with standard treatment. However, the authors included several different outcome measures (i.e., walking speed and postural balance). Moreover, Cano Porras et al. (56) in a systematic review found only three studies focusing on the BBS as primary outcome in patients with MS and VR rehabilitation, with inconclusive results.

Evidence on the role of VR in rehabilitative management of patients with MS is scarce, even though, in 2016, Massetti et al. (57) performed a systematic review on the effects of VR in patients affected by MS, including also observational studies and considering mixed outcomes. Although this approach widened the number of studies included, the low quality of the studies precluded to perform a meta-analysis. Furthermore, a recent meta-analysis performed by Nascimento et al. (58) suggested that VR could induce benefits that can be similar or greater than conventional exercises in patients with MS. However, taken together, all these studies were unable to draw strong conclusion about the real impact of VR on balance improvement in patients with MS, even though the effects of this approach are promising, considering the evidence obtained in other chronic neurological disorders (59, 60).

Concerning exergames, Mura et al. (45), found that in mixed neurological pathologies, including MS, they might significantly improve executive functions and visuospatial perception compared with no intervention or standard rehabilitative treatment. Concerning balance, successive studies in mixed neurological diseases confirmed that exergames might be at least equivalent to conventional therapy (59) and are able to improve balance dysfunction (60).

In the present systematic review and meta-analysis, we found that VR and exergaming might significantly improve balance in terms of the BBS compared with standard treatment alone in patients affected by MS. Among balance assessment, we assessed the BBS as primary outcome, since it is widely used and recommended in different neurological settings for patients with MS with EDSS ranging from 0 to 7.5 (61). Given that the esteemed minimal clinically important difference for the BBS is 3 points (62), most of the selected studies showed a clinically significant difference between standard

treatment and exergaming/VR interventions. Furthermore, VR and exergames might improve balance proposing simultaneous motor and cognitive tasks (63) that might also be addictive, improving both the motivation and treatment adherence (64). In this study, repetitive practice and observation are crucial for motor learning and VR might induce plastic changes in central nervous system that has been associated with mirror imagery in other neurological disorders such as stroke survivors through a facilitation effect on sensorimotor networks (65). The high adherence observed in patients performing exergaming might be due to the low practical barriers, high accessibility, low cost of the consoles, and the social impact because of the potential involvement of family members in multiplayer games (21). Moreover, exergames provide visual and auditory feedback, currently altered in patients affected by MS (66), thus improving the self-awareness of the patients during the training. Furthermore, Yazgan et al. (67) demonstrated a significant improvement in terms of fatigue and gait after exergaming treatment. The authors suggested that these improvements were obtained thanks to the less anxiety and greater confidence in the balance raised by the videogame approach and not a low energy expenditure compared to standard treatments.

This systematic review and meta-analysis have also some clinical implications for the rehabilitation clinical practice, considering that VR resulted to be an intriguing alternative for balance training in patients with MS, with psychological advantages that could enhance their motivation and treatment adherence (68). Clinicians should strike the right balance between too difficult and too easy tasks and as such keeping the motivation of the patients high. Objective progression and extrinsic feedback encourage robot-assisted rehabilitation that might play a critical role on neuroplasticity (69, 70). Lastly, it should be considered that VR might be home based, with a telerehabilitation approach, which is highly encouraged during coronavirus disease 2019 (COVID-19) pandemic, due to psychological and hospitalization issues (71–73).

We are aware that our systematic review considered only a small number of RCTs due to the limited evidence available in the literature. Hence, further high-quality studies investigating exergames and VR effects in improving balance in patients with MS compared with conventional rehabilitation treatment are still warranted and the use of relatively recent exergaming devices is not created specifically for neurorehabilitation. Moreover, to improve the strength of evidence on VR, future RCTs addressing this specific issue in patients with MS are warranted.

CONCLUSION

This study suggested that rehabilitative interventions using exergames and VR appear to be more effective than conventional rehabilitation to improve balance in patients with MS. More in detail, exergames showed to have a significant efficacy in improving balance outcomes and considering its safety and its effects on neuroplasticity, sensorimotor training, and motivation of the patients, it could be implemented as an effective technique in the complex rehabilitative treatment framework of neurological diseases including MS. Starting from these promising data, further evidence is warranted in the next future to focus on VR and its role in the rehabilitative approach to neurological disorders.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

DC and AS contribute to the study design and conceptualization. AS contributes to the databases searching. DC, CC, and AC-S contribute to the data screening. AA, FFo, and AS contribute to the data extraction. DC, MI, and AS contribute to the data synthesis and interpretation. NM contributes to the statistical analysis. DC contributes to the manuscript drafting. MI and AS contribute to the critical revision, study supervision, and study submission. AA, NM, FFo, TP, FFe, CC, and AC-S contribute to the visualization. All the authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.773459/full#supplementary-material

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REVIEW
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How Does Stroke Affect Skeletal Muscle? State of the Art and Rehabilitation Perspective

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Long-term disability caused by stroke is largely due to an impairment of motor function. The functional consequences after stroke are caused by central nervous system adaptations and modifications, but also by the peripheral skeletal muscle changes. The nervous and muscular systems work together and are strictly dependent in their structure and function, through afferent and efferent communication pathways with a reciprocal "modulation." Knowing how altered interaction between these two important systems can modify the intrinsic properties of muscle tissue is essential in finding the best rehabilitative therapeutic approach. Traditionally, the rehabilitation effort has been oriented toward the treatment of the central nervous system damage with a central approach, overlooking the muscle tissue. However, to ensure greater effectiveness of treatments, it should not be forgotten that muscle can also be a target in the rehabilitation process. The purpose of this review is to summarize the current knowledge about the skeletal muscle changes, directly or indirectly induced by stroke, focusing on the changes induced by the treatments most applied in stroke rehabilitation. The results of this review highlight changes in several muscular features, suggesting specific treatments based on biological knowledge; on the other hand, in standard rehabilitative practice, a realist muscle function evaluation is rarely carried out. We provide some recommendations to improve a comprehensive muscle investigation, a specific rehabilitation approach, and to draw research protocol to solve the remaining conflicting data. Even if a complete multilevel muscular evaluation requires a great effort by a multidisciplinary team to optimize motor recovery after stroke.

Keywords: neurologic disorders, rehabilitation, chronic stroke, skeletal muscle, disability, long-term care

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INTRODUCTION

Stroke is the second leading cause of death worldwide (1), with chronic disability remaining in up to 50% of survivors (2). The improved acute care and the advances in early drug interventions after stroke, as the use of thrombolytic factors, have significantly increased the number of stroke survivors with a reduction of mortality (3). However, stroke survivors must cope with the long-term effects of stroke, suffering from persistent functional limitations that reduce autonomy in activities of daily life. Long-term disability caused by stroke is largely due to motor function impairment, and it is determined by primary and secondary changes to the acute event. The impairments can manifest progressively in the long-term, causing further modifications and adaptations: the

lesions of descending neural pathways lead to altered neuromotor control and functional and structural changes of muscle tissue (4). Common symptoms in patients with stroke are weakness, hypotrophy, fatigability, and altered motor control, resulting from the combination of denervation, disuse, remodeling, and spasticity (5). Traditionally, the rehabilitation effort has been oriented toward the treatment of the central nervous system (CNS) damage with a central approach, which exploits the plastic capacity of the neural cells to recover the best motor control. In this paradigm, muscle tissue is often overlooked (6). In our opinion, to ensure greater effectiveness of rehabilitation, new protocol approaches are needed, focused on muscle modifications over time. The knowledge of the cascade of transformation at different scales—genetic, molecular, histological, biomechanical, morphological, neurophysiological, and clinical changes—could help to understand the temporality of the occurrence of these changes and prevent them. Here, we summarized the current knowledge on skeletal muscle changes and primary and secondary changes induced by stroke, looking for the actual literature evidence on specific rehabilitative treatments targeting the muscle. Our idea is that only a "multi-target" rehabilitation treatment, which considers both the periphery and the CNS, can improve outcomes for stroke survivors until the best possible recovery. Based on this aim, we analyzed the current knowledge on modification of muscle in stroke, considering three fundamental aspects: morphology, metabolism, and electro-mechanical properties. For each of them, we resumed the principal treatment proposals available in the literature.

MORPHOLOGICAL CHANGES

Morphological changes may occur in parallel at a different level, including intrinsic fiber muscle phenomena (loss of muscle mass, muscle thickness, and decrease in the physiological cross-section area), but also at a more general tissue rearrangement, referring to sarcomere shortening and histological changes in the extracellular matrix. These two phenomena may mutually influence each other's and be hardly individualized, but for a clearer and more identifiable discussion they will be treated differently in this review. In the first section, we described the "stroke-induced sarcopenia," referring to muscle atrophy as a specific intrinsic fiber muscle phenomenon, and in the second section, we refer to "stiffness" as general tissue rearrangement. Furthermore, it should be mentioned that in several neurological disorders, characterized by spastic paresis, a dedicated term is used to qualify the specific muscle contracture (spastic myopathy), characterized by both increased muscle tension and stretch-sensitive evolution (7).

Stroke-Induced Sarcopenia

In healthy people, muscle tissue is gradually lost during aging, resulting in a decrease in mass and strength, a condition described as sarcopenia (8). In specific pathological conditions, especially in those that may invoke inflammatory processes, disease-related immobility or malnutrition, sarcopenia can occur as secondary, defining a "specific sarcopenia" (6). Recently, the muscle atrophy, consequent to the stroke has been defined as a new condition called "stroke-induced sarcopenia" or "stroke-related sarcopenia"; it has also been associated with worse clinical outcomes and physical dysfunction (6, 9). Furthermore, the impaired function predisposes stroke survivors to inactivity that might contribute to deconditioning, fatigue, and further functional loss (10, 11). Stroke-induced sarcopenia arises from the combination of multiple mechanisms, including immobilization and dysfunctional atrophy, impaired feeding, inflammation, sympathetic overactivation, and denervation (6). The prevalence of stroke-related sarcopenia is higher than the one of general population, matching age, gender, and race of healthy individuals, indicating a specific pathway (12). Furthermore, this prevalence during the first month is 50% and it is ∼34% after 6 months (13), suggesting that the adaptive responses in muscle tissue may be most pronounced early after stroke (5). Moreover, the loss of muscle mass after stroke is commonly accompanied by fat deposition, often associated with a common stroke risk factor such as obesity, worsening the outcome (14). These early changes in muscle, such as loss of muscle mass, reduced fiber cross-sectional area (CSA), and increased intramuscular fat deposition, occur between 3 weeks and 6 months after stroke in both paretic and non-paretic limbs (15–18). In a recent study it was shown that the presence of sarcopenia, associated or not with obesity (sarcopenic-obesity), affects the improvement of activities of daily living (ADL), dysphagia, and discharge rates to home, so the researchers stated that the treatment of stroke-induced sarcopenia in a rehabilitative setting is crucial (19). The same researchers also demonstrated that skeletal muscle mass gain at the end of rehabilitative treatment is significantly associated with improved functional outcomes in patients with sarcopenia after stroke (20).

Some researchers suggested that sarcopenia could be due to the activation of catabolic pathways, especially the ubiquitin–proteasome system (UPS), autophagy, and apoptosis (21, 22). These mechanisms seem to be in part due to the downregulation of the gene of Sirtuin1 (SIRT1), a key regulatory factor of the energetic status of the cell, counteracting metabolic and age-related disorders. Reduced expression of the SIRT1 gene and reduced SIRT1 activity, resulting in skeletal muscle atrophy, have been demonstrated in post-stroke animal models; similarly, attenuation of muscle atrophy was found when SIRT1 is overexpressed (23). Moreover, it was demonstrated that the expression levels of myostatin mRNA, which downregulate the skeletal muscle growth, are 40% higher in the paretic than non-paretic muscles in stroke survivors (24). This could be due to intramuscular fat accumulation, consequent to stroke, that may cause insulin resistance, and the subsequent hyperinsulinemia has been shown to increase serum myostatin (14). The knowledge of the molecular mechanisms of stroke-induced sarcopenia allows to identify specific therapeutic approaches. In fact, in a pre-clinical study, the use of resveratrol (RESV), an exercise mimetic drug, during the early acute phase of stroke, limited muscular atrophy, through the activation of SIRT1, and normalized the hypertrophy of slow-twitch muscle fibers (I, IIa), suggesting that RESV may improve oxidative metabolism in stroke-affected muscles (25). In humans, it is well-known that

exercise is the most effective method for sarcopenia treatment (6). Indeed, a recent study highlighted that resistive training for 12-weeks (3 times/week) could reduce the myostatin mRNA expression levels and stimulates significant muscle hypertrophy and intramuscular fat reductions (24). Furthermore, it is known that a stroke patient could suffer from malnutrition, and its early recognition or misdiagnosis significantly affects the outcomes; in fact, malnutrition aggravates sarcopenia because muscle and adipose tissue wasting occurs (26, 27). In this regard, it becomes essential to evaluate the nutritional status and provide nutritional management in association with specific exercise interventions, to ensure the best result; therefore, as described in the literature, the combination of exercise and nutritional therapy is the most appropriate choice to obtain a positive effect on the increase of skeletal muscle mass (20, 26, 27).

Finally, in a very recent study, it was highlighted that muscles of the trunk undergo atrophy in a later post-stroke phase, causing a worsening of the balance (28); this suggests the need to accurately plan both the type of rehabilitation and the timing: patients should be treated pointing on different aims at different stroke phases, for example, in addition to continuous motor control training over time, strengthening and endurance training of trunk muscles could be helpful during the chronic phase.

Stiffness

Paresis induced by stroke leads to a reduced active voluntary movement and a reduced joint range of motion (ROM), often associated with an active or passive mobilization hyper-resistance or stiffness.

Stiffness can be due to "neural" or "non-neural" phenomena, such as spasticity, spastic dystonia, or respectively, muscle contractures and soft-tissue fibrosis (29).

Consequently, long-term secondary complications, such as soft tissue contractures, pain, pressure sores, decreased ADL, social isolation resulting in decreased quality of life, can occur (30, 31). These phenomena seem to be linked to structural changes of intrinsic muscle properties over time, with an increase of intramuscular connective tissue and fat content (32). It has been shown that these changes depend on the deposition of hyaluronan in the extra-cellular matrix (ECM) (33), intramuscular fat (34), and lead to increased viscosity and could immobilize muscle in the shortened position (29). Indeed, fibrosis and abnormal accumulation of materials in the ECM leads to an increased collagen content and an altered orientation of collagen that likely contributes to a greater transverse tensile stiffness against radial expansion and fascicle shortening. There are several approaches to stiffness management (35). An early passive motion and stretching are the most used techniques to prevent and treat muscle shortening. In particular, it was demonstrated that fixed muscle length induces muscle atrophy, by activation of specific gene expression (36). However, a recent Cochrane systematic review concluded that stretching procedures performed for 3 months or less do not improve joint mobility (37), even if in a recent study 1 year of stretching was found to be effective in counteracting muscle architecture modification (fascicle length, thickness) among plantar flexors, linked with a clinical meaningful gain in ankle dorsiflexion angle (38). This suggests that, in clinical chronic conditions, stretch interventions may need to be continued for longer than just a few weeks (29).

Stiffness in the muscle will generate a constant stimulation of its spindles, triggering the activation of Ia fibers, further tension, failure to release contraction, and a muscle change as serious as the hyperactivity severity (spasticity) (39). When stiffness is linked to spasticity or spastic dystonia the more effective and safe, recommended treatment in a rehabilitation setting is the inoculation of Botulinum Toxin Type A (BoNT-A) (40). BoNT-A blocks the release of acetylcholine at the neuromuscular junction, producing a chemical denervation, with the aim of reducing excessive muscle activity without producing significant functional weakness (41). Unfortunately, the effect of BoNT-A serial injections in muscle, largely used to treat spasticity and spastic dystonia in stroke, is poorly investigated, although in an animal model research, a noxious BoNTA-related effect on muscle has been suggested (42); and in humans, the histological recovery of muscle seems to remain incomplete after the BonTA injection (43). To avoid this potentially damaging effect, a tempestive treatment, integrated with early stretching treatment, could be a proper strategy. Indeed, even if BoNT-A injections are the gold standard in patients with spasticity in the chronic phase of stroke (44), recent studies showed that BoNT-A treatment performed within 3 months since stroke onset in naïve patients with spasticity can achieve the maximum effect on muscle tone, allowing better control of spasticity in chronic phase and a reduction of serial injections (45–47). Moreover, a careful systematic follow-up of treated patients is necessary (48).

Resuming, stiffness is a complex phenomenon consisting of the "reflex-" and "nonreflex-mediated" resistance to passive movement, so each of these needs to be quantified uniquely and related with its corresponding clinical facets. An appropriate treatment of stiffness should consider both aspects, for example, different adjuvant rehabilitation treatments could be useful to reduce soft tissue contracture ("nonreflex-mediated" resistance, rheological aspect), and combined with BoNT-A injection could boost its effect on "reflex-mediated resistance" (49); in fact, allowing a decrease of muscle overactivity may not be sufficient to obtain morphological changes such as an increase in sarcomeres or fascicle length. In addition, an adequate and time-dependent treatment could be designed, also regarding any unresponsive patients in which alternative treatments (e.g., surgical therapy) should be considered.

MUSCULAR METABOLISM CHANGES

Stroke patients exhibit impaired metabolism compared to healthy subjects, with increased tissue lactate and glycerol production, delayed and impaired glucose utilization, and slightly increased energy expenditure (4). This contrasts with the "normal" age-related sarcopenia process, where there is a shift from fast-twitch type IIa/b to slow-twitch type I fibers, which is mainly attributed to the disuse of fast fibers (50, 51). The paretic muscle of chronic stroke patients shows a smaller overall fiber cross-sectional area (CSA) with a shift toward a low oxidative

type IIX fiber content and a reduced type I and type IIA fiber content (52). As a consequence, muscle resistance in affected limbs is likely decreased, because type IIX fibers are more prone to fatigue, leading to impaired muscle performance (50). Acute stroke patients rely on carbohydrate utilization during prolonged walking, while healthy individuals rely mostly on fatty acids oxidation; this carbohydrate utilization likely indicates preferentially anaerobic metabolism and potentially limits the ability to walk for a long time (53). Conversely, in the chronic phase, other researchers did not find differences in skeletal muscle tissue substrate metabolism between paretic and not paretic leg, even if the energy consumption seems to be higher in the not paretic one; in these studies the increased glycolytic activity and reduced lipolytic activity in post-stroke skeletal muscle suggest a bilateral shift in fiber type (54, 55). However, it is noteworthy that in some specific conditions, such as sarcopenic obesity post-stroke (mentioned above), fast-type muscle fibers switch to slow-type muscle fibers resulting in decreased muscle mass and strength, as in age-related sarcopenia (14). Although these data seem to be in contrast, they actually highlight the importance of careful characterization of a patient's muscular metabolism through a specific evaluation over time. In a rehabilitative view, focusing on muscles could identify ways to reverse stroke-induced metabolic alteration; indeed, different therapeutic physical interventions (i.e., aerobic exercise or neuromuscular electrical stimulation) could exert different biological effects and can improve physical performance (56). High-intensity training, aimed to increase type IIA fiber percentages, might contribute to muscle power and endurance, crucial for functional capacity (52, 57). Aerobic exercise normalized the CSA of type I and IIb muscle fiber and increased peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) protein content, which is indicative of increased aerobic capacity (25). To date, these contradictions are not completely clarified and become more evident in the analysis of motor unit activity changes, as discussed in the Electromechanical changes section. Research efforts should be aimed at resolving these apparent contradictions, correlating them with the time course of the chronicity of stroke, and the first step could be to reposition the main movement effector, the muscle, in the crosshairs.

ELECTROMECHANICAL CHANGES

Impaired voluntary muscle motion is also caused by a change in the motor unit (MU) activation. In the first phase post-stroke (in 4 h), there is an initial reduction of MU number with a larger amplitude of the outlier surface of MU action potential (MUAP) and a decrease in compound muscle action potential (CMAP) amplitude, that could continue for a long time (58–60). It may be related to the trans-synaptic inhibition of the spinal alpha-motor neurons, as a result of upper motor neuron involvement (58, 61). Despite this, in the chronic phase, it was reported that the number of MUs increased, particularly in patients with mild stroke (62); in the researchers opinion, this suggests that the initial decrease of MUs is due to functional inactivity and, therefore, its recovery is realistic over time (62, 63). Regarding the larger MUAPs amplitude described in chronic stroke patients, it could indicate enlarged MU, possibly due to reinnervation (collateral sprouting) (64). Furthermore, normal recruitment order, based on the size of the MUs, is also altered in the muscles of the paretic limb: the recruitment of larger MUs at higher muscle contraction levels is less evident in the paretic muscles than in the contralateral ones. Additionally, the threshold strength range for MU recruitment has been compressed to a lower level on the affected side, indicating a different type of MU fiber (65), with a hypertrophy of slow-twitch skeletal muscle fibers and an atrophy of fast-twitch fibers (66). It is confirmed by the study of muscle fiber conduction velocity (MFCV). The MFCV is inferior in the paretic than in the non-paretic muscles of stroke patients (67). Similarly, this might indicate an increase in the proportion of type I fibers compared to type II (68). The same pathophysiology observed in the paretic limb may be present in the non-paretic limb, although to a lesser degree, due to the presence of the ipsilateral corticospinal tract in humans; indeed, in some individuals, up to 30% of corticospinal axons may descend in the ipsilateral ventral tract (58, 69). Nevertheless, the reduction in MUs' number correlates with the reduced muscle mass in paretic limbs, but not in the non-paretic one, suggesting other factors for the reduced muscle mass in these patients as described above (58). Using conventional surface EMG, different parameters (such as power spectrum, spike distribution, clustering index) were described to be different in hemiparetic muscle and healthy ones, and for some of these different hypotheses were suggested, including central and peripheral process (increased motor unit synchronization, impairments in motor unit control properties, loss of large motor units, and atrophy of muscle fibers) (70–72).

Other information could be provided from the analysis of electromechanical delay (EMD), which represents the time elapsed from the onset of active state in skeletal muscle (onset of signal to surface electromyogram—sEMG), and the onset of voluntary strength development. Indeed, a recent study found that the EMD is longer in the paretic than in the non-paretic triceps surae muscles. The longer EMD on the paretic side may be associated with the reduced torque-generating capacity, and it could be linked to the modified intrinsic properties of muscle tissues. The elongation of the EMD is likely attributable to electrochemical processes (i.e., altered ion conductance at neuromuscular junction level, alterations in the excitation–contraction coupling mechanism, disturbed propagation of MUAPs), but also, with a predominant role, to mechanical processes. In particular, the longer EMD on the paretic side may potentially support the hypothesis of a fast-to-slow fiber shift. Moreover, longer EMD is also associated with higher shear wave speed, an elastography ultrasound biomarker of muscle stiffness; so, a stiffer muscle may potentially lead to longer EMD, since a greater muscle activation may be needed to deform muscle shape and to shorten fascicles to generate an adequate strength in a stiffer paretic muscle (73). While the biopsy and metabolism studies results suggest a prevalence of type 2 fiber in stroke muscles, the increased activation of low-threshold MUs and the EMD elongation indicate a relative increase in type 1 MU. These discrepancies could be explained by several hypotheses. First, often different studies focused their attention on different muscles (large muscles of limbs vs. muscles of the hand); second, sometimes the samples are very heterogeneous

with patients at different post-stroke times. So, it is possible that the two alterations coexist and that the underlying mechanisms occur in different post-stroke phases. It might be interesting to draw a longitudinal study by monitoring muscle changes with different methods (metabolic and electrophysiological) to better understand how and when they occur, allowing to manage a specific and timely rehabilitation intervention aimed at recovery.

From a rehabilitative point of view, there is a positive correlation between the root mean square of MUAP and Fugl–Meyer score, which indicates a relation between MU properties and clinically assessed motor recovery (64). In this sense, the altered MU activation might be a target of rehabilitative treatment: it is shown that a rehabilitative treatment provided by robotic-assisted locomotion system (Lokomat) induces a significant increase in firing rate, not accompanied by an increase in strength; this could suggest an effect of training on motoneuronal firing rate that thus contributes to muscle motor control (74, 75).

LIMITATIONS

For the preparation of this review, we did not apply the methodology of a systematic review with subsequent limitations. Systematically traceable search criteria are not represented and PRISMA criteria have not been considered. Furthermore, we focused on the muscle properties trying to separate this from motor control disorder, so some factors of muscle weakness (i.e., recruitment and firing rate) are only partially mentioned from a rehabilitative point of view. Despite the growing number of publications, the data still show some conflicting findings and methodological limitations, probably due to the lack of patient stratification based on correct functional assessment.

CONCLUSIONS AND RECOMMENDATIONS

From this review, it is clear that changed descending neural output, caused by stroke, leads to functional and structural changes in skeletal muscle. The main muscle changes are morphological modifications, alteration in muscular metabolism, and electromechanical features. For each of these aspects, specific treatment approaches (medical or rehabilitative) are present in several preclinical studies, showing effectiveness in improving motor function and ability to modify the muscular features recovering the "normal." Despite this, the same approach in clinical studies is not equally carried out. Indeed, also in specific rehabilitative settings, a realistic evaluation of muscle function is not performed yet: often the only muscle evaluation is limited to subjective functional assessment measure without any attention to the morphological, metabolic, and electro-mechanical properties of muscle. In our opinion, the focus onto the muscle means to consider that the impaired motor function in stroke is the result of both reduced central motor control activity and muscle modifications. In this perspective, for optimal stroke management, it would be necessary to investigate the two components simultaneously, investigating the alterations of the descending motor pathways using techniques such as transcranial magnetic stimulation and motor-evoked potentials, and verifying the peripheral muscle modifications, not only with a clinical assessment, but also with an instrumental evaluation through ultrasound techniques, bioimpedance analysis, or more sophisticated metabolic and gene analyses. A second aim of our review was to focus on the need for specific muscular rehabilitation protocol in clinical practice, suggesting an integrated approach for the best motor recovery. To achieve this ideal management, research must aim to solving the contradictions still present in skeletal muscle modifications, by better investigating the muscle during the different phases of stroke, from the onset to the chronic rehabilitation phase. Therefore, it would be appropriate to design a specific longitudinal study in which muscle changes are investigated using different methods to define the time course of the specific variations and to manage a specific and timely rehabilitation intervention aimed at recovery. In particular, it must be clear that at different stages it would be necessary to modulate and change the type and the aim of the treatment. This ambitious goal must be positioned as an outcome of a multidisciplinary intervention, in which several experts work together to integrate the bottom-up with the classic top-down paradigm with a "multi-target" rehabilitation approach.

Based on the current literature available, we can make the following recommendations for optimal stroke management:

- Muscle assessment in stroke patient should be performed together with CNS evaluation, to address a specific patient-tailored rehabilitation.
- Muscle assessment should be conducted through a multi-level screening:
  - Morphological evaluation: ultrasound techniques, bioimpedance analysis, elastography, or magnetic resonance.
  - Metabolic change should be directly investigated through immunohistochemical analysis or indirectly by dosing metabolic substrates.
  - Electromechanical changes (EMG and sEMG).
- Nutritional screening might be performed to assess energy requirements and provide adequate integration for muscle mass gain.
- Designs of specific treatment protocols based on the modifications highlighted (aerobic training, resistance training, stretching, or medical therapy for stiffness).
- The treatment should be time-dependently designed.
- Verify treatment effect at muscle level over time (longitudinal study).
- Multidisciplinary approach is strongly recommended.

AUTHOR CONTRIBUTIONS

VA and SD: conceptualization, writing, draft preparation, and writing the original article. VA wrote the manuscript with support from SD. SD and CC: provided critical feedback and helped shape the manuscript. All authors contributed to the final version of the manuscript and approved the submitted version.

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Stroke Telerehabilitation in Calabria: A Health Technology Assessment

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Introduction: Telerehabilitation (TR) is defined as a model of home service for motor and cognitive rehabilitation, ensuring continuity of care over time. TR can replace the traditional face-to-face approach as an alternative method of delivering conventional rehabilitation and applies to situations where the patient is unable to reach rehabilitation facilities or for low-income countries where outcomes are particularly poor. For this reason, in this study, we sought to demonstrate the feasibility and utility of a well-known TR intervention on post-stroke patients living in one of the poorest indebted regions of Italy, where the delivery of rehabilitation services is inconsistent and not uniform.

Materials and Methods: Nineteen patients (13 male/6 female; mean age: 61.1 ± 8.3 years) with a diagnosis of first-ever ischemic ($n = 14$) or hemorrhagic stroke ($n = 5$), who had been admitted to the intensive rehabilitation unit (IRU) of the Institute S. Anna (Crotone, Italy), were consecutively enrolled to participate in this study. After the discharge, they continued the motor treatment remotely by means of a home-rehabilitation system. The entire TR intervention was performed (online and offline) using the Virtual Reality Rehabilitation System (VRRS) (Khymeia, Italy). All patients received intensive TR five times a week for 12 consecutive weeks (60 sessions, each session lasting about 1h).

Results: We found a significant motor recovery after TR protocol as measured by the Barthel Index (BI); Fugl-Meyer motor score (FM) and Motricity Index (MI) of the hemiplegic upper limbs.

Conclusions: This was the first demonstration that a well-defined virtual reality TR tool promotes motor and functional recovery in post-stroke patients living in a low-income Italian region, such as Calabria, characterized by a paucity of specialist rehabilitation services.

Keywords: telerehabilitation, stroke, motor and functional recovery, virtual reality rehabilitation system, rehabilitation

INTRODUCTION

Stroke is one of the most important causes of death (1) and disability worldwide (2). The decline of mortality (3) contributed to long-term outcomes, such as sensory, motor, cognitive, and visual impairments, representing great challenges to be addressed by the survivors.

The presence of disabilities following a stroke has also an important impact on society in terms of costs for the healthcare system as well as for the quality of life of patients and their families (4). The amount of time in acute care after stroke is getting shorter and the rehabilitative phase is increasingly shifted toward an outpatient setting. Nevertheless, the successive discharge does not always coincide with an adequate functional recovery, which requires longer time and many resources (5). Moreover, since there are limited healthcare resources and infrastructures, stroke survivors often receive medical assistance according to nonclinical factors, such as geographical location and personal wealth (6–8). This is particularly evident in Italy, where the chronic public health management crisis is exacerbated in the poorest southern areas, such as Calabria, where the delivery of post-stroke rehabilitation services is not uniform, inconsistent, and deeply indebted. Furthermore, traveling to hospital services is extremely challenging for both rural and urban dwellers with disabilities, due to the mountainous terrains of the region and the limited transport facilities. All these factors contributed to health migration from the Calabria healthcare system.

For this reason, it is mandatory to identify new effective and efficient models of care to improve the increasing demand for stroke rehabilitation services, considering the complex geographical and territorial socio-economic problems in Calabria.

In recent years, telemedicine has also been used as a method of intervention and support to families of patients with stroke (9). Technologies related to remote health services also offered an alternative solution for extending neurological interventions to patients who do not live near a qualified care provider, thus, addressing inequalities in access to health (10). Telephone, internet-based video conferencing, virtual reality protocols, and sensors can be used as means of communication between patients and healthcare experts, providing an alternative and effective method of delivering conventional rehabilitation (5, 11, 12). Telerehabilitation (TR) can ensure the continuity and/or prolong the treatment that started in rehabilitation units (13) and improve, as an additional treatment, the quality and the amount of conventional therapy. Moreover, different types of rehabilitative treatments can be delivered by TR systems, like physiotherapy, speech, occupational, and cognitive therapy, besides teleconsultations (14). Finally, it has been demonstrated that the neurofunctional changes underlying recovery from stroke are similar in patients who underwent conventional rehabilitation, as well as TR (5, 15, 16). For all these reasons, TR appears as a promising and effective intervention for neurological patients, supporting the healthcare system, and going beyond territorial difficulties and isolation (4).

This study aims to evaluate, for the first time, the utility and feasibility of a well-known and validated TR tool for post-stroke patients living in a low-income Italian region such as Calabria.

MATERIALS AND METHODS

Participants

The study was realized on post-stroke patients who required long-term motor/cognitive assistance, consecutively enrolled, from January 2020 to May 2021, at the time of their discharge from the Intensive Rehabilitation Unit (IRU) at the S. Anna Institute (Crotone, Italy). The inclusion criteria were: (1) Age $>$ 18 years; (2) stable clinical condition; (3) absence of infections; (4) availability of receiving in-home neuro-rehabilitation service; and 5) availability of a home internet connection. The exclusion criteria were: (1) patients with a history of regular prior and/or current drug and/or alcohol abuse; (2) patients with cognitive impairment (Mini Mental State Examination (MMSE) score $>$ 24); (3) patients with aphasia, as assessed by the Aachener Aphasie Test (AAT); (4) prior or current psychiatric diseases; and (5) presence of other severe pathologies influencing the outcome, such as cardiorespiratory instability or other medical illness potentially interfering with the treatment.

All the participants gave written informed consent. The study was approved by the Ethical Committee of the Central Area Regione Calabria of Catanzaro (prot n° 168; 20/07/2017), according to the Helsinki Declaration.

Design and Procedure

A within-subject design divided into four main stages was used. After the recruitment of the patients (1° phase), in the second stage, occupational and physical therapists blindly assessed the clinical scales before and after treatment. Next, the participants underwent neuro-rehabilitation training for five times a week for 1-h per session in 12 consecutive weeks. For remote rehabilitation treatment, we used the Virtual Reality Rehabilitation System (VRRS), which is recognized as one of the most advanced, comprehensive, and clinically employed virtual reality systems for rehabilitation (14, 17) and TR (18, 19). This is a technological innovation tool that allows delivering motor (13), cognitive, and speech (19, 20) neurological treatments *via* remote advanced technological devices (23). It is designed as a hub-and-spoke system and includes the telecockpit (hub) and the home tablet (spoke) (http://khymeia.com). The therapist by the VRRS Telecockpit (workstation) manages the home tablet and remotely guides the patient training. The VRRS tablet is delivered to the patient and contains the exercises to be performed by means of sensors (Khymu and K-Wand) (**Figures 1A,B**). For telerehabilitation protocols, the VRRS system provides a non-immersive virtual reality (VR) tool at home, which patients can navigate using a keyboard/mouse into a virtual environment displayed on a computer screen. All motor and logopedic exercises are tailored to the clinical status of stroke patients. More specifically, the motor exercises included in the software reflect those of in-patient rehabilitation programs administered during the conventional treatment. Applying the sensors (khymu) both

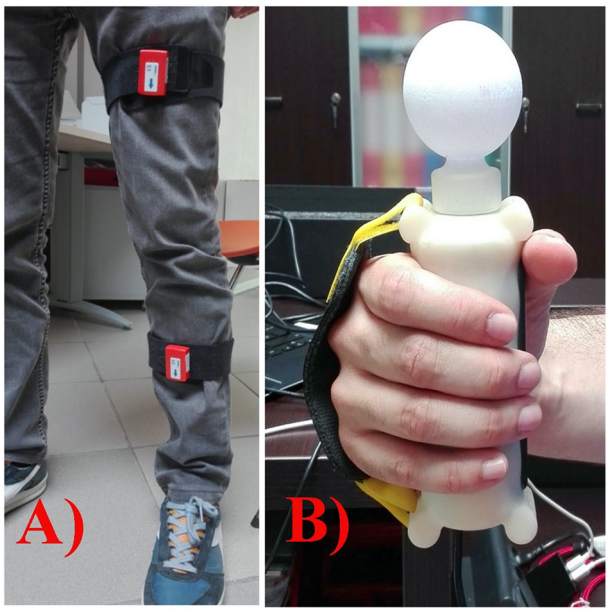

FIGURE 1 | Khymu **(A)** and KWand **(B)** devices for telerehabilitation.

to the trunk and the upper/lower limbs, or reaching the target holding the K-wand, it is possible to train the different body segments.

The software contains specific exercises for the trunk (flexion and extension, rotation, lateral inclination, and dorsal mobilization), for the singular right or left upper limb (shoulder adduction and abduction, shoulder flexion and extension, shoulder intra- and extrarotation, elbow flexion and extension, and forearm pronation and supination), and for singular (hip abduction, adduction, flexion and extension, knee flexion and extension, and ankle flexion and extension) or both lower limbs (squats, get up on the tips, and march on the spot). Other exercises, namely, "functional exercises" reproduced activities of daily living (ADLs) such as ironing, opening a jar, and bringing a glass to the mouth. Furthermore, the same exercises can be performed in two modalities: online (the therapist controls the tablet and interacts with the patient) or offline (the patient carries out on his/her own exercises), by using a system of non-immersive VR.

Prior to rehabilitation, the patients were trained to the employment of the VRRS Tablet. Since the pandemic restrictions, both assessment and training for the use of the VRRS tablet were remotely conducted.

Finally, Khymeia provides an efficient system that captures all necessary information for remote medical services which meets all our security and privacy requirements, i.e., patient's privacy (anonymity), data confidentiality, and data integrity.

Clinical Evaluation

The Fugl-Meyer (FM) (21, 22) and the Motricity Index (MI) scales were used to assess the motor functions. The first one was used to assess the motor performance of the upper and lower limbs, as well as control of sitting and standing balance, while the second scale measures the strength in the upper and lower paretic extremities (23). The Barthel Index (BI), developed as a measure to assess disability in patients with neuromuscular and musculoskeletal conditions, was used to assess the independence in the ADL (23). The possible presence of depressive symptoms was investigated by means of the Post-Stroke Depression Rating Scale (PSDRS), specifically designed for patients with stroke (24).

A satisfaction questionnaire was included in the protocol and was sent by email at the end of the treatment to the patients/caregiver who enrolled in the study. The purpose of this questionnaire was to find out their opinion and the difficulties and satisfaction degree in relation to the TR service. The questionnaire was structured as a Likert scale and included 9 items: 1–5 multiple answers, scored from lowest to the highest level of satisfaction (not much – 1; enough – 2; much – 3; very much - 4); 6 and 7 closed answers (Yes or No); and 8 and 9 open answers (for more information see **Supplementary Materials**).

TABLE 1 | Demographic and clinical data at admission to telerehabilitation (TR) protocol.

Variables	
Number	19
Sex (% male)	68%
Age (years)	61.1 ± 8.3 [44–73]
Educational Level (years)	12.4 ± 4.3 (5–18)
Time from event (days)	595 ± 688.3 [43–3,396]
Etiology	73.6% Ischemic
	26.4% Hemorrhagic
MMSE	25.86 ± 3.0 [24–29.4]
PSDRS	2.74 ± 2.8 [0–9]

Data are shown as mean ± SD including minimal and maximal values. MMSE, Mini-Mental State Examination; PSDRS, Post-Stroke Depression Rating Scale.

Statistical Analysis

Data analyses were performed using SPSS version 23.0 (IBM, New York, USA). The assumptions for normality were tested for all continuous variables using the Kolmogorov–Smirnov test. Clinical variables were normally distributed. A paired-sample *t*-test (two-sided) was used to verify any statistically significant changes in motor scales before and after TR treatment. For all tests, a p-value <0.05 was statistically significant.

RESULTS

Patients

Nineteen stroke patients (ischemic, $n = 14$; hemorrhagic stroke, $n = 5$) (**Table 1**) completed all phases with a higher level of adherence to the home tele-treatment and were included in the statistical analysis (**Figure 2**). The TR protocol has included patients in the entire Calabria region (**Figure 3**). The qualitative evaluation of personal satisfaction opinion about TR showed a very good level with the following mean percentages: (i) "Excellent" 64.6%; "Very Good" 24.8%; "Satisfactory" 16%. One

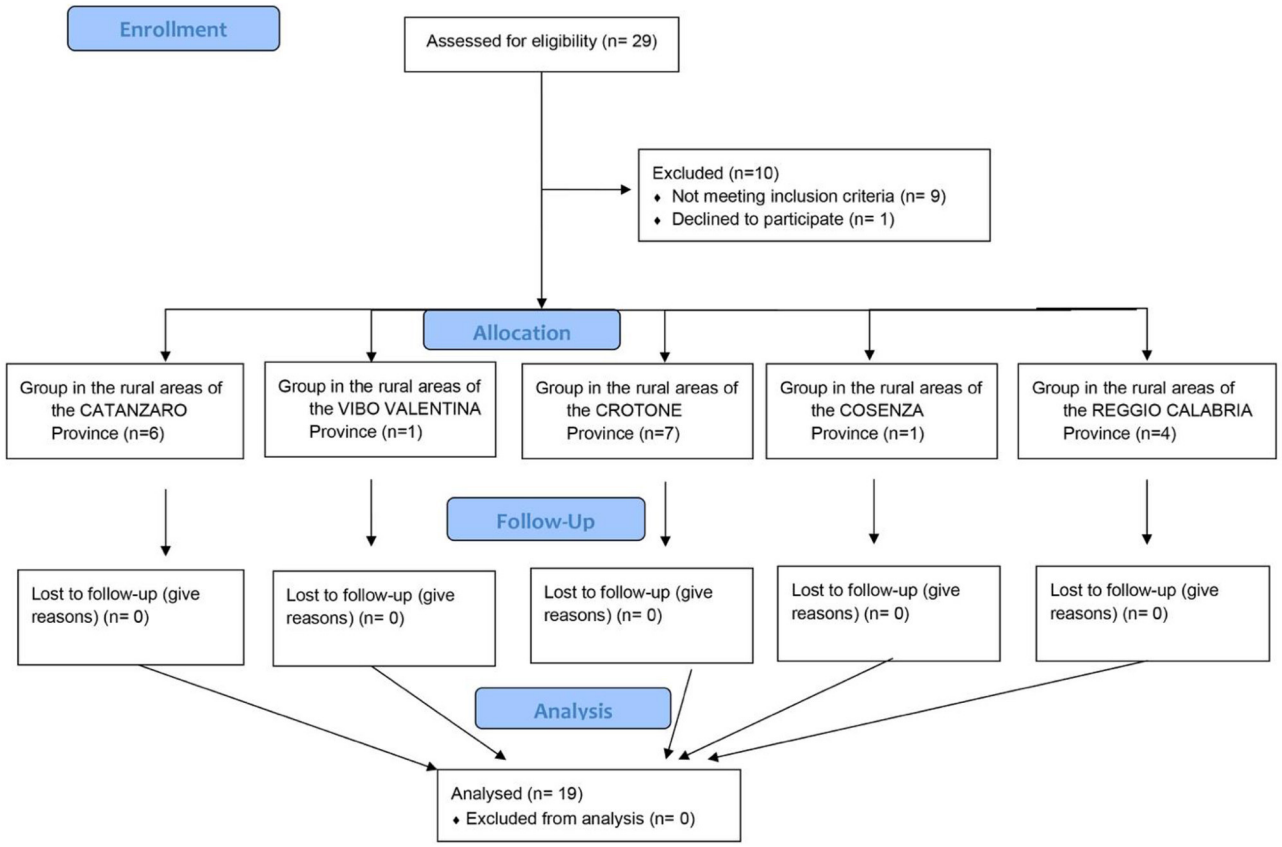

FIGURE 2 | Flow diagram showing the phases of parallel trial of patients with stroke who underwent TR treatment in Calabria provinces.

hundred percent of the interviewed patients answered positively to items 6 and 7, while the problems encountered during the treatments were only related to the internet speed connection.

Motor Outcome After TR

To longitudinally assess the motor recovery after TR protocol, a comparison within groups was performed (**Table 2**). We found a significant improvement in the BI, FM, and MI performance of the left hemiplegic upper limbs. A trend toward relevant improvement was also detected in the right hemiplegic upper/lower limbs, without reaching a significant threshold.

DISCUSSION

This study assessed the feasibility and the utility of a TR approach for providing effective intervention in post-stroke patients living in a low-income Italian region. Our findings confirmed that during a TR protocol, better motor and functional recoveries were detected after discharge from the hospital. Despite the lack of a control group that did not allow us to quantify the real magnitude of recovery, our study supports the use of this advanced technological tool to improve the access to rehabilitation services.

Telemedicine is generally underdeveloped in Italy and disparities exist among the different regions with regard to the provision of healthcare (4). The increasing commitment of resources for the national healthcare system has reached a dramatic condition, leading some regions to be placed under temporary administration. Calabria is one of the most indebted regions, as also characterized by the presence of several rural places and paucity of specialist rehabilitation services. For this reason, urgent efforts are needed to promote early and continuous interventions at distance and to reduce the long waiting lists and the costs for the healthcare system. To provide an objective quantification of the actual healthcare system status in Calabria, Guerriero et al. (25) described the reorganization problems faced by local authorities in defining the hospital network of the region of Calabria. Based on real data used for evaluating the status of public health care service network (i.e., number of hospitals, number of beds in the department, connection cost expressed in terms of travel time between home and the hospital location; and demand from center), they compared the current hospital network in Calabria with the ideal localization obtained by solving some classical facility computational location models. The results showed that the current hospital network configuration in Calabria leaves some of the demand uncovered, thus, generating inefficiencies for the

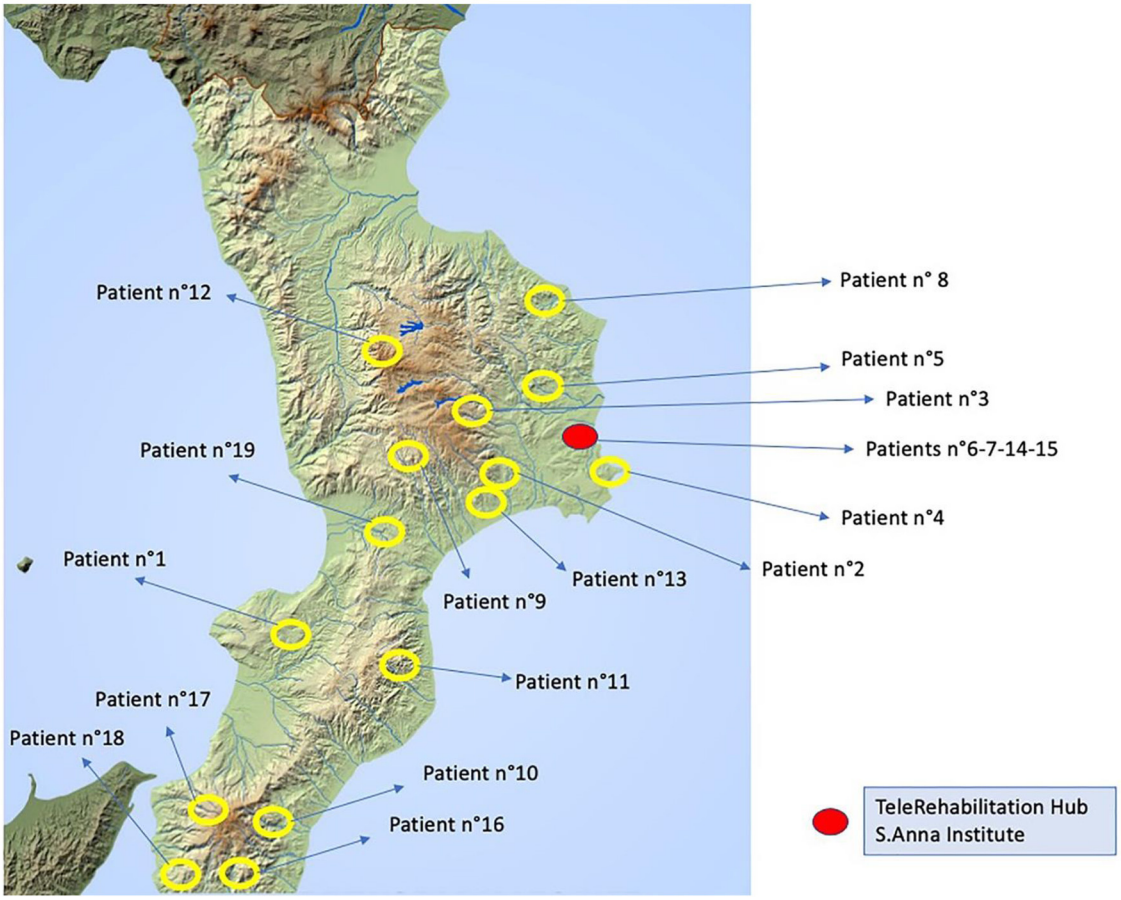

FIGURE 3 | Physical map of the Calabria region showing patients' localizations during TR treatment.

TABLE 2 | Clinical improvements within post-stroke patients before (pre-) and after the (post-) TR protocol.

	Pre-TR ***(n = 19)***	**Post-TR** ***(n = 19)***	***p-value***	***t-value***
BI	72.11 ± 22.7	81.8 ± 17.6	0.002*	−3.74
FM	74.53 ± 22.7	79.3 ± 23.6	0.001*	−3.77
MI upper limbs *(paretic limb)*	68.6 ± 24.1	71.32 ± 23.6	0.02*	−2.73
MI upper limbs (non-*paretic limb)*	90.21 ± 20.5	91.63 ± 18.5	0.06	−1.82
MI lower limbs *(paretic limb)*	72.84 ± 20.7	72.26 ± 20.3	0.34	−0.94
MI lower limbs *(non-paretic limb)*	88.61 ± 20.2	93.05 ± 12.8	0.11	−1.7

*TR, Telerehabilitation protocol; BI, Barthel Index; FM, Fugl-Meyer; MI, Motricity Index. Data are shown as mean ± SD. *Significant at $p < 0.05$.*

healthcare system that may also directly impact stroke patients requiring access to rehabilitation services.

As recently reviewed by Maresca et al. (4), there are few studies that were carried out in Italy to evaluate the reliability and efficacy of TR protocols on stroke patients. Using the Human Empowerment Aging and Disability rehabilitation program, Isernia et al. (26) demonstrated in a heterogeneous neurological population of Northern Italy (n° 30 with Parkinson's Disease, n° 32 with Multiple Sclerosis, and n° 45 with stroke in chronic stage) that TR is effective in ameliorating autonomy in daily routines. Torrisi et al. (27) evaluated the efficacy of TR on 40 patients with post-stroke who were living in Sicily and were randomly divided into experimental and control groups. The experimental group underwent cognitive rehabilitation training using the VRRS-Evo, whereas, the control group performed a traditional rehabilitation program. After an initial training phase performed during the IRU period, the patients continued rehabilitation at home with a tablet remotely connected with clinicians. These authors

found a significant increase in global cognitive functioning, attentional processes, verbal fluency, short-term memory, and mood (anxiety and depression) after TR protocol with respect to the control group. Finally, in two distinct works, Piron et al. (28, 29) demonstrated the effectiveness of TR using a virtual reality-based system delivered *via* the Internet to induce the motor recovery of the upper limbs in post-stroke patients. In particular, they found a significant increase of performance only in the FM scale with respect to the control group who underwent traditional physical therapy for the upper limbs. They claimed that TR can stimulate learning of the arm's motor skills away from the healthcare facilities, with reduced healthcare costs.

Our study is perfectly in agreement with the literature showing that a well-validated TR tool induces motor and functional recovery in chronic post-stroke patients. The telemedicine system employed in this study is the VRRS. This tool has been developed in the last few years for the TR of a wide spectrum of pathologies, demonstrating high feasibility in promoting motor or cognitive recovery in patients with multiple sclerosis (30) or Parkinson's disease (31). The strengths of VRRS are as follows: (a) the modular organization integrating telerehabilitation games and exercises in addition to teleconsulting, with remote territorial and home control (32); and (b) the possibility to employ different rehabilitation modules for training motor, cognitive and orthopedic deficits. This is achieved by the interaction between the virtual system, therapist, and patient with a series of synchronized and integrated customizable devices, adapting to the patient's disabilities and needs.

Limitations

The small sample size and the lack of a control group are the main limitations of this study. Although we are aware of these limitations, it is important to bear in mind that the effectiveness of TR in recovering motor/functional abilities with respect to conventional treatment has previously been demonstrated in several neurological domains (4). The main target of this study was to demonstrate, for the first time, that this healthcare system might also be applied in a low-income Italian region rather than evaluating its effectiveness with respect to other approaches. Thus, our study should be considered as a pilot, with promising future applications to overcome the barriers related to access to services caused by distance or difficulty of patient's mobility in Calabria (25).

CONCLUSIONS

A clear advantage of TR is to increase access for people living in isolated or far from rehabilitation services. This means that a TR service makes a competent rehabilitation team available for all the geographical zones, where the technology is present but the access to health services is complex or lacking (rural and remote regions), and for all people with restricted mobility (5). In this study, we demonstrated that TR interventions for functional recovery may be successfully delivered in patients with post-stroke, overcoming geographical and organizational barriers characterizing the healthcare configuration of Calabria. Our study also highlights the need for additional investments in community-based stroke rehabilitation services to make this new model of care suitable and available for a larger group of post-stroke patients (32).

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 study was approved by the Ethical Committee of the Central Area Regione Calabria of Catanzaro (prot n° 168; 20/07/2017) in accordance with the Helsinki Declaration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The statistical analysis was done by MC. The study design was done by MC, FA, PT, and AC. The manuscript drafting was done by MC, FA, and AC. Clinical data collection was made by FA, TM, GN, MLP, AI, and MQ. The literature search, data interpretation, and manuscript revision were done by FA, MC, LP, PT, and AC. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.777608/full#supplementary-material

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SYSTEMATIC REVIEW
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Transcranial Direct Current Stimulation (tDCS) as a Useful Rehabilitation Strategy to Improve Cognition in Patients With Alzheimer's Disease and Parkinson's Disease: An Updated Systematic Review of Randomized Controlled Trials

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Alzheimer's disease (AD) and Parkinson's disease (PD) are neurodegenerative disorders characterized by cognitive impairment and functional decline increasing with disease progression. Within non-pharmacological interventions, transcranial direct current stimulation (tDCS) might represent a cost-effective rehabilitation strategy to implement cognitive abilities with positive implications for functional autonomy and quality-of-life of patients. Our systematic review aimed at evaluating the effects of tDCS upon cognition in people suffering from AD and PD. We searched for randomized controlled trials (RCTs) into PubMed, Web of Science, and Cochrane Library. Three review authors extracted data of interest, with neuropsychological tests or experimental cognitive tasks scores as outcome measures. A total of 17 RCTs (10 trials for AD and 7 trials for PD) were included. Compared with sham stimulation, tDCS may improve global cognition and recognition memory in patients with AD and also some executive functions (i.e., divided attention, verbal fluency, and reduction of sensitivity to interference) in patients with PD. Criticism remains about benefits for the other investigated cognitive domains. Despite preliminary emerging evidences, larger RCTs with common neuropsychological measures and long-term follow-ups establishing longevity of the observed effects are necessary for future research in applied psychology field, alongside improved clinical guidelines on the neurodegenerative disorders pertaining electrodes montage, sessions number, duration and intensity of the stimulation, and cognitive battery to be used.

Keywords: transcranial direct current stimulation, cognition, rehabilitation, randomized controlled trials, Alzheimer's disease, Parkinson's disease

INTRODUCTION

Application of Transcranial Direct Current Stimulation (tDCS) in Cognitive Rehabilitation

The tDCS is a neurostimulation method, painless, substantially devoid of the significant side effects, economic, simple to apply and even suitable for a home environment administration under supervision of remote therapist, also in case of the neurological disorders (1–4). In such a technique, a weak current—usually 1/2 mA at constant frequency—is applied to the scalp through one or two stimulation electrodes in targeted brain regions, as single or bilateral configuration modes (5). The current leads to changes in the extracellular *milieu* that, in turn, affects the resting membrane potential of the neuronal populations in the proximity of electrodes placement (6). However, although stimulation is applied over limited brain areas, the distribution of the current that reaches the cortex depends on intensity, modulation duration, electrodes montage and size, and orientation of the electric field in relation to anatomical features of the cortex (7). While the anodal tDCS increases cortical excitability in the brain region under and around the electrode placement, the cathode tDCS decreases it (8). Short-term effects of the tDCS occur through non-synaptic mechanisms by depolarization of resting membrane potential, while long-term effects likely occur through NMDA-dependent mechanisms and appear to be consistent with synaptic plasticity (9, 10).

Despite potential associated adverse events (e.g., tingling, itching, burning sensation, mild headache, bright flashes of light and skin burn, etc.) (6), tDCS is globally considered as a safe, tolerable and low-cost rehabilitation strategy. Contraindications only pertain to metallic implants in the head/body, craniotomy or history of seizure (11, 12). As a result, tDCS has been applied with promising results to many neurological disorders (13–16) and neuropsychiatric conditions (17–20), resulting in an exponential growth of studies in the last decades.

Cognitive Deficits in Alzheimer's Disease and Parkinson's Disease

Recently, the development of novel non-invasive methods of brain stimulation, such as transcranial magnetic stimulation (TMS) and tDCS has increased the interest in neuromodulatory approaches as potential tools to counteract a progressively more severe cognitive deterioration related to the course of neurodegenerative disorders, such as AD and PD.

On one side, AD is a progressive neurodegenerative disorder and accounts for most of dementia in elderly people, currently affecting 5.8 million people in the US alone (21). This percentage is dramatically estimated to increase, by reaching 65.7 million people affected by AD in 2030 worldwide (22). The number of new cases of AD significantly increases with aging, with an incidence of 76 of every 1,000 people of 85 years and older (21). AD has a devastating effect on patients and their caregivers and determines a tremendous socioeconomic impact on the health system. Usually, cognitive deficits are present in patients prior to the time of AD onset (i.e., mild cognitive impairment due to AD) (23), and typically affect episodic memory and executive functions domains (24). Usually, memory impairment is the earliest representing the core symptom of the disease and functional autonomy of patients decreases with progression of AD, also as a consequence of a wider range of supplementary cognitive deficits (25). Cholinesterase inhibitors are considered as the main pharmacologic treatment for patients with AD although response is quite limited (26–28).

On the other side, PD represents another chronic neurodegenerative disorder leading to a progressive decrement of functional autonomy of the patients. It affects about 1% of people who are aged older than 60 years and reported standardized incidence rates of PD are 8–18 per 100.000 person-years (29). Because of the dopamine reduction in the *pars compacta* of the *substantia nigra*, typical motor symptoms are characterized by resting tremor, rigidity, bradykinesia, and postural instability. Patients with PD show additional motor deficits including gait disturbance and motor complications, such as dyskinesia in the course of the disease (30). Despite its nosographic definition remarking motor deficits, PD has been progressively conceived as a "complex brain disease" including non-motor symptoms, such as cognitive disturbances (31, 32). In PD, there is a *spectrum* of cognitive dysfunction, ranging from mild cognitive impairment (PD-MCI) to PD dementia (PDD). Cognitive impairment is quite common in PD, affecting approximately 30–40% of the patients (33). Cognitive deficits might be present at early stages of the disease and are usually characterized by executive functions and visuospatial deficits (34–36). Neurocognitive deterioration pertaining to the frontal domains and attention system is a consequence of dopamine reduction (i.e., frontal-striatal syndrome). Structural abnormalities of fronto-parietal areas and subcortical regions (37) and temporo-parietal regions (38) implicated in visual stimuli analysis have been observed in patients with PD, too. A particular impairment of implicit motor sequence learning (IMSL) is also displayed by patients with PD, consisting of difficulties in acquisition of multiple single movements to be performed in a sequential order without conscious awareness needed for retrieval (39).

Alternative non-invasive neurostimulatory techniques such as tDCS require urgent development in the next future, both for AD and PD. However, performed investigations on tDCS effects upon cognition in patients with AD and PD to date present some limitations. They did not focus only on randomized controlled trials (RCTs) (22, 40, 41), mixed results from TMS and tDCS (42, 43), encompassed adjunctive cognitive or physical training (22, 40, 44, 45) to tDCS or adopted inclusion criteria for selecting studies encompassing vascular dementia or other neurological disorders, as well as patients with mild cognitive impairment (46).

Our systematic review tried to bypass the aforementioned limitations and represents an update systematic review of RCTs evaluating the effects of tDCS upon cognition in AD and PD as a stand-alone technique (i.e., without combined cognitive or physical training) compared with sham (i.e., placebo) stimulation.

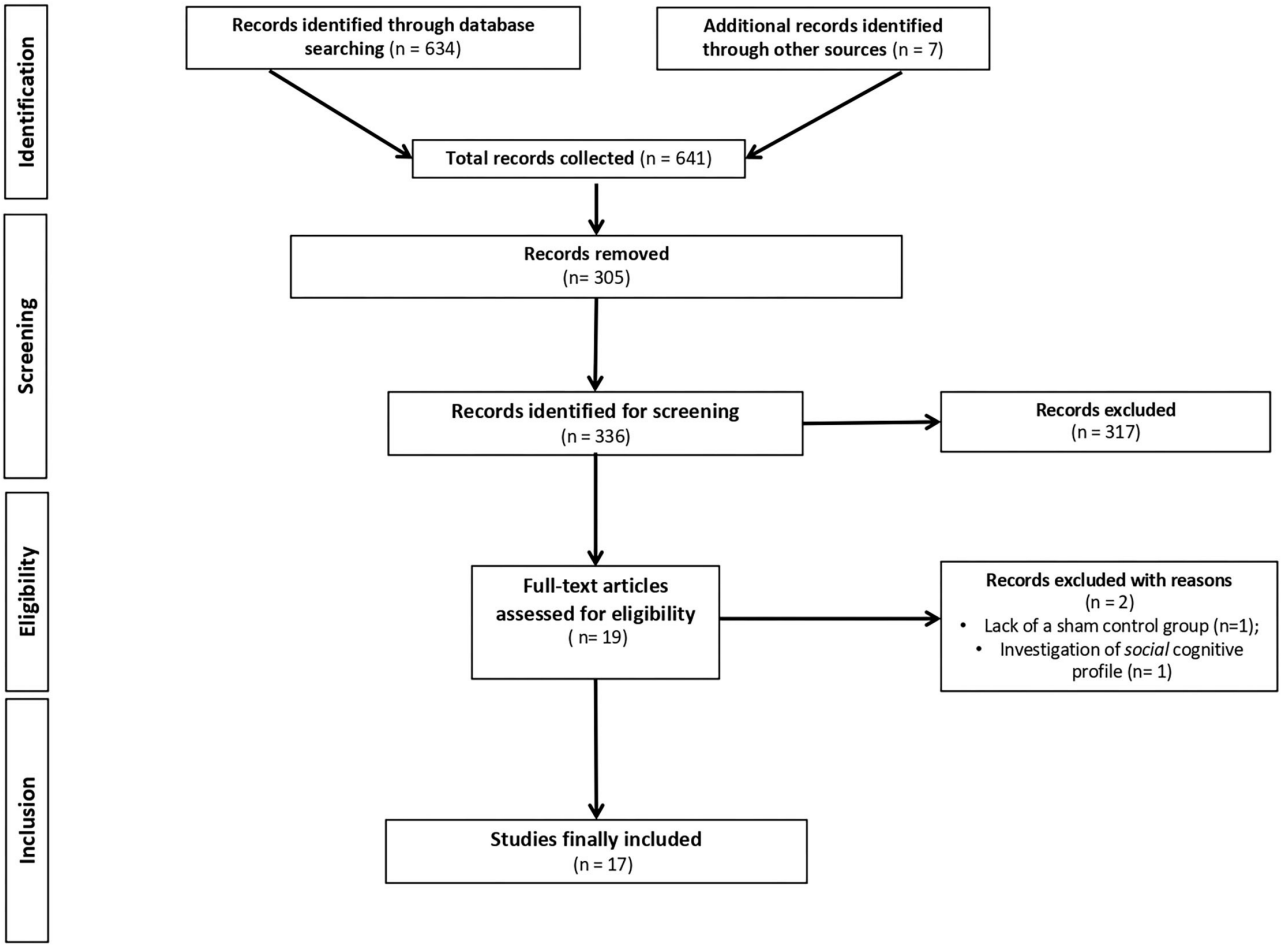

FIGURE 1 | PRISMA (Preferred reporting of systematic reviews and meta-analysis) flowchart of search results.

METHODS

Search Strategy

This update systematic review adheres to the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) *Statement* (47). PubMed, Web of Science, and Cochrane Library databases were systematically screened for RCTs using the following terms: "Alzheimer's Disease" or "Parkinson's disease" and "transcranial direct current stimulation" and "cognition" or "cognitive abilities" or "cognitive deficits" or "cognitive impairment" (only upper time limit: September 31, 2021). Additional titles were added based on the bibliographies of the relevant issues and through the use of hand search of journals and other pertinent resources. **Figure 1** shows the PRISMA flowchart.

Study Selection Criteria

Studies from the literature search were selected if they met the following criteria: (1) assessing the effects of tDCS on cognitive functioning; (2) including patients with AD or PD selected by recognized international diagnostic criteria, i.e., NINCDS–ADRDA criteria for AD (48) and UK Brain Bank criteria for PD (49), respectively; (3) RCT as study design; (4) measures of cognition as primary or secondary outcomes; (5) presence of sham (i.e., placebo) stimulation. Exclusion criteria encompassed: (1) multicomponent interventions (e.g., tDCS *plus* physical or cognitive training) or high-definition tDCS techniques; (2) other noninvasive brain stimulation techniques (e.g., TMS); (3) studies recruiting individuals with neurological disorders different from AD and PD (i.e., other dementia types or vascular dementia, mild cognitive impairment, stroke, multiple sclerosis, traumatic brain injury, focal brain disorders, etc.) or classified as having mild/major neurocognitive disorder and also psychiatric diseases and other relevant medical conditions that might interfere with cognitive functioning; (4) studies recruiting healthy older adults; (5) animal studies; and (6) manuscripts written in other languages than English.

Quality of the Studies and Assessment of Risk of Bias Evaluation

Three independent reviewers (DMC, FC, and RC) first evaluated methodological criteria used by RCTs examining tDCS effects upon cognition in AD (**Table 1**) and PD (**Table 2**) patients

TABLE 1 | Evaluation of methodological criteria used by RCTs examining tDCS effects for AD.

References	1	2	3	4	5
Ferrucci et al. (50)	+	+	+	+	-
Boggio et al. (51)	+	-	+	+	+/-
Boggio et al. (52)	+	+/-	+	+/-	+
Khedr et al. (53)	+	+	+	+	+
Suemoto et al. (54)	+	+	+	+/-	+
Bystad et al. (20)	+	+	+	+	+/-
Im et al. (12)	+	+	+/-	+	+/-
Khedr et al. (55)	+	+	+	+	+
Gangemi et al. (56)	+	+	+	+	+/-
Gangemi and Fabio (57)	+	+/-	+	-	+

(1) The diagnosis of AD is based on validated criteria [NINCDS-ADRDA, (48)]; (2) Inclusion and exclusion criteria of the study are specifically described; (3) The study has sufficient statistical power (n ≥ 10 per group); (4) Intervention, measurements and outcomes are fully described; (5) Potential adverse effects are indicated and confounding variables are discussed.

TABLE 2 | Evaluation of methodological criteria used by RCTs examining tDCS effects for PD.

References	1	2	3	4	5
Boggio et al. (10)	+	+	+	+	+
Doruk et al. (58)	-	+/-	+	+	+/-
Ferrucci et al. (59)	-	+/-	-	-	-
Dagan et al. (60)	+	+	+	+	+/-
Bueno et al. (61)	+	+/-	+	+	+
Lau et al. (62)	+	+/-	-	+	+/-
Firouzi et al. (39)	+	+/-	-	+	+/-

(1) The diagnosis of PD is based on validated criteria [i.e., UK brain bank criteria; (49)]; (2) Inclusion and exclusion criteria of the study are specifically described; (3) The study has sufficient statistical power (n ≥ 10 per group); (4) Intervention, measurements and outcomes are fully described; (5) Potential adverse effects are indicated and confounding variables are discussed.

and then assessed the risk of bias according to the *Quality Assessment Tool for Quantitative Studies* (63) developed by the *Effective Public Health Practice Project* (EPHPP) (**Tables 3**, **4** for AD and PD, respectively). In both the cases, disagreement was discussed until a consensus among reviewers was definitely reached.

RESULTS

Studies Selection, Evaluation, and Report

Initially, 634 records were identified through databases and manual search (**Figure 1**). After removing duplicates (n = 305), we screened the titles and the abstracts of the remaining records and identified 19 articles for a full-text inspection. Two studies (64, 65) were excluded because of different reasons (see **Figure 1**). Finally, 17 articles were included in our systematic review, 10 pertaining AD (12, 20, 50–57) and 7 pertaining PD (10, 39, 58–62). The evaluation of methodological criteria used was first shown in **Tables 1**, **2**. The assessment of risk of bias (**Tables 3**, **4**) reported that 15 studies were of moderate quality whereas only 2 studies were of strong quality (12, 53).

Outcomes: tDCS Effects on Cognitive Domains

A summary of the included studies was reported in **Tables 5**, **6** for patients with AD and for patients with PD, respectively. A total of 9 study designs were parallel ones (12, 20, 53–58, 61) whereas 8 study designs were crossover ones (10, 39, 50–52, 59, 60, 62). More specifically, the *washout* period of the latter studies performing different tDCS stimulations presented in counterbalanced order across participants, substantially varied from 48 h (10, 51) to 71.1 ± 5.8 days (52). A total of 5 studies (52–54, 58, 59) performed a follow-up, varying from 1 week (53, 54, 59) to 2 months (53), with 2 investigations reporting a prolonged tDCS effect upon cognition, particularly on the visual recognition memory (52) and divided attention (58). Furthermore, Gangemi et al. (56) adopted the longest intervention of stimulation (i.e., 10 days a month for 8 months).

Remarkably, participants of AD recruited from the studies were different in terms of global cognition at baseline. A range of Mini Mental State Examination (MMSE) scores was present among studies, with that of (54) (i.e., 15.0 ± 3.1 for the tDCS group and 15.2 ± 2.6 for the sham group) reporting the lowest ones. Such a discrepancy was not revealed for the PD selected studies.

In patients with AD, recognition memory—both verbal and visual one—improved at different current intensities, stimulation duration, and number of sessions (i.e., from 1.5 to 2 mA, from 15 to 30 min, from 3 to 5 sessions, respectively) by tDCS of the temporal cortex (50–52) while a clear-cut effect on the global cognition was obtained after a 2 mA stimulation for 25 of 30 min of the left DLPFC (12), both on the anodal and cathodal modality (53) or anodal stimulation of the frontotemporal cortex (56, 57). Visuoconstructive ability (55) and language abilities (i.e., naming) (12) seemed to ameliorate after daily sessions (2 mA for 20/30 min) of tDCS, too.

In patients with PD, executive efficiency was enhanced either thanks to the stimulation of DLPFC as a single brain area through variable sessions of treatment (i.e., 1–10 sessions) at 1–2 mA of 20-min current stimulation (10, 58, 61) or thanks to the combined stimulation of DLPFC and primary motor cortex (PMC) at 1.5 mA after a 3-session intervention of 30 min (60). Finally, beneficial effects of anodal tDCS over the primary motor cortex were found in relation to IMSL in such patients (39) after 1 week from the intervention (i.e., 2 mA intensity for 20 min per session during the cognitive task). In four cases, no cognitive improvement was revealed after tDCS intervention (20, 54, 59, 62).

Transcranial DCS was well tolerated by the patients even if some side effects were sometimes reported (i.e., tingling, sleepiness, mild headache, neck pain, skin redness, scalp pain, scalp burning, somnolence, and trouble concentrating) [e.g., (53, 54, 58)].

TABLE 3 | Assessment of risk of bias of the included RCTs pertaining tDCS in AD.

References	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropout	Overall
Ferrucci et al. (50)	***	**	*	**	*	***	**
Boggio et al. (51)	***	*	*	*	**	***	**
Boggio et al. (52)	***	**	**	**	*	***	**
Khedr et al. (53)	***	***	***	**	***	***	***
Suemoto et al. (54)	***	***	*	***	*	***	**
Bystad et al. (20)	***	***	*	**	***	**	**
Im et al. (12)	***	***	***	**	***	**	***
Khedr et al. (55)	***	**	***	**	***	*	**
Gangemi et al. (56)	***	***	*	**	*	***	**
Gangemi and Fabio (57)	***	**	**	**	*	***	**

*, *Weak quality*; **, *Moderate quality*; ***, *Strong quality*.

TABLE 4 | Assessment of risk of bias of the included RCTs pertaining tDCS in PD.

References	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropout	Overall
Boggio et al. (10)	***	*	*	**	*	***	**
Doruk et al. (58)	**	***	*	**	***	***	**
Ferrucci et al. (59)	*	**	*	*	*	***	**
Dagan et al. (60)	*	**	*	**	***	***	**
Lau et al. (62)	**	**	**	**	*	***	**
Bueno et al. (61)	***	**	*	**	**	***	**
Firouzi et al. (39)	***	**	***	*	**	***	**

*, *Weak quality*; **, *Moderate quality*; ***, *Strong quality*.

DISCUSSION

This systematic review aimed to provide a comprehensive overview of the current knowledge about the effects of tDCS stimulation upon cognition for patients with AD and PD when compared with sham (*placebo*) stimulation. Transcranial DC stimulation seems to ameliorate cognitive vitality of patients in relation to global cognition and recognition memory in AD and divided attention, verbal fluency, and reduction of sensitivity to interference in PD, respectively. From a neuropsychological point of view, criticism remains about potential usefulness of tDCS for working memory, processing speed and visual attention, visuospatial abilities and verbal learning performances while initial proof arises about language improvement after tDCS.

Heterogeneity of the patients (i.e., age, disease onset, severity and duration, premorbid level of functioning), tDCS delivery settings (i.e., clinics, hospitals, and home treatment), concomitant pharmacological therapy and concurrent psychopathological symptoms, particularly depression and apathy not routinely evaluated except for some investigations represent confounding variables that make difficult to compare among studies [cf. (66)].

In four cases (20, 54, 59, 62), we reported the lack of results about cognition improvement after tDCS. In our opinion, it should be because of the use of the neuropsychological assessment/experimental tasks adopted for the evaluation of cognitive functions associated to the stimulated brain areas and/or small sample size.

Some researchers (12, 53, 54) stimulated the DLPFC in patients with AD, as a brain area critically associated with working memory and to a repertory of the frontal abilities, including planning, abstract reasoning, mental flexibility, and attentional set shifting. A recent investigation using [11C]-raclopride positron emission tomography demonstrated that tDCS of the DLPFC enhance attention system and executive functioning because of an increased release of dopamine neurotransmitter (67) in healthy males, probably allowing a more accurate performances on cognitive tests requiring an additional recruitment of attentional resources and executive control.

Other researchers (10, 58, 60) investigated the activation of the same brain area in patients with PD with encouraging findings, given that it has been related to executive deficits because of the dopaminergic dysfunction of the fronto-striatal network and to top–down attentional deficits due to alterations of the cholinergic fronto-parietal circuits, commonly reported in these patients (68). Remarkably, the enhancement of locomotor skills of patients with PD may benefit from executive efficiency (69) too. It has also been suggested that a possible beneficial effect of tDCS specific stimulation for patients with PD could be the induction of dopamine release in the caudate nucleus *via* the glutamatergic corticostriatal pathway, as shown in animal studies (70). Transcranial DC stimulation might also have a neuroprotective role in PD, by reducing the oxidative damage

TABLE 5 | Summary of main results of the selected studies of tDCS in AD.

References	Participants	Procedure and brain region/s involved	Intervention for active groups	Current intensity and electrodes position according to the 10-20 EEG international system	Neuropsychological assessment/ experimental cognitive tasks	Follow-up	Main findings of the active group/s at the end of the intervention
Ferrucci et al. (50)	10 patients Sex: M = 3; F = 7; Mean age: 75.2 ± 7.3; Pharmacotherapy: ChEI	Anodal, cathodal or sham tDCS of the TPC	3 sessions at intervals of 1 week	Anodal or cathodal 1.5 mA current delivered for 15 min bilaterally over the TPC (P3-T5 left side; P4-T6 right side); Cathodal electrode: right deltoid muscle	Word recognition task (modified from Adas-cog); c-attentional cue task (E-Prime computer-controlled Posner paradigm)	-	Word recognition memory improvement after anodal tDCS
Boggio et al. (51)	10 patients Sex: M = 4; F = 6; Mean age: 79.1 ± 8.8 Pharmacotherapy: ChEI (not for all patients), BDZs, antipsychotics, TCAs	Anodal tDCS of the TC, DPFC, or sham tDCS	3 sessions at intervals of 48 h	2 mA intensity delivered for 30 min over the left DLPFC (F3) or left TC (T3); Cathodal electrode: SO	Stroop test; digit span (backward and forward); computer-based recognition memory task	-	Visual recognition memory improvement both after temporal and prefrontal tDCS
Boggio et al. (52)	15 patients Sex: M = 8; F = 7 Mean age: 71.1 ± 5.8; Pharmacotherapy: not reported	Anodal or sham tDCS of the TC	5 consecutive days sessions	2 mA current delivered for 30 min bilaterally (T3, T4) Cathodal electrode: right deltoid muscle	MMSE, Adas-Cog, c-VRT, c-VAT	At 1 week and at 1 month	Visual recognition memory improvement and maintenance 4 weeks after the intervention
Khedr et al. (53)	34 patients Sex: M = 19; F = 15 Mean age of anodal group: 68.5 ± 7.2 Mean age of cathodal group: 70.7 ± 5.4 Mean age of sham group: 67.3 ± 5.9 Pharmacotherapy: no patients took cholinomimetics, antidepressants, neuroleptics, sedative-hypnotics drugs for at least 1 week before assessment	Anodal, cathodal or sham tDCS of the DLPFC	10 daily sessions	2 mA intensity delivered for 25 min Anodal/sham group: anodal electrode over the left DLPFC (F3), cathodal electrode: contralateral SO Cathodal group: cathodal electrode over the left DLPFC (F3), and anodal electrode over the contralateral SO	MMSE, WAIS-III	At 1 and 2 months	Global cognition (MMSE) improvement both after anodal and cathodal tDCS

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TABLE 5 | Continued

References	Participants	Procedure and brain region/s involved	Intervention for active groups	Current intensity and electrodes position according to the 10-20 EEG international system	Neuropsychological assessment/ experimental cognitive tasks	Follow-up	Main findings of the active group/s at the end of the intervention
Suemoto et al. (54)	40 patients Sex: M = 12; F = 28 Mean age of anodal group: 79.4 ± 7.1 Mean age of sham group: 81.6 ± 8.0 Pharmacotherapy: ChEI	Anodal or sham tDCS of the DLPFC	6 sessions over a period of 2 weeks	2 mA intensity delivered for 20 min Anode electrode: left DLPFC (F3) Cathodal electrode: contralateral SO	Adas-Cog	At 1 week	No improvement
Bystad et al. (20)	25 patients Sex: M = 14; F = 11 Mean age of anodal group: 70.0 ± 8.0 Mean age of sham group: 75.0 ± 8.7 Pharmacotherapy: ChEI	Anodal or sham tDCS of the TC	6 sessions for 10 days	2 mA intensity delivered for 30 min Anode electrode: left temporal lobe (T3) Cathodal electrode: right frontal lobe (Fp2)	CVLT, MMSE, CDT, TMT	-	No improvement
Im et al. (12)	18 patients Sex: M = 3; F = 15 Mean age of anodal group: 71.9 ± 9.2 Mean age of sham group: 74.9 ± 5.0 Pharmacotherapy: ChEI	Anodal or sham tDCS of the DLPFC	Daily sessions for 6 months	2 mA intensity delivered for 30 min Anode electrode: left DLPFC (F3) Cathodal electrode: right DLPFC (F4)	MMSE, Digit span forward and backward, BNT, RCFT, CDT, SVLT, contrasting program, Go-No-Go test, COWAT, Stroop test	-	Improvement of global cognition (MMSE) and language (BNT); preventive decrease of executive functions
Khedr et al. (55)	44 patients Sex: M = 26; F = 18 Mean age of anodal group: 64.2 ± 3.64 Mean age of sham group: 65.2 ± 4.5 Pharmacotherapy: Memantine and piracetam	Anodal or sham tDCS of the right and left temporal lobe	5 sessions/wk for 2 consecutive weeks	2 mA intensity delivered for 20 min for each side Anode electrode: right TL/left TL (T3-P3/T4-P4) Cathodal electrode: deltoid muscle of the left arm	Modified-MMSE, CDT, Montreal Cognitive Scale	-	A significant improvement in the total score of each cognitive rating scale in the real group

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TABLE 5 | Continued

References	Participants	Procedure and brain region/s involved	Intervention for active groups	Current intensity and electrodes position according to the 10-20 EEG international system	Neuropsychological assessment/ experimental cognitive tasks	Follow-up	Main findings of the active group/s at the end of the intervention
Gangemi et al. (56)	Study 1 26 patients Sex: M = 10; F = 16 Mean age of anodal group: 67.25 ± 2.8 Mean age of sham group: 69 ± 6.1 Study 2 18 patients Sex: M = 5; F = 13 Mean age of anodal group: 68.5 ± 2.8 Mean age of sham group: 68.7 ± 3.1 Pharmacotherapy: ChEI	Anodal or sham tDCS of the left frontotemporal lobe	Study 1: daily sessions for 10 consecutive days Study 2: daily sessions for 10 consecutive days each month for 8 months	2 mA intensity delivered for 20 min Study 1 Anode electrode: left frontotemporal lobe (F7-T3); Cathodal electrode: right frontal lobe (Fp2).	MMSE MODA	-	tDCS intervention was effective both in the short- and the long-term to slow down the progression of AD on temporal and personal orientation, attention, calculation, and recall
Gangemi and Fabio (57)	26 patients Sex: M = 14; F = 12 Mean age of anodal group: 72 ± 4.4 Mean age of sham group: 75 ± 4.4 Pharmacotherapy: ChEI	Anodal or sham tDCS of the left frontotemporal cortex	10 sessions	Anode electrode: DLPFC (F3-F7), and left (F7) Cathodal electrode: right SO	MODA subscales (temporal orientation, spatial orientation, personal orientation, family orientation, autonomy, reversal learning, verbal intelligence, story test, words production, token test, digital agnosia, constructive apraxia, Street test, attentional test)	-	Improvements of temporal orientation, spatial orientation, reversal learning, verbal intelligence, story test, word production and attention

AD, Alzheimer's disease; ChEI, cholinesterase inhibitors; TPC, Temporoparietal Cortex; DBZs, benzodiazepines; TCAs, Tricyclic antidepressants, SSRIs, Selective serotonin reuptake inhibitors; TC, Temporal Cortex; DLPFC, Dorsolateral Prefrontal Cortex; MMSE, Mini Mental State Examination; Adas-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; c-VRT, computerized Visual Recognition Task; WAIS-III, Wechsler Adult Intelligence Scale Third Edition; CVLT, California Verbal Learning Test; c-VRT, computerized Visual Recognition Task; WAIS-III, Wechsler Adult Intelligence Scale Third Edition; CDT, Clock Drawing Test; TMT, Trail Making Test; BNT, Boston Naming Test; RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test; TL, Temporal lobe; MODA, Milan Overall Dementia Assessment; HD-tDCS, High-definition tDCS.

TABLE 6 | Summary of main results of the selected studies of tDCS in PD.

Study	Participants	Procedure and brain region/s involved	Intervention for active groups	Current intensity and electrodes position according to the 10-20 EEG international system	Neuropsychological assessment/experimental cognitive tasks	Follow-up	Main findings of the active group/s at the end of the intervention
Boggio et al. (10)	18 patients (9 patients for each experiment) Sex: M = 12; F = 6 Mean age: (Experiment 1): 59.2 ± 9.9 Mena age: (Experiment 2): 61.0 ± 12.1; Pharmacotherapy: patients were withdrawn from antiparkinsonian drugs for 12 h	Anodal tDCS of the DLPFC or PMC and sham tDCS	3 sessions at intervals of 48 h	1 mA or 2 mA intensity delivered for 20 min Anode electrode: left DLPFC (F3) or PMC (C3); Cathodal electrode: contralateral RSO	Three-back letter WM paradigm (during tDCS)	-	WM improvement after anodal tDCS of the DLPFC
Doruk et al. (58)	18 patients Sex: M = 7; F = 9 Mean age: 61.0 ± 8.0 Pharmacotherapy: Stable medication (L-dopa) regimen 1 month prior the study	Anodal tDCS of the DLPFC and sham tDCS	10 session over 2 weeks	2 mA intensity delivered for 20 min; Anode electrode: left DLPFC (F3) or right DLPFC (F4) Cathodal electrode: contralateral SO	TMT (Part A and B), WCST, PCL, WMT, Stroop Test	At 1 month	Prolonged improvement of divided attention (TMT Part B)
Ferrucci et al. (59)	9 patients Sex: M = 5; F = 4 Mean age: 74.3 ± 7.9; Pharmacotherapy: Stable medication (L-dopa) regimen 2 months prior the study	Anodal cerebellar tDCS, anodal MC and sham tDCS	5 consecutive session in a week at intervals of 1 month	2 mA intensity delivered for 20 min; Anode electrode: over the right and left cerebellum/motor cortex bilaterally (C3 and C4); Cathodal electrode: right deltoid muscle	Word recall task, VAT, SRTT	At 1 week and 1 month	No improvement
Dagan et al. (60)	20 patients Sex: M = 17; F = 3 Mean age: 68.8 ± 6.8 Pharmacotherapy: Stable medication (L-dopa) regimen 1 month prior to the study	Anodal tDCS of the PMC and DLPFC simultaneously, PMC only and sham tDCS	3 sessions at intervals of 48 h	1,5 mA intensity delivered for 20 min; Anode electrode: Medial motor cortex (CZ) and left DLPFC (F3)/medial motor cortex (CZ); Cathodal electrode: not reported	Catch-Game, Go-No-Go task, Stroop Test, Staged Information Processing Speed and NeuroTrax	-	Decrease of sensitivity to interference (Stroop Test) after combined stimulation

(Continued)

TABLE 6 | Continued

Study	Participants	Procedure and brain region/s involved	Intervention for active groups	Current intensity and electrodes position according to the 10-20 EEG international system	Neuropsychological assessment/experimental cognitive tasks	Follow-up	Main findings of the active group/s at the end of the intervention
Lau et al. (62)	10 patients Sex: M = 5; F = 5 Mean age: 62.7 ± 6.6 Pharmacotherapy: antiparkinsonian medications	Anodal or sham tDCS of the DLPFC	2 sessions with an interval of 2 weeks	2 mA intensity delivered for 20 min; Anode Electrode: left DLPFC (F3); Cathodal electrode: contralateral SO	MMSE, a visual working memory task and a go/no-go test	-	tDCS is ineffective in improving cognitive tasks administered
Bueno et al. (61)	20 patients Sex: M = 8; F = 12 Mean age: 64.45 ± 8.98 Pharmacotherapy: antiparkinsonian medications	Anodal or sham tDCS of the DLPFC	2 session with a one-week interval	2 mA intensity delivered for 20 min; Anode electrode: left DLPFC (F3); Cathodal electrode: right OFC	TMT, Stroop Test, Verbal Fluency	-	Improvements in verbal fluency and sensitivity to interference
Firouzi et al. (39)	11 patients Sex: M = 8; F = 3; Mean age: 77.1 ± 4.88 Pharmacotherapy: Levodopa medication (stable regimen)	Anodal/sham tDCS intervention during the SRT task.	4 sessions with an interval of 1 week between the first and the second session and between the third and the fourth and 3 weeks between the second and the third ones.	2 mA intensity delivered for 20 min during the SRT task. Anode electrode: C3 or C4, Cathodal electrode: Fp1 when the active electrode was on C4; on Fp2 when the active electrode was on C3.	SCOPA-COG, MMSE SRT task	-	Positive effects on implicit motor sequence learning (IMSL)

DLPFC, dorsolateral prefrontal cortex; PMC, primary motor cortex; WM, working memory; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; PCL, Probabilistic Classification Learning; WMT, Working Memory task; MC, motor cortex; VAT, Visual Attention Task; SRTT, Serial Reaction Time Task; PD-MCI, Parkinson's disease-Mild Cognitive Impairment.

of dopamine neurons and by modulating functional connectivity of the corticostriatal and thalamocortical circuits of the human brain (40).

The selected studies of Boggio et al. (51, 52) and Bystad et al. (20) stimulated the medial temporal cortex in patients with AD, as a brain area critically associated with different memory performances [cf. (71, 72)]. Alterations of the medial temporal lobe which might influence visual recognition memory are well recognized in patients with AD (73, 74). Patients with AD also report a selective hypoactivation of the temporoparietal cortex (TPC) that is normally involved in word recognition memory tasks (75). Transcranial tDCS of the TPC seems to enhance such a memory process (50), too.

Despite the difficulty of drawing definitive conclusions, results from the RCTs globally show a tendency toward positive effects of tDCS for patients with AD and PD, however, it is less clear which stimulation procedure leads to the best results. Evidence-based guidelines developed by Lefaucheur et al. (76) on the therapeutic use of tDCS reported no recommendation for the efficacy of specific tDCS parameters (i.e., electrodes placement, number and timing of sessions and duration, intensity and time of stimulation), by concluding that the optimization of tDCS protocols should be better addressed in the next future to offer a more pronounced therapeutic effect also in case of patients with AD and PD. Recently, given that tDCS has showing promising clinical results, a team of experts in conducting systematic reviews of the clinical trials have concluded that such rehabilitation technique is probably effective in PD, both for motor and cognitive aspects (77).

Some studies have shown that connections between different areas of the AD brain are impaired at specific time points, and that stimulation of other brain areas not primarily associated with commonly impaired cognitive functioning could yield promising results. A fundamental aspect of AD pathophysiology is based on the dysfunction of long-range cortical networks (78). As an illustration, not only the hippocampus and the associative cerebral cortices are involved in memory processes but also the posterior parietal cortex (PPC) exerts a key role for attentional resources in supporting memory processes (79), i.e., notoriously damaged in AD. Recently, a notable investigation has shown that mechanisms of cerebellar-cortical plasticity are impaired in AD (80) too. Given its role in the higher cognitive functions, new potential therapeutic strategies should be also built up in the next future to modulate neural activity in the cerebellum.

Focus on the neurophysiological aspects of other neurostimulation techniques, such as TMS/transcranial alternating current stimulation (tACS) and EEG activity, may offer supplementary information able to deeply investigate brain circuitry modulation. For example, mechanisms of cortical plasticity have been investigated in patients with AD by TMS protocols, such as theta brust stimulation (TBS) showing a clear impairment of long-term potentiation (LTP) cortical-like plasticity and a relative sparing of long-term depression (LTD) mechanisms in AD (78). There is also evidence that spike-timing-dependent plasticity (STDP) is compromised in AD, as revealed by studies adopting paired associates stimulation (PAS) protocols (81). Similarly, some interesting studies using cerebellar continuous TBS have reported promising results that may help identifying specific neurophysiological phenotypes as that shown by a group of patients clinically diagnosed as PD with normal dopaminergic functional imaging defined as SWEED (Scans Without Evidence of Dopaminergic Deficit). Patients with SWEED present with a mild impairment in cerebello-thalamo-cortical circuit and this neurophysiological phenotype differs from the that observed in PD and dystonic patients, suggesting a distinct involvement of this pathway in the pathophysiology of disorders (82).

These observations could lead researcher to implement neurostimulation techniques exploring different sites of stimulation or to even consider multisites techniques that could give more insight on the correct parameters to be used. A recent area of interest is represented by an implementation of tDCS technique, namely, high-definition tDCS (i.e., HD-tDCS), a novel approach that uses smaller electrodes whose configuration can be optimized for targeting specific brain regions (83). Such a technique offers some advantages then conventional method, as follows: (i) it can stimulate more precisely a target cortical region; (ii) aftereffects last at least 30 min longer than those obtained with conventional tDCS; (iii) it potentially reduces the likelihood of side effects; (iv) it determines less discomfort and improves applicability in the elderly (84).

Given the relatively minor neurodegenerative changes, tDCS appears to be more promising in early phases of the disease, i.e., MCI due to AD and in the Parkinson's disease mild cognitive impairment (PD-MCI), as confirmed by preliminary investigations also when it is delivered alongside cognitive or physical training (85–88). Accordingly, it has already been documented how tDCS stimulation is less effective in patients with AD in the advanced stages of the disease (43, 89). Moreover, tDCS can modulate brain activity in a manner similar to TMS with the advantages of being easily applied and substantially safe. Our review confirms that tDCS is well-tolerated by the patients with slight side effects not frequently reported (i.e., tingling, sleepiness, mild headache, neck pain, skin redness, scalp pain, scalp burning, somnolence, and trouble concentrating). Transcranial DC stimulation is also reliably blinded by placebo (i.e., sham stimulation) in the clinical settings.

Despite emerging evidences, the larger RCTs are welcome in the next future for replicating preliminary results on patients with AD and PD and for measuring the effects on different outcomes beside cognition (i.e., psychopathological dimensions such as depression and/or apathy, health-related quality-of-life, personal and instrumental autonomy and also motor functioning for patients with PD) allowing researchers to depict a more comprehensive analysis of tDCS potential.

Cortical plasticity and connectivity result to be impaired in the neurodegenerative conditions and neurophysiological findings could provide more robust evidence about the implementation of tDCS protocols for these diseases. The optimization of tDCS protocols should also start from early response of the patient to the treatment. Future tDCS studies would also take advantage of computational models to ensure a calibration of the stimulation technique on specificity of the patient (90). Finally, tDCS should be widely delivered to patients with neurological disorders as an

at-home rehabilitation strategy under supervision of therapists, in order to improve personalized medicine purposes [cf. (91–93)].

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

DMC made the most substantial contribution in data conception, knowledge synthesis, acquisition, analysis, interpretation of data, and as well as manuscript writing. FC and RC were involved in checking for quality of the studies and risk of bias evaluation. UB and GC revised the paper for intellectual content. All the authors approved the final version of the manuscript.

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Myoelectric Arm Orthosis in Motor Learning-Based Therapy for Chronic Deficits After Stroke and Traumatic Brain Injury

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Background: Technologies that enhance motor learning-based therapy and are clinically deployable may improve outcome for those with neurological deficits. The MyoPro™ is a customized myoelectric upper extremity orthosis that utilizes volitionally generated weak electromyographic signals from paretic muscles to assist movement of an impaired arm. Our purpose was to evaluate MyoPro as a tool for motor learning-based therapy for individuals with chronic upper limb weakness.

Methods: This was a pilot study of thirteen individuals with chronic moderate/severe arm weakness due to either stroke ($n = 7$) or TBI ($n = 6$) who participated in a single group interventional study consisting of 2 phases. The in-clinic phase included 18 sessions (2x per week, 27hrs of face-to-face therapy) plus a home exercise program. The home phase included practice of the home exercise program. The study did not include a control group. Outcomes were collected at baseline and at weeks 3, 5, 7, 9, 12, 15, and 18. Statistics included mixed model regression analysis.

Results: Statistically significant and clinically meaningful improvements were observed on Fugl-Meyer (+7.5 points). Gains were seen at week 3, increased further through the in-clinic phase and were maintained during the home phase. Statistically significant changes in Modified Ashworth Scale, Range of Motion, and Chedoke Arm and Hand Activity Inventory were seen early during the in-clinic phase. Orthotic and Prosthetic User's Survey demonstrated satisfaction with the device throughout study participation. Both stroke and TBI participants responded to the intervention.

Conclusions: Use of MyoPro in motor learning-based therapy resulted in clinically significant gains with a relatively short duration of in-person treatment. Further studies are warranted.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03215771.

Keywords: stroke, traumatic brain injury, upper extremity, rehabilitation, robotics, exoskeleton device, orthotics

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INTRODUCTION/BACKGROUND

Chronic upper limb deficits after Traumatic Brain Injury (TBI) and stroke are prevalent and often severely debilitating (1). Approximately 17% of individuals with TBI (1) and upwards of 50% of individuals with stroke (2) do not fully recover upper limb function. These persistent upper limb deficits limit function and negatively impact quality of life (1, 3). Motor learning-based therapy (ML) utilizing high repetition and timely progression of task-oriented movements is one of the most effective neurorehabilitation methods available (4–6). However, implementation of ML principles is challenging because it requires a high dose of face-to-face therapy. As a result, many individuals do not fully recover and those most severely impaired see the least amount of functional return in response to interventions (7). Adjuvant technologies that facilitate ML and that are easily deployable in the current health care milieu are highly desirable, particularly for those with severe impairment. One such technology that warrants further study is the MyoPro (Myomo Inc, Cambridge MA).

The MyoPro is a customized myoelectrically controlled orthosis that utilizes volitionally generated electromyographic (EMG) signals from paretic muscles to assist movement of an individual's affected arm (8–10). The device completes the movement initiated by the user and encourages practice of coordinated movement (such as mitigating co-contraction of agonist and antagonist muscles). Both aspects are essential elements of ML (6). Previous studies of MyoPro in arm rehabilitation after stroke provide positive preliminary evidence for improvement in motor control (8–12), self-reported function (9), and perception of recovery (13). These studies offer an important framework for utilization of a myoelectrically controlled orthotic device in ML therapy, but do not fully evaluate it in a structured clinical program that includes both in-clinic and home use. As a result, gains were variable across studies, (8, 10–13) relatively modest (11, 12) or equivocal compared to task practice alone (12), and the outcomes lacked a broad spectrum of assessments (8, 13).

The purpose of the current study was to assess the use of MyoPro in ML for individuals with chronic upper limb motor impairment after either stroke or TBI. To address limitations in prior studies, we report longitudinal response to the study intervention, which included an elbow-hand version of the MyoPro, across the International Classification of Functioning (ICF) domains of impairment, function, and participation during both in-clinic therapy and home phases.

METHODS

Overview of Study Design

This was a prospective single arm mixed cohort interventional pilot study. After orthosis fitting/fabrication, individuals participated in two study phases: in-clinic therapy (9 weeks) and home phase (9 weeks) (**Figure 1**). Current clinical practice guidelines for outpatient rehabilitation for chronic stroke motor deficits suggests application of ML therapy at a minimum frequency of 45 minute sessions delivered 2 to 5 days per week for 8 weeks (14). Consistent with this, our in-clinic therapy phase consisted of 2 weekly sessions each lasting 1.5 h under the direction of a physical therapist trained in the application of motor learning-based upper limb intervention and use of the MyoPro. Sessions were divided into 45 min of training in the device and 45 min of training outside of the device. A customized home exercise program (HEP) was devised to complement in-clinic practice and consisted of in-device and out-of-device exercises tailored to the individual's needs. At the conclusion of the in-clinic phase, individuals transitioned to the home phase during which they were instructed to complete their customized HEP as prescribed. If needed, the HEP was adjusted/progressed during the testing sessions of the home phase. Outcome measures were collected during study participation as follows: at baseline (week 1); during the in-clinic phase (weeks 3, 5, 7, and 9); and during the home phase (weeks 12, 15, and 18) (**Figure 1**).

Participant Selection

Participants were recruited by word of mouth and clinician referral within the medical center and surrounding local healthcare systems. The main inclusion criteria were as follows: first ever stroke or TBI $\geq$ 6 months prior to study entry; upper limb impairment that impeded function; medically stable; cognition sufficient to participate in training; caregiver support as needed; and ability to generate detectable EMG signals of the target muscles for training. Prior to study entry, participants provided informed consent or consent was provided by their legal guardian. The study was approved and monitored by the local Institutional Review Board of the medical center.

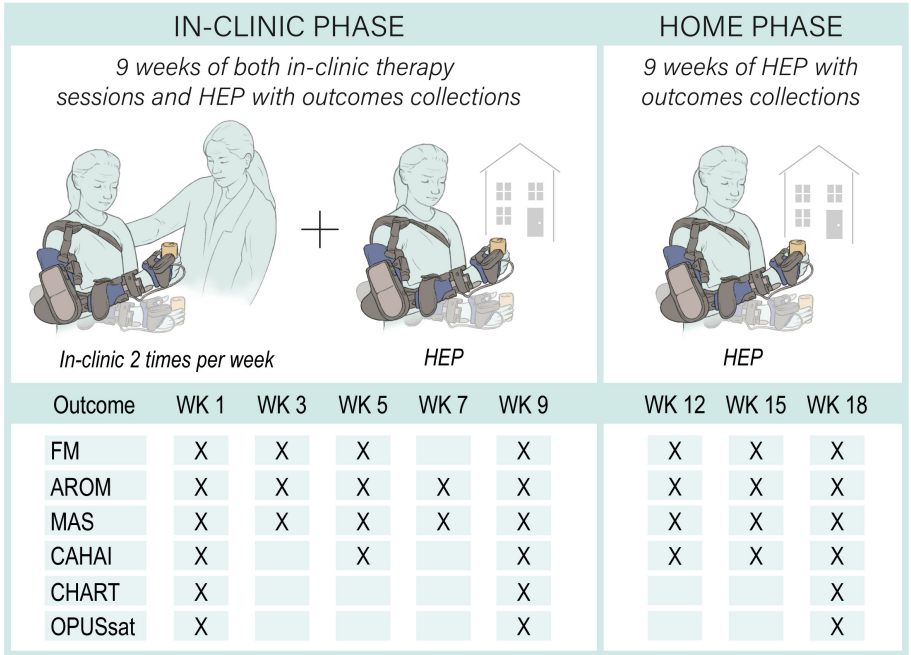
Technology

The MyoPro is a commercially available, custom-fabricated myoelectric elbow-wrist-hand orthosis (**Figure 2**). EMG sensors placed over the biceps, triceps, finger flexors and finger extensors record the user's volitionally generated EMG (**Figure 2A**). When the EMG surpasses a threshold level set by a clinician, motors within the orthosis activate to assist with completion of the desired movement (**Figure 2B**).

Orthosis Fitting/Fabrication and Monitoring

Each participant was fit with a custom MyoPro by a certified and licensed orthotist at the beginning of the study. After fitting, participants and their caregivers were trained in proper donning/doffing and operation of the device. Typically, within 2 sessions, individuals demonstrated competence with these tasks and took the MyoPro home from therapy sessions to practice during non-therapy days. Device fit was continuously monitored throughout study participation for signs of pressure or discomfort. If a participant noted any discomfort or persistent redness from device wear, adjustments were made by the treating therapist and/or orthotist.

Abbreviations: FM, Fugl-Meyer for upper limb; MAS, Modified Ashworth Scale; CAHAI, Chedoke Arm and Hand Activity Inventory; AROM, active range of motion; PROM, passive range of motion; CHART, Craig Handicap Assessment and Reporting Technique; OPUSsat, Orthotic and Prosthetic Users' Survey satisfaction module; TBI, traumatic brain injury.



Outcome	WK 1	WK 3	WK 5	WK 7	WK 9	WK 12	WK 15	WK 18
FM	X	X	X		X	X	X	X
AROM	X	X	X	X	X	X	X	X
MAS	X	X	X	X	X	X	X	X
CAHAI	X		X		X	X	X	X
CHART	X				X			X
OPUSsat	X				X			X

FIGURE 1 | Study overview. FM, Fugl-Meyer for upper limb; MAS, Modified Ashworth Scale; ROM, active range of motion; CAHAI, Chedoke Arm and Hand Inventory; CHART, Craig Handicap Assessment and Rehabilitation Tool; OPUSsat, Orthotic and Prosthetic User's Survey Satisfaction Module; HEP, home exercise program; WK, week.

Intervention

Principles of motor learning that provided the theoretical framework for training included: movement practice as close to normal as possible, high repetition, progression of challenge, part vs. whole task practice, and knowledge of results (intrinsic/extrinsic feedback) (15). Based on these principles, treatment was customized to meet the specific capabilities of each participant and consisted of a combination of MyoPro training and ML therapy. The focus of the part or whole tasks included grasp/release, hand to mouth movements, forward reaching movements, bimanual tasks, and fine motor manipulation of objects. Training within the device was progressed using a hierarchy of challenge to increase complexity of movement (4, 5, 9). Initially, single muscles were trained to activate and relax. Training was progressed to include agonist/antagonist muscle training of a single joint; individual muscle activation of contiguous joints; and finally, agonist/antagonist coordination training of contiguous joints. For example, at commencement of elbow flexion training, individuals trained activation and relaxation of the biceps muscle in isolation. Then, training progressed to using EMG from both the biceps and triceps muscles simultaneously where to flex the elbow, the user had to activate the biceps while concomitantly relaxing the triceps. Similarly, for elbow extension, the user was trained to relax the biceps while activating the triceps. Training progressed from activation of single muscles of contiguous joints, such as activating the biceps while flexing the fingers in a hand to mouth movement to, finally, training more functionally complex movements. The goal was to produce activation/relaxation of agonist/antagonist pairs across contiguous joints such as bending the elbow and grasping an object, bringing it to the mouth, and then reaching out and placing it back on the table.

Motor learning-based exercises without MyoPro followed the same motor control hierarchy (4, 5), incorporating training of movements that could not be accomplished with the device, along with those that were trained with the device. Movement quality was carefully monitored, and training practice was incrementally progressed as soon as the participant demonstrated improved ability to perform a given task or movement component. Participants were instructed to perform the home program on non-clinic days and to increase repetition as they were able to tolerate. If a participant reported any discomfort related to exercise or activity at home, the therapist altered the HEP. After conclusion of the in-clinic phase, individuals transitioned to the home phase where they continued to utilize the custom HEP. They returned to the clinic at defined intervals for testing sessions and the treating therapist conducted weekly phone calls to maintain contact with participants and answer any questions. If any issues arose (i.e., need for device setting adjustments, home exercise progression), then an appointment was scheduled, and the participant was seen in the clinic.

Outcome Measures

Data were collected according to the schedule in **Figure 1**. All measures were collected with the device doffed.

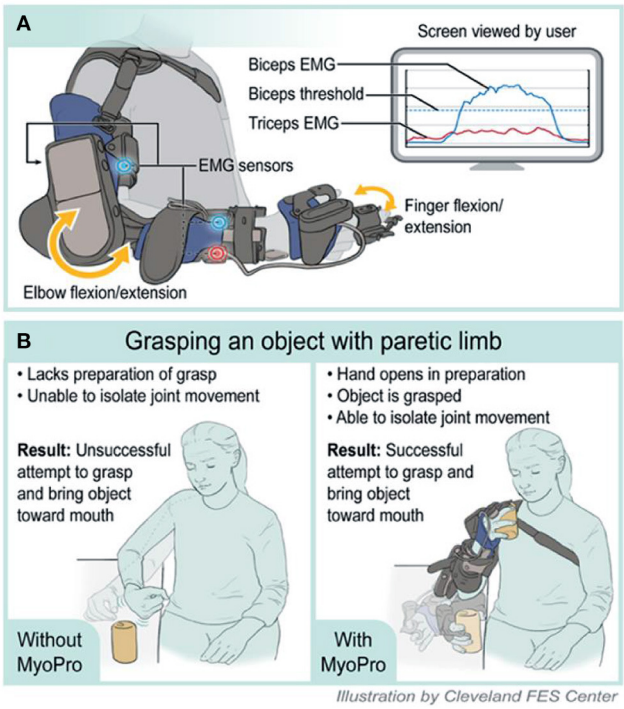


FIGURE 2 | Illustration of MyoPro use and implementation in motor learning. **(A)** Device function. **(B)** Grasping an object with paretic limb. EMG, Electromyography.

Fugl-Meyer (FM) for upper limb (the primary outcome measure) is one of the most widely used quantitative measures of motor impairment (16) with a Minimal Clinically Important Difference (MCID) of 5.25 points overall for upper limb function (16) in chronic stroke and 6 points in chronic TBI (17). Thirty-three items of movement coordination and reflex activity are scored with a 3-point Likert scale (0-66 points total) where higher scores represent less arm impairment. It has good intrarater (Intraclass Correlation Coefficient, ICC = 0.99) and interrater (ICC = 0.96) reliability for use with stroke patients (18).

Range of Motion (ROM) was assessed using standard clinical methods. Active ROM (AROM) and passive ROM (PROM) for elbow flexion/extension and wrist flexion/extension were measured using a goniometer (19). AROM was expressed as a percent of PROM, and a higher score was indicative of better performance.

Modified Ashworth Scale (MAS) was used to assess muscle tone. Using a 5-point scale, the clinician evaluates resistance to passive movement about a joint. A lower score represents less resistance to passive movement. The MAS has been widely used to quantify muscle tone following stroke. Interrater reliability of MAS for arm assessment has been reported as kappa = 0.92 or percent agreement = 97.4% (20). The following 9 muscle groups were assessed: shoulder internal rotators, biceps, triceps, pronators, supinators, wrist flexors, wrist extensors, finger flexors and finger extensors. Scores were then summed to give the overall MAS score (4).

Chedoke Arm and Hand Activity Inventory (CAHAI) was used to assess performance of activities of daily living (ADLs). This measure is suitable for populations with upper limb paresis (21) and consists of 13 functional tasks. Scoring is based on a 7-point scale (1 = unable; 7 = normal performance; maximum score is 91 points), where higher scores represent better performance of ADLs. MCID is 6.3 points in chronic stroke (22).

Craig Handicap Assessment and Rehabilitation Technique (CHART) is a life-role participation survey measuring the level of handicap using objectively observable behaviors in five dimensions: physical, social, cognitive, mobility, and occupation (23). Survey responses are combined in formulas for each domain. Although very social or active patients may score higher, the score in each domain is capped at 100 (total score range: 0–500). Higher scores represent better self-reported participation.

Orthotic and Prosthetic User's Survey satisfaction module (OPUSsat) is an 11-item patient-reported survey that assesses satisfaction with device using a 5-point Likert scale (24). Satisfaction with device is the sum of the scores (score range: 11–55), where higher scores indicate better satisfaction.

Orthosis utilization is the number of full and partial repetitions of elbow flexion/extension and hand open/close that were recorded by software within the MyoPro while the participant used the device. Purposeful movement cycles, defined as an EMG signal followed by 30° of motion and 1 s of no motion, were logged by the MyoPro motors.

Self-reported changes during study participation were recorded by study staff. Participants were queried at the beginning of intervention sessions and during testing visits of the home phase as to whether they experienced any changes in arm performance during their daily lives.

Statistical Analysis

First, all variables and outcomes were examined univariately for association with injury type (stroke or TBI). Continuous variables were evaluated using Welch two sample *t*-tests, not assuming equal variance between the injury type groups; categorical variables were evaluated using Fisher's exact tests. Longitudinal linear mixed effects models were then fit to model the trajectory of outcomes through all time points. Two-sided significance level was set at 0.05 given only a single primary outcome was identified for this pilot study. For *post-hoc* analyses comparing changes from baseline with zero at different time points, *p*-values were adjusted for multiple testing using the Holm-Bonferroni correction. Longitudinal models included fixed effects for time (all the time points that data were collected during in-clinic and home phases), adjusted for corresponding baseline value and injury type, and random effects for subjects to account for within-subject correlation. Serial correlations among same subject outcomes were modeled. Covariance model selection was based on the model fit statistic-2 Res Log Likelihood. Analyses were performed using SAS Software (SAS Institute, Inc., Version 9.4, Cary, NC).

TABLE 1 | Participant characteristics and device use at home.

Subject	Age	Sex	Months post injury	Affected arm	Dominant arm	Injury type	Device use at home (hrs)
1	74	male	118	right	right	Stroke	48.1
2	49	female	15	left	right	Stroke	2.3
3	82	male	48	right	right	Stroke	35.7
4	69	female	18	left	right	Stroke	12.8
5	59	female	23	left	right	Stroke	52.0
6	56	female	67	left	right	Stroke	52.7
7	69	female	20	right	left	Stroke	147.0
Stroke Mean (SD) or count %	**65.4 (11.4)**	**71.4 (% female)**	**44.1 (37.8)**	**42.9 (% right)**	**85.7 (% right)**		**50.1 (47.0)**
8	24	male	41	left	right	MVA	NC
9	25	male	89	left	right	GSW	653.1
10	52	female	344	left	left	MVA	69.6
11	43	female	354	right	right	MVA	50.2
12	29	male	29	left	right	GSW	1.9
13	27	female	125	left	right	GSW	35.1
TBI Mean (SD) or count %	**33.3 (11.5)**	**50.0 (% female)**	**163.7 (147.7)**	**16.7 (% right)**	**83.3 (% right)**		**162.0 (275.6)**
Total cohort Mean (SD) or count %	**50.6 (19.9)**	**61.5 (% female)**	**99.3 (116.8)**	**30.8 (% right)**	**84.6 (% right)**		**96.7 (179.3)**
P-value for two-group comparison	**<0.001**	**0.59**	**0.11**	**0.56**	**1.00**		**1.00**

TBI, traumatic brain injury; MVA, motor vehicle accident; GSW, gunshot wound; NC, not collected.

RESULTS

Participant Characteristics, Baseline Scores

Sixteen individuals with chronic stroke ($n = 8$) or TBI ($n = 8$) were enrolled in the study. Thirteen individuals completed the study (stroke = 7; TBI = 6). Three participants withdrew due to issues unrelated to the study protocol. Participant's characteristics are provided in **Table 1**. The TBI cohort was younger than the stroke cohort ($p < 0.001$). Other baseline characteristics were not significantly different between the two injury type cohorts.

Table 2 lists baseline scores for all outcome measures by each participant and the means (SD) by injury type and for the whole cohort. The stroke cohort was more impaired than the TBI cohort at baseline according to AROM for wrist flexion/extension, and shoulder flexion ($p = 0.009$, 0.009 and 0.04, respectively). FM was marginally better but not statistically different in the TBI cohort ($p = 0.07$) compared with the stroke cohort. Baseline motor function (according to CAHAI) was significantly higher for the TBI cohort compared to the stroke cohort ($p = 0.03$).

Trajectory of Change Over the Course of the Study

Changes from baseline for all outcome measures over the course of study participation are provided in **Table 3**. **Figure 3** shows the results of longitudinal mixed model analysis adjusted for baseline score and injury type. *Post-hoc* analysis was used to assess for differences between the time points. Given sample size constraints, we only adjusted for injury type and baseline score, understanding that interpretation of results related to the injury type are intertwined with age differences.

FM for Upper Limb (FM)

The F test for overall differences among changes from baseline across time points was significant for FM ($F_{5,60} = 11.42$, $P < 0.001$). Statistically significant changes *from baseline* were observed by week 3 of the in-clinic phase ($p = 0.03$). FM scores continued to improve after week 3 through the end of the clinic phase (week 9, $p < 0.001$) and were maintained during the home phase (weeks 12, 15, and 18, $p < 0.001$, **Table 3**, **Figure 3A**). Compared with week 5, statistically significant improvements were observed at weeks 9, 12 ($p < 0.001$) and 18 ($p = 0.01$). Neither baseline FM score nor injury type were associated with change in FM in response to therapy. A spaghetti plot of the individual participant data for the FM is provided in **Figure 4A**.

MAS

The F test for overall differences among changes from baseline to all time points was significant for MAS ($F_{6,71} = 11.80$, $P < 0.001$). MAS improved by week 3 ($p < 0.001$) and remained reduced through the end of the home phase ($p < 0.001$, **Table 3**, **Figure 3B**). Individuals with higher muscle tone at baseline demonstrated greater improvement in MAS score [estimate (95% CI) = −0.12 (−0.20, −0.04), $p = 0.0023$]. Injury type did not influence change in MAS in response to therapy.

AROM

A significant F test for overall differences from baseline across time points was found only for wrist extension AROM ($F_{6,59} = 3.54$, $P = 0.0046$). However, after adjustment for multiple testing, *post-hoc* pairwise analysis among time points did not show any significant results for wrist extension AROM. There was

TABLE 2 | Baseline outcome measure scores.

Subject	FM	MAS	Elbow extension AROM	Elbow flexion AROM	Shoulder abduction AROM	Shoulder flexion AROM	Wrist extension AROM	Wrist flexion AROM	CAHAI	CHART	OPUSsat
1	32	9.5	55.2	55.2	100.0	57.1	18.2	18.2	30	331	70
2	23	10.5	58.1	58.1	22.2	33.3	0.0	0.0	17	271	NA
3	28	4	84.0	84.0	94.4	75.0	30.8	30.8	22	361.5	42
4	26	7.5	53.6	53.6	61.1	40.0	0.0	0.0	16	218	NA
5	26	11.5	39.3	39.3	72.2	39.1	0.0	0.0	25	497	47
6	19	5.5	15.4	15.4	72.2	43.5	0.0	0.0	16	244	66
7	16	11	0.0	0.0	61.1	42.3	0.0	0.0	14	329.8	86
Stroke mean (SD)	**24.3 (5.4)**	**8.5 (2.9)**	**43.6 (28.3)**	**43.6 (28.3)**	**69.1 (25.6)**	**47.2 (14.3)**	**7.0 (12.5)**	**7.0 (12.5)**	**20.0 (5.9)**	**321.8 (92.9)**	**62.2 (17.9)**
8	18	13.5	22.2	22.2	62.2	41.7	NA	NA	16	291.9	60
9	37	11	97.9	97.9	100.0	93.1	55.2	62.1	33	293	45
10	47	8	m	m	m	m	m	m	61	500	22
11	26	7	75.9	75.9	94.4	65.4	46.9	46.9	31	216	28
12	46	3.5	96.6	93.1	100.0	84.6	74.2	74.2	59	394	35
13	36	9	87.1	87.1	100.0	92.9	30.0	30.0	45	458	60
TBI mean (SD)	**35 (11.3)**	**8.7 (3.4)**	**75.9 (31.3)**	**75.2 (30.8)**	**91.3 (16.5)**	**75.5 (22.0)**	**51.6 (18.4)**	**53.3 (19.1)**	**40.8 (17.5)**	**358.8 (109.7)**	**41.7 (16.1)**
Total cohort mean (SD)	**29.2 (10.0)**	**8.6 (3.0)**	**57.1 (32.7)**	**56.8 (32.3)**	**78.3 (24.3)**	**59.0 (22.4)**	**23.2 (26.5)**	**23.8 (27.4)**	**29.6 (16.2)**	**338.9 (98.5)**	**51.0 (19.3)**
***P*-value for two-group comparison**	**0.07**	**0.93**	**0.10**	**0.11**	**0.10**	**0.04**	**0.009**	**0.009**	**0.03**	**0.53**	**0.08**

FM, Fugl-Meyer for upper limb; MAS, Modified Ashworth Scale; AROM, active range of motion calculated as percent of passive range; CAHAI, Chedoke Arm and Hand Inventory; CHART, Craig Handicap Assessment and Rehabilitation Tool; OPUSsat, Orthotic and Prosthetic Users' Survey Satisfaction Module; m, missing.

a statistically significant improvement from baseline in AROM for elbow flexion and elbow extension (**Table 3**, **Figures 3C,D**). Elbow flexion AROM improved by week 5 ($p < 0.001$) and was maintained through the end of the home phase ($p < 0.001$ for weeks 7, 9, 12, 15 and $p = 0.0021$ for week 18). Elbow extension AROM improved by week 3 ($p = 0.048$) and was maintained through the end of the in-clinic phase ($p = 0.0063$, 0.0091 and 0.018 for weeks 5, 7, and 9, respectively). There were no changes in AROM for shoulder abduction, shoulder flexion, wrist flexion or wrist extension (**Table 3**). For individuals with higher baseline AROM for elbow extension, their improvement in AROM was less [estimate (95% CI) = −0.23 (−0.46, −0.01), $p = 0.045$]. Similarly, individuals with higher baseline AROM for elbow flexion, their improvement in AROM was less [estimate (95% CI) = −0.36 (−0.42, −0.30), $p < 0.001$]. Injury type was not associated with change in ROM in response to therapy.

CAHAI

The F test for overall differences among changes from baseline of all time points was significant for CAHAI ($F_{4,48} = 3.05$, $P = 0.026$). Statistically significant improvement from baseline was noted for CAHAI by week 3 ($p < 0.001$) and scores continued to improve through the end of the home phase ($p < 0.001$, **Table 3**, **Figure 3E**). Compared with week 5, statistically significant improvements were observed at the end of home phase ($p = 0.028$). Neither baseline CAHAI score nor injury type influenced change in CAHAI in response to therapy.

Chart

There were no significant changes in CHART ($p = 0.10$ and 0.074 for week 9 and 18, respectively, **Table 3**). Neither baseline CHART score nor injury type influenced change in CHART score in response to therapy.

OPUSsat

A statistically significant improvement from baseline in OPUSsat was observed by the end of the in-clinic phase (week 9, $p < 0.001$) and was maintained at the end of the home phase (week 18, $p < 0.001$, **Table 3**, **Figure 3F**). Higher baseline score for OPUSsat was associated with lower improvement [estimate (95% CI) = −0.9 (−1.6, −0.2), $p = 0.01$]. Injury type did not influence change in OPUSsat score in response to therapy.

Orthosis Utilization

Use of the device at home was similar during the two study phases (**Table 4**). There was no statistically significant difference between the TBI and stroke cohorts, although individual utilization varied (**Table 1**, last column). Change in FM plotted against the individual participant's orthosis utilization during study participation is provided in **Figure 4B**.

TABLE 3 | Outcome measure changes at different time points (mean (SD)).

		Week 3	Week5	Week 7	Week 9	Week 12	Week 15	Week 18
FM	**Stroke**	2.6 (3.4)	3.9 (4.1)		6.0 (3.9)	7.6 (3.8)	6.6 (3.9)	6.7 (4.4)
	TBI	4.3 (4.2)	6.7 (3.4)		8.7 (4.0)	9.2 (4.2)	7.3 (3.2)	8.3 (2.8)
	All	3.4 (3.7)	5.2 (4.0)		7.2 (4.0)	8.3 (3.9)	6.9 (3.5)	7.5 (3.7)
MAS	**Stroke**	−1.9 (0.9)	−1.7 (1.6)	−1.5 (1.5)	−2.1 (1.6)	−1.9 (0.8)	−1.6 (1.1)	−1.9 (1.1)
	TBI	−2.0 (0.9)	−2.5 (1.5)	−2.5 (1.7)	−3 (1.9)	−2.8 (1.4)	−2.5 (2.7)	−2.8 (1.4)
	All	−1.9 (0.9)	−2.1 (1.5)	−2.0 (1.6)	−2.5 (1.7)	−2.3 (1.2)	−2.0 (2.0)	−2.4 (1.3)
Elbow ext. AROM	**Stroke**	9.1 (10.6)	19.3 (16.1)	12.8 (8.7)	18.6 (15.4)	14.7 (23.1)	14.6 (17.2)	19.5 (26.7)
	TBI	11.3 (16.1)	6.5 (7.9)	1.4 (5.8)	0.8 (5.3)	4.7 (6.1)	−0.3 (7.1)	10.4 (23.3)
	All	10.0 (12.5)	14.7 (14.7)	8.7 (9.4)	12.1 (15.2)	11.1 (18.9)	9.2 (15.8)	15.8 (24.7)
Elbow flex. AROM	**Stroke**	9.1 (10.6)	25.4 (15.7)	17.9 (10.3)	25.0 (15.6)	26.2 (20.6)	21.5 (19.8)	26.2 (26.9)
	TBI	12.0 (15.5)	7.4 (7.1)	2.3 (4.2)	1.7 (4.6)	5.5 (5.4)	0.1 (5.4)	11.1 (22.9)
	All	10.3 (12.3)	18.9 (15.7)	12.2 (11.4)	16.5 (17)	18.7 (19.3)	13.7 (19)	19.9 (25.4)
Shld. abd. AROM	**Stroke**	−2.4 (18.1)	8.7 (16.9)	7.9 (17.2)	3.2 (13.6)	15.9 (21.6)	11.9 (26.1)	10.2 (28.8)
	TBI	1.4 (2.8)	1.4 (2.8)	1.4 (2.8)	1.4 (2.8)	1.4 (2.8)	1.4 (2.8)	−2.4 (8.9)
	All	−1.0 (14.2)	6.1 (13.7)	5.6 (13.8)	2.5 (10.6)	10.6 (18.3)	8.1 (21.0)	4.4 (22.2)
Shld. flex. AROM	**Stroke**	2.2 (12.2)	4.3 (15.8)	6.6 (11.1)	2.6 (8.7)	1.6 (12.8)	5.7 (9.7)	1.7 (11.8)
	TBI	9.5 (2.8)	6.5 (6.9)	8.6 (6.4)	6.7 (6.0)	6.4 (7.5)	2.2 (7.1)	0.1 (12.6)
	All	4.8 (10.3)	5.1 (12.9)	7.3 (9.3)	4.1 (7.8)	3.3 (11.0)	4.4 (8.7)	0.9 (11.6)
Wrist ext. AROM	**Stroke**	10.8 (13.8)	9.6 (10.4)	18.1 (15.2)	14.0 (8.0)	9.5 (10.6)	10.3 (11.9)	19.8 (13.4)
	TBI	−9.5 (9.9)	3.1 (5.3)	0.9 (9.7)	7.2 (8.5)	5.1 (12.9)	−6 (12.0)	5.0 (8.6)
	All	3.4 (15.7)	7.2 (9.2)	11.9 (15.6)	11.5 (8.5)	7.9 (11.1)	4.4 (14.0)	13.9 (13.6)
Wrist flex. AROM	**Stroke**	9.8 (14.3)	9.6 (10.4)	17.2 (16.2)	14.2 (9.8)	11.4 (9.0)	15.1 (13.6)	13.8 (12.4)
	TBI	−11.2 (6.6)	1.4 (5.7)	0.9 (9.7)	5.5 (9.8)	−1.6 (13.1)	−7.8 (14.6)	3.3 (9.8)
	All	2.2 (15.8)	6.6 (9.6)	11.3 (15.9)	11.0 (10.3)	6.7 (12.0)	6.8 (17.6)	9.6 (12.1)
CAHAI	**Stroke**		5.9 (3.8)		5.7 (3.1)	6.4 (3.7)	6 (2.2)	8.1 (4.7)
	TBI		4.2 (4.1)		9.5 (5.0)	8.2 (5.1)	10.3 (7.3)	9.7 (6.6)
	All		5.1 (3.9)		7.5 (4.4)	7.2 (4.3)	8 (5.5)	8.8 (5.5)
OPUSsat	**Stroke**				15.8 (23.7)			15.2 (24.5)
	TBI				32.7 (19.6)			36.3 (20.0)
	All				25.0 (22.2)			26.7 (23.7)
CHART	**Stroke**				23.1 (26.4)			55.5 (81.5)
	TBI				6.0 (30.5)			13.0 (26.8)
	All				15.2 (28.5)			35.9 (64.1)

FM, Fugl-Meyer for upper limb; MAS, Modified Ashworth Scale; AROM, active range of motion calculated as percent of passive range; CAHAI, Chedoke Arm and Hand Inventory; CHART, Craig Handicap Assessment and Rehabilitation Tool; OPUSsat, Orthotic and Prosthetic Users' Survey Satisfaction Module; ext., extension; flex., flexion; shld., shoulder; abd., abduction.

Self-Reported Changes During Study Participation

Participants reported several changes in their daily activities (**Table 5**). Improvements were reported with selfcare, feeding, home making, and mobility.

No serious device or study related events were observed and the device was well-tolerated by all participants.

DISCUSSION

This study provides encouraging results of using MyoPro, a myoelectrically controlled elbow-wrist-hand orthosis, as a tool in ML therapy for individuals with chronic arm deficits after stroke and TBI. Significant improvements were observed at the levels of impairment and function. Injury type and baseline impairment did not influence response to the study intervention. The MyoPro was well-tolerated, with no adverse events occurring during study participation.

Clinically Meaningful Changes Utilizing a Short Face-to-Face Readily Deployable Therapy Protocol

High dose of rehabilitation is critical to improve motor performance (6), and it is likely that a dose that exceeds what is currently provided in clinical practice is needed (25). Furthermore, high dose must be combined with other key motor learning principles such as movement as close to normal as possible, knowledge of performance, and precise grading of progression to maximize its effectiveness (6). Studies have reported application of ML guided by these important principles

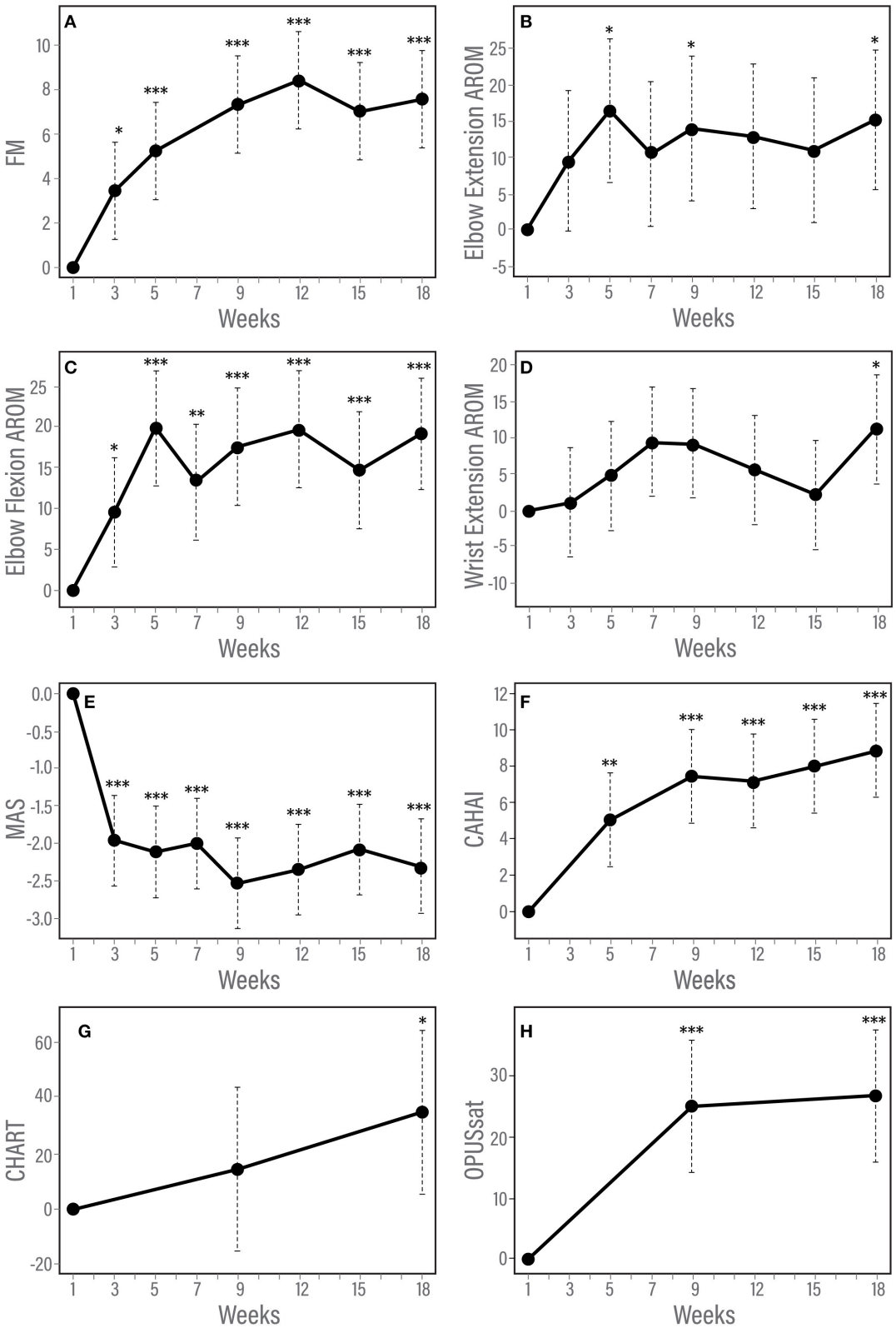


FIGURE 3 | (A–H) Trajectory of changes in response to therapy according to measures of impairment, function and satisfaction. Results of longitudinal linear mixed effects model adjusted for baseline score and injury type. **(A)** Fugl-Meyer for upper limb, **(B)** Modified Ashworth Scale, **(C)** Elbow flexion active range of motion, **(D)** Elbow extension active range of motion, **(E)** Chedoke Arm and Hand Activity Inventory, and **(F)** Orthotic and Prosthetic Users's Survey satisfaction module. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

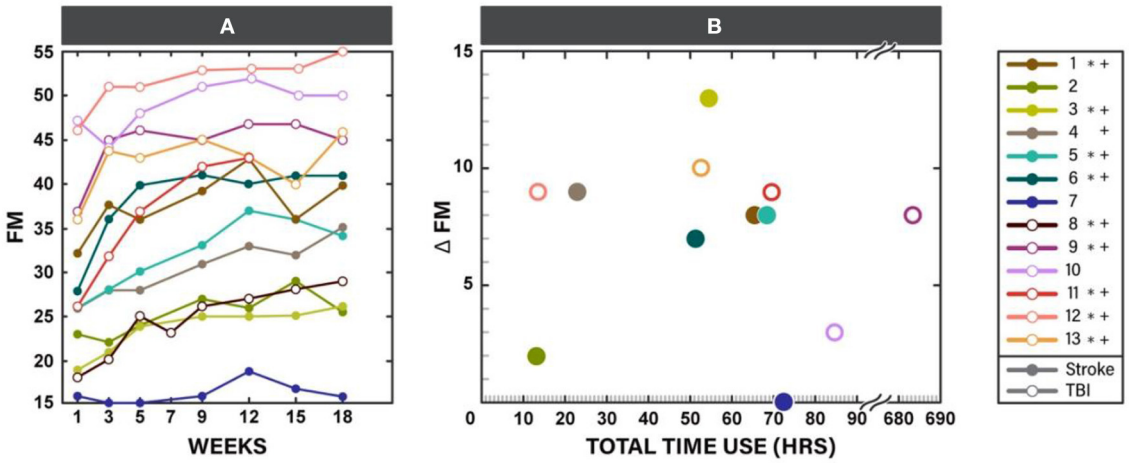


FIGURE 4 | Fugl-Meyer for upper limb (FM) scores for each participant throughout the study participation **(A)** and scatter plot of change in FM at the end of the study (week 18) vs. total time of Myopro use **(B)**. * Marks Minimal Clinically Important Difference (MCID) for FM (5.25 points) at the end of the in-clinic phase (week 9); + marks MCID for FM at the end of the home phase (week 18).

TABLE 4 | Orthosis utilization for the whole cohort.

In-clinic phase		
	Hours used in clinic	17.1 (5.4)
	Number of days used in clinic*	23.25 (2.5)
	Hours used at home	49.5 (86.4)
	Number of days used at home	27.0 (17.1)
	Hours/day at home	1.4 (1.5)
	Elbow Reps/day at home	85.8 (99.2)
	Hand Reps/day at home	194.5 (83.4)
Home phase		
	Hours	47.2 (93.8)
	Number of days	23.0 (23.3)
	Hours/day	1.5 (2.2)
	Elbow Reps/day	88.5 (91.5)
	Hand Reps/day	189.6 (127.1)
Total		
	Hours	113.9 (183.9)
	Elbow Reps	6847.3 (6785.4)
	Hand Reps	14493.8 (10066.0)

Including testing sessions.

(4, 5, 26). These studies demonstrated clinically significant improvement in individuals with moderate to severe chronic motor deficits after stroke in response to ML (4, 5, 26). However, these studies employed much higher dosing of in-person training compared to the current work. For example, after 90 h of face-to-face motor learning-based training, in a group of moderately impaired chronic stroke survivors (modified FM = 26 at baseline), median gain of FM was 6 points at the end of the intervention and 11 points at 6-month follow up (26). Following 300 h of in-person group motor-learning based training, there was a 9.7 point change on FM (4). At the 150 h midpoint, Daly et al. (4) reported a 5 point gain on FM, with additional improvement as therapy continued for another 150 h similar to the McCabe et al. study (4, 5). Thus, high doses of ML in-person therapy that carefully apply key motor learning principles can achieve clinically meaningful gains in motor abilities even in presumably plateaued individuals with chronic moderate to severe deficits. Unfortunately, the high-dose in-person therapeutic approach is challenging to implement in the current clinical milieu and alternative methods are desirable. Our protocol included only 27 h of face-to-face therapy, yet the results were similar to the studies with 90–300 h of in-person training (4, 5, 26). Though our cohort was more heterogenous in both injury type and level of baseline FM, it is encouraging that results were achieved with less face-to-face therapy hours.

Ability to achieve significant results with a clinically manageable amount of in-person contact hours is of great interest to the rehabilitation community. In fact, MyoPro has already been tried in clinical practice as a rehabilitation tool. In an uncontrolled observational study of MyoPro use in a group clinical setting, individual's chronic arm impairment after stroke demonstrated clinically meaningful improvement on FM of 9 points (8), however treatment application was highly varied across the individuals and home use was not tracked. The data collection and therapy delivery in this study aligned with those of general clinical practice; where data collection was not conducted in a systematic manner (i.e., collected at different timepoints based on the individual's performance) making group comparison challenging (8). Importantly, MyoPro appears to be easily deployed as a therapy tool in clinical practice.

We observed improvements across a spectrum of domains, i.e., impairment and function. The life role participation measure had a non-statistically significant trend toward improvement. The gain of 7.5 points on FM, an impairment measure, was in line with MCID for both stroke and TBI populations (17, 27). A statistically significant decrease in muscle tone according to

TABLE 5 | Self-reported improvements in arm impairment and functional use.

Categories	Proportion of participants reporting	Examples of self-reported changes
Impairment	12/13	Increased grip strength Decreased stiffness
		Increased sensory awareness
		Emergence of finger movement/extension (e.g., pincer grasp)
Self-care	4/13	Ability to zip coat
		Holding toothbrush in hand instead of between legs
		Putting on deodorant
		Holding shower hose during bathing
Feeding	4/13	Using spoon
		Eating finger foods
		Drinking from a cup or bottle
		Peeling a grapefruit
Home making	9/13	Answering the phone
		Folding laundry
		Opening the refrigerator door
		Winding up an extension cord
		Carrying a paint can downstairs
		Opening a garbage bag
		Carrying a bag of grapes
		Getting a knife out of the drawer
		Washing dishes
		Feeding dog treats
Mobility	3/13	Maneuvering wheelchair more independently in the home environment
		Easier to walk up the stairs due to improved control of grasp on the railing
		Ability to maintain grasp on walker during walking

MAS was observed in the first few weeks of in-clinic therapy and maintained for the duration of study participation. Though no definitive MCID value has been established for MAS in chronic stroke, a recent study of individuals undergoing rehabilitation attempted to interpret change on MAS in terms of clinical importance (28). It was found that a 0.76 point decrease in summed MAS score (consisting of elbow, wrist and finger flexors) was clinically significant in a group of 150 individuals followed longitudinally after stroke. In our cohort, we observed a decrease of 2 points in summed MAS of 9 muscle groups. While direct comparison with the clinical significance value cannot be made, it is encouraging that we observed a value exceeding that benchmark. At the level of function, statistically significant improvement in CAHAI was observed at the end of the in-clinic phase and continued into the home use phase. The mean improvement on CAHAI at the end of the in-clinic (7.4 points) and home phases (8.8 points) exceeded the established Minimal Detectable Change value of 6.3 points (22). On measures of satisfaction with device, there was statistically significant improvement in OPUSsat scores at the end of the in-clinic phase that was maintained at the end of the home phase. Improvement across the domains of impairment, function and satisfaction lends further support that this therapeutic approach is likely to be beneficial in the chronic phase of neurorecovery.

Our cohort was heterogeneous in level of impairment (baseline FM ranging 16–47) and included different types of injury (stroke and TBI). Furthermore, there was an age difference, with the TBI group younger than those with stroke. However, improvement was observed among individuals regardless of these factors. More treatment options exist for those with mild impairment after neurological injury (29) compared to those with severe deficits. Identification of clinically deployable approaches to treat the most severely impaired individuals are greatly needed (7). With this combination approach, individuals in the severe category demonstrated they could attain clinically meaningful improvement according to FM. Additionally, effective treatment methods that could be applied with different types of neurological diseases are desirable. We obtained similar results regardless of injury type (stroke vs. TBI) indicating in this preliminary study that the treatment approach was effective across diagnoses. Further studies are needed to test this approach in a controlled trial, but our current results are promising.

Change in Motor Impairment and Relationship to Device Utilization

Practice patterns with the device varied within the cohort. Seven participants recorded orthosis utilization of approximately 50–70 h during study participation. Six out of these seven individuals had FM improvement that reached clinical significance. However, participants 4 and 12 also had clinically significant improvement on FM with only 10–25 h of orthosis utilization. Participant 4 presented with weakness, however early on during training she was able to regain the ability to activate her finger extensors outside of the device. Once she realized she was able to do this, she began using her hand in a more functional way and this may have contributed to her improvement on FM. Participant 12 had sufficient baseline motor function necessary to perform good quality motor task training outside of the orthosis and thus improved well on FM. Participant 9 demonstrated significantly higher device utilization than any of the other participants (over 600 h). While this participant had clinically significant improvement on FM, based on the relatively large amount of orthosis utilization it might be reasonable to expect change to be even greater. However, this participant reported wearing the device functionally throughout the day rather than continuously practicing the HEP with the device during the hours of wear. Lastly, participant 7 with severe motor impairment at baseline did not demonstrate change in FM despite having relatively high device utilization. The underlying reason why this participant did not improve on FM in the same manner as others is unknown, however it is possible that other impairments such as high tone may have impeded performance. In future studies, understanding predictors of response to intervention will allow for targeting of an intervention to those most likely to respond.

Motor Learning-Based Therapy Principles Implemented Using Myoelectrically Controlled Device

Technological advancements within the rehabilitation field are occurring at an unprecedented pace and the options available to patients and clinicians have expanded greatly. It is incumbent upon the rehabilitation research community to identify technologies that are most likely to enhance current training methods.

MyoPro is the only commercially available assistive mechatronic upper limb device that is wearable, portable, and acts at 2 joints (29). Specific attributes of MyoPro make it an attractive technology to pair with ML. First, it is patient controlled. That is, the patient must generate volitional EMG for the device to assist with movement. Second, it is highly adjustable and portable. Settings can be incrementally adjusted to ensure adequate challenge during a given exercise and training is not constrained to activities in a stationary position (e.g., patients can wear the device and move about their environment to work on complex functional motor tasks). Training complexity can be progressed within the device. Initially, individuals may be able to control only a single muscle at a time. As they improve, the device can then be used to train coordination of multiple muscles to produce a functional movement. Third, it encourages patient-driven movement at high repetition with consistent repeatability. Motors within the device activate only when the individual's volitionally generated EMG reaches a threshold level; this then activates the device to assist the patient to complete a movement. The user can perform multiple repetitions of upper limb movement that may otherwise not be possible. This is particularly beneficial when trying to encourage high quality movement in the home setting for those with more severe deficits.

These special MyoPro attributes helped implement the three main motor-learning principles (repetition, close to normal movement, and task specific practice) and achieve clinically meaningful gains with only 27 h of a face-to-face therapy protocol. Specifically, the device facilitated implementation of progressive motor-learning principles even for those with severe impairment. Also, the device provided the ability to have meaningful practice of coordinated movement not only in clinic, but also at home. And, finally, the device motivated high-repetition practice. That is, participants experienced the movement when they volitionally attempted to activate a target muscle that otherwise would not occur (**Figure 1**). Therefore, the combination of therapist guided training with the device, motor learning during in-clinic practice, and the use of a complimentary individualized HEP using the device may have contributed to the current results approaching those of prior higher-dosed interventions (4, 5).

Maintenance of Functional Gains

We observed maintenance of the achieved improvement through the home phase on all outcome measures. The maintenance of gains on FM at the end of in-clinic phase was similar to the maintenance of gains in other higher-dose studies (4). It is clinically assumed that maintenance of improvements is dependent on the level of impairment. In other words, individuals who are not too severe and able to incorporate their gains functionally in daily activity will maintain and continue to improve. The MyoPro provides meaningful continuous practice for those with severe deficits, which can be implemented in their own home setting.

LIMITATIONS

While the results are encouraging, this study has several limitations. The sample size was small, no blinding was employed, and no comparison group was included. This curtails generalization of the results. However, we saw changes across impairment and function that deserve further study with a more rigorously controlled study design. Furthermore, this was a cohort of mixed diagnoses and heterogenous in terms of level of impairment. Regardless, both cohorts demonstrated response to the intervention.

CONCLUSIONS

MyoPro might be a useful tool for ML in individuals with chronic stroke and TBI. Reduction in impairment, gains in function, and satisfaction with the device were observed in response to the intervention despite a lower dose of face-to-face therapy than prior studies. Further study using a randomized controlled design is warranted.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study involving human subjects was reviewed and approved by the Louis Stokes Cleveland VA Medical Center Institutional Review Board. The participants or their legal guardians provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SP, SF, JM, and MS: conceptualization, methodology, and project administration. MS, JM, SP, SF, ZC, and CT: formal analysis. JM, MS, JN, and SP: investigation. SP, SF, JM, AS, and MS: data curation. SP and JM: writing—original draft preparation. JM, SP, SF, MS, AS, JN, ZC, and CT: writing—review and editing. SP and SF: supervision. SF: funding acquisition. All authors contributed to the article and approved the submitted version.

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

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Efficacy of Transcranial Direct Current Stimulation Over Dorsolateral Prefrontal Cortex in Patients With Minimally Conscious State

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Background: The treatment of patients in a minimally conscious state (MCS) remains challenging. Transcranial direct current stimulation (tDCS) is a non-invasive therapeutic method in treating neurologic diseases by regulating the cortical excitability. The aim is to investigate the effect of tDCS in patients with MCS in this study.

Methods: Eleven patients in MCS were enrolled in the study. All the patients received 5 daily sessions of 20-min sham tDCS, followed by 10 sessions of 20-min real tDCS. The anodal electrode and cathodal electrodes were placed over the left dorsolateral prefrontal cortex (DLPFC) and the right eyebrow, respectively. Assessment of Coma Recovery Scale-Revised (CRS-R) scores and resting-state functional MRI (rs-fMRI) scans was conducted three times in each patient: before tDCS (baseline, T0), post-sham tDCS at week 1 (T1), and post-real tDCS at week 2 (T2). The whole-brain functional connectivity (FC) was obtained by bilaterally computing FC from six seed regions: precuneus, middle frontal gyrus, supplemental motor area, angular gyrus, superior temporal gyrus, and occipital lobe. One-way repeated measure ANOVA was used to compare the differences of CRS-R scores and FC at T0, T1, and T2. The false discovery rate correction of $p < 0.001$ was adopted for controlling multiple comparisons in FC analysis.

Results: Five patients with MCS showed obvious clinical improvement represented by increased CRS-R scores post- 2-week real tDCS. The CRS-R scores did not change post- 1-week sham treatment. No side effects were reported during the study. The FC of the bilateral supplementary motor area, right angular gyrus, and right superior temporal gyrus were significantly enhanced after 2-week real tDCS compared with that after 1-week sham-tDCS. In addition, FC of bilateral occipital lobe and right precuneus were significantly enhanced post- 2-week real tDCS compared with the baseline.

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Conclusion: Our findings indicated that tDCS over DLPFC could serve as a potentially effective therapy for improving the consciousness state in patients with MCS. The FC in rs-fMRI can be modulated by tDCS at both the stimulation site (left DLPFC) and the distant regions.

Keywords: minimally conscious state, transcranial direct current stimulation, coma recovery scale-revised score, functional connectivity, left dorsolateral prefrontal cortex

INTRODUCTION

Minimally conscious state (MCS) is a disorder of consciousness (DoC), showing a partial retention of consciousness of self or environment, usually caused by neurological diseases, such as brain trauma, post-anoxic encephalopathy, and cerebrovascular accident tumor (1, 2). As MCS has the potential of continuous improvement and could attain favorable outcomes, the primary therapeutic goal of MCS is to promote arousal and awareness by pharmacological and non-pharmacological treatments (3). Even though many different pharmacological interventions have been used to date, the evidence for their effectiveness is limited (2). Therefore, research on non-pharmacological strategies for improving arousal outcome in MCS is highly warranted (2, 4). Although traditional non-pharmacological strategies, such as physical therapy and sensory stimulation, could promote arousal, to some extent, they cannot promote the recovery of the damaged consciousness-related neural networks in MCS (5). With growing understanding of the neural network changes of consciousness disorders, the novel rehabilitation method, which directly modulates the cortical excitability and neural network, provides new opportunities for the treatment of MCS (6).

Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique that can modulate cortical excitability (7). It has been used in treating neurological and psychiatric diseases, including Alzheimer's disease, stroke, and Parkinson's disease (8–10). Anodal stimulation of tDCS in left dorsolateral prefrontal cortex (DLPFC) has been shown to improve cognitive abilities in healthy individuals as well as patients with stroke (5). However, few studies have focused on the effect of tDCS in patients with consciousness disorders, such as vegetative state and MCS, in clinical trials (11, 12). The potential mechanism of such treatment may be related to the critical role of long-range fronto-parietal connections in consciousness (13). Nevertheless, its specific mechanism on neuroplasticity is still unclear, which limits the clinical application of tDCS in MCS (4).

Resting-state functional MRI (rs-fMRI) is a non-invasive and powerful tool to investigate the brain activation even without the proactive cooperation of the subjects in MCS (14). The resting-state functional connectivity (FC) in the brain is a stable and useful index to identify the functional interaction between brain regions, which has been used to understand the neural mechanisms in MCS (15). Several previous studies have demonstrated that the FC changes over time in the resting state were significantly correlated with the level of conscious state, which was often indexed by a subjective behavioral assessment, such as Coma Recovery Scale-Revised (CRS-R) (16, 17). Even though some studies reported significant changes in FC caused by tDCS in stroke and Parkinson's disease, it is unclear to what extent the functional connectivity alterations would occur in MCS by administering tDCS (18, 19).

Based on the hypothesis that tDCS could improve the conscious state by regulating brain activity and modulating brain network in MCS, we conducted the current study to assess the effects of tDCS stimulation over DLPFC on clinical status in patients with MCS, accompanied by exploring the underline mechanism through detecting the functional connectivity changes between specific regions by rs-fMRI.

METHODS

Participants

The participants were all recruited from the hospital named "999 Brain Hospital of Guangdong Province" between September 2017 and October 2018. All enrolled participants must meet the inclusion criteria: (1) age over 18; (2) meet the criteria for minimally conscious state according to Aspen Neurobehavioral Conference Workgroup (20), with a stable level of responsiveness assessed by 3 times of the Chinese version of coma recovery scale-revised (CRS-R) in 2 weeks before enrollment; (3) time from the onset $\geq$ 1 month; (4) no history of contraindication to MRI; (5) no history of sedative use; and (6) no other neuromodulation therapy (e.g., transcranial magnetic stimulation) performed. The conventional physical therapy of the patient was continued during the whole experimental period. The study was approved by the Institutional Review Board in 999 Brain Hospital of Guangdong Province. Informed consent was obtained from legal representative of patients.

Study Overview

The study consisted of three phases. The first phase was baseline assessment of CRS-R and fMRI scanning followed by a 1-week of the sham tDCS phase, which involved a daily sham tDCS for 5 days. Then, all the patients had the second assessment of CRS-R and fMRI scanning. After that, a 2-week real tDCS treatment phase was performed for 10 daily sessions. Last, all the patients performed the third assessment of CRS-R and fMRI scanning. The patients were required not to change their original medication regimen during the study. The research protocol is illustrated in **Figure 1**.

Stimulation Protocol

The tDCS was applied by using the DC stimulator (Soterix 1X1, Model 1300A, USA), which is a battery-powered constant-current stimulator. The transcranial direct current was delivered

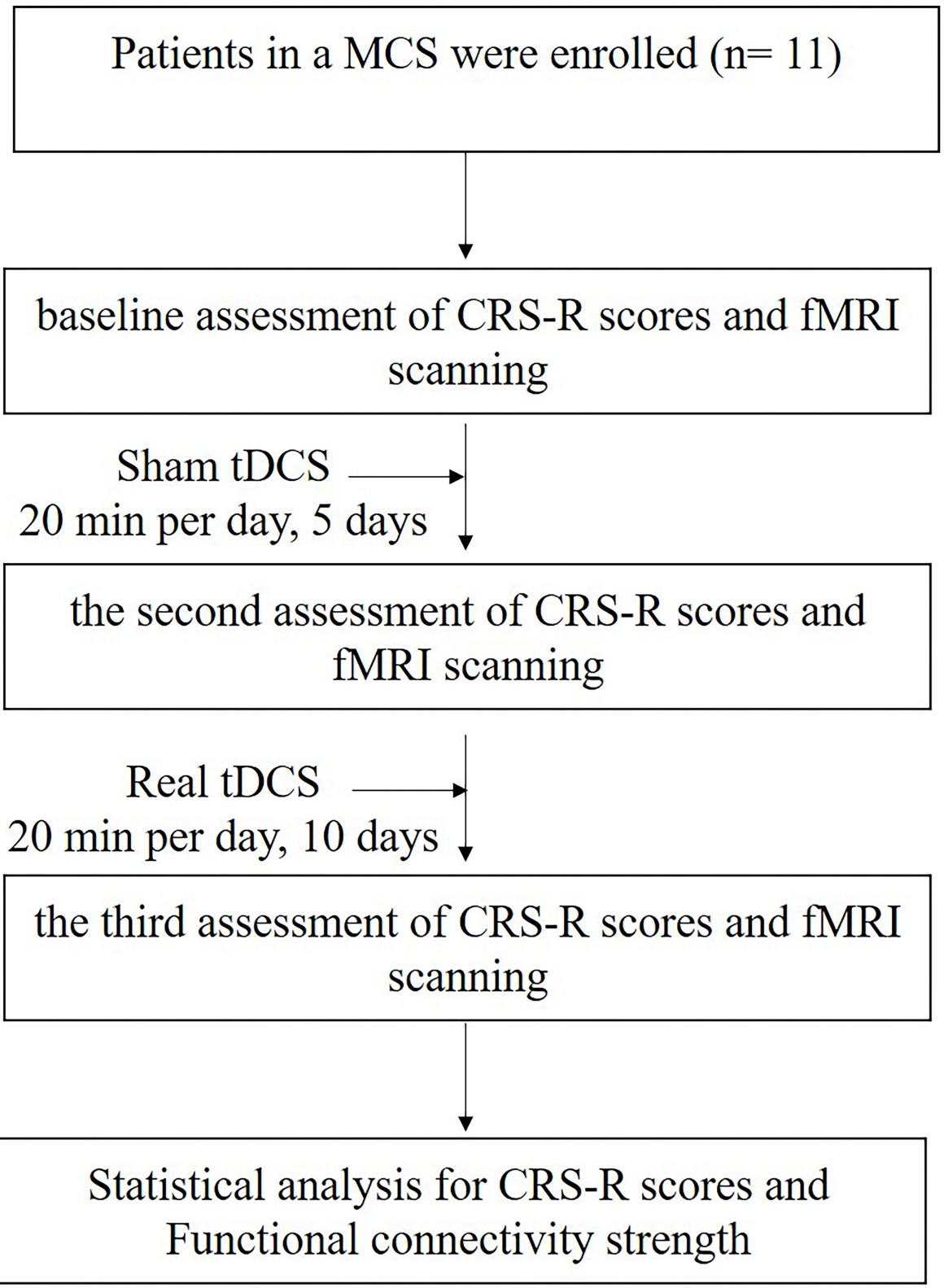

FIGURE 1 | A flow chart illustrating the process for the study. MCS, minimally conscious state; tDCS, transcranial direct current stimulation; CRS-R, Coma Recovery Scale-Revised.

via saline-soaked surface sponge electrodes (7 × 5 cm). The anode was placed over the left DLPFC, which is located at F3 from the 10–20 international electroencephalogram system. The cathode was placed on the right supraorbital area (Fp2). The same electrode placement was used for both sham and real tDCS stimulations. For sham tDCS, the current was applied up to 2 mA with a ramp-in and ramp-out phase of each 30 s, and then the current was kept at 0 mA for the rest of the 20 min to build up a placebo mode. The 1-week sham tDCS was delivered once a day, for 5 weekdays. For the real tDCS, the stimulating current raised to 2 mA within 30 s and lasted for 20 min. The 2-week real tDCS was delivered once a day, for 10 weekdays.

Behavioral Assessments

The consciousness level of each participant was evaluated right prior to fMRI scan using one CRS-R assessment. The CRS-R is a common scale for the assessment of consciousness, which was used to differentiate vegetative state (VS) from MCS and identify patients who have emerged from MCS (21). The CRS-R is comprised of six subscales, including auditory, visual, motor, oromotor, communication, and arousal function organized in 29 hierarchically items to reflect the level of consciousness and to track behavioral recovery, and each item has specific scoring criteria (22, 23). In addition, adverse events related with the stimulation like allergies and redness of the skin were also recorded in the study.

MRI Data Acquisition

Structural MRI and rs-fMRI were conducted with a 3T GE MR750 scanner equipped with a standard bird cage head coil. All the MRI data were collected within 24 h after enrollment of the participants; the 1-week sham-tDCS and the 2-week real-tDCS stimulation, respectively. We collected the high-resolution T1-weighted images from all the patients to reconstruct their individual structural brain anatomy. The parameters were as follows: repetition time (TR) = 8.2 ms, echo time (TE) = 3.2 ms, flip angle (FA) = 15°, flip angle (T1) = 450 ms, field of view (FOV) = 240 × 240 mm, slice thickness = 1 mm, voxel size = 0.93 mm × 0.93 mm × 1.00 mm^3, matrix = 256 × 256, number of layers = 164. We adopted an echo planar imaging sequence to gain the resting state fMRI data (TR = 2,000 ms, TE = 30 ms, FOV = 240 × 240 mm, FA = 78°, voxel size = 3.75 mm × 3.75 mm × 1.00 mm^3), repetitive times = 240.

Functional Connectivity Analysis

The rs-fMRI data were analyzed using the Statistical Parametric Mapping (SPM8), with a MATLAB toolbox (R2013a) named Data Processing Assistant for Resting-State fMRI (24, 25). The following steps were done automatically by the method: convert DICOM files into NFTI images, slice-timing correction, head motion realignment, normalization into Montreal Neurological Institute (MNI-152) space, smoothing with 6-mm full width at half maximum Gaussian kernel, remove a linear tread to diminish the influence of covariates, and image filtering (0.01–0.08 Hz) for getting rid of the high-frequency signal.

The Resting-State fMRI Data Analysis Toolkit was then used for the computation of brain functional connectivity (FC). We computed the whole-brain FC by analyzing the FC from six regions of interest (ROIs) bilaterally: occipital lobe, precuneus, supplementary motor area, angular gyrus, superior temporal gyrus, and middle frontal gyrus. FC refers to the sum of the energy and energy connections between each voxel and all other voxels in the entire brain (17). Functional connectivity reflects effective correlations between different regions in neuronal information processing. The ROI-based correlation was used to do the FC analysis in the present study. The larger FC of the selected ROI has, the closer its inter-relationship with other brain regions is. Peak coordinates of ROIs were selected according to pieces of literature, in which 10-mm-radius and 4-mm-radius spheres around peak x, y, and z coordinates were delineated for cortical areas and subcortical structures, respectively (17, 26). The peak x, y, and z coordinates of each ROI are listed in **Supplementary Table 1**.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Data are described as means ± standard deviations (SDs). A one-way repeated-measures ANOVA was performed to compare the difference of a behavioral outcome, including CRS-R total and subscales scores between the three time points (T0, T1, and T2), in which the least significant difference test was performed for multiple comparison corrections. A statistical significance was set at $p < 0.05$. To compare the differences of FC between the time points (T0, T1, and T2), ANOVA analysis was performed, and false discovery rate (FDR) correction of $p < 0.001$ was used for controlling multiple comparisons.

RESULTS

Baseline Characteristic

Eleven patients with MCS were enrolled, including 10 patients with traumatic brain injury and one patient with hemorrhagic stroke. The baseline features of the patients include age, gender, and time from the onset, which are presented in **Table 1**. The average time from the onset was 3.36 ± 1.36 months. Seven of the 11 patients with MCS were caused by diffuse axonal injury. The tDCS stimulations were well tolerated by all the patients with no significant adverse events linked to the stimulation.

Behavioral Outcome

The CRS-R scores of 11 patients at the baseline (T0), post-1-week sham tDCS (T1), and post-2-week real tDCS (T2) are also shown in **Table 1**. The CRS-R subscales scores at each assessed time point are provided in **Supplementary Table 2**. The CR-R scores did not change in post-1-week sham tDCS compared to the baseline. However, the CRS-R scores were significantly improved post-2-week real tDCS compared with those at the baseline and post-1-week sham tDCS. Importantly, five out of the 11 patients showed an obvious improvement of CRS-R scores. As to the CRS-R sub-domains, the changes were significant in the auditory function ($p = 0.03$) and motor function ($p = 0.02$) of post-2-week real tDCS compared with those post-1-week sham tDCS. In contrast, the scores of visual, oromotor, communication, and

TABLE 1 | Demographic and clinical characteristics of the 11 patients with MCS.

Patient	Age (year)	Gender	Etiology	Lesion location	Time from onset (month)	CRS-R scores		
						T0	T1	T2
P1	19	Male	TBI	Bilateral frontal parietal lobes	1	10	10	16
P2	40	Male	TBI	Diffuse axonal injury	2	14	14	14
P3	37	Male	TBI	Diffuse axonal injury	3	12	12	17
P4	35	Male	TBI	Diffuse axonal injury	3	9	9	14
P5	62	Female	TBI	Right frontotemporal lobes	3	15	15	15
P6	37	Male	Stroke	Left frontotemporal and parietal lobes	3	9	9	16
P7	55	Male	TBI	Diffuse axonal injury	4	13	13	13
P8	51	Male	TBI	Diffuse axonal injury	4	13	13	13
P9	31	Male	TBI	Right temporal lobe and right basal ganglia	5	10	10	16
P10	44	Male	TBI	Diffuse axonal injury	3	13	13	13
P11	62	Female	TBI	Diffuse axonal injury	6	14	14	14

TABLE 2 | CRS-R total and subscales scores of the 11 patients with minimally conscious state (MCS) at each time point.

	T0	T1	T2	F	*p*-value
CRS-R	12.00 ± 2.14	12.00 ± 2.14	14.63 ± 1.43	6.79	0.004
Auditory	2.27 ± 0.65	2.27 ± 0.65	2.91 ± 0.54	3.95	0.03
Visual	1.73 ± 0.47	1.73 ± 0.47	2.09 ± 0.54	2.00	0.15
Motor	3.55 ± 1.37	3.55 ± 1.37	4.82 ± 0.60	4.34	0.02
Oromotor	1.36 ± 0.50	1.36 ± 0.50	1.55 ± 0.52	0.46	0.63
Communication	1.00 ± 0.00	1.00 ± 0.00	1.09 ± 0.30	1.00	0.38
Arousal	2.09 ± 0.30	2.09 ± 0.30	2.18 ± 0.40	0.26	0.77

arousal functions were not significantly different with post-2-week real tDCS (**Table 2**).

FC Data Reflected in rs-fMRI

To investigate the possible local and remote effects of tDCS in the brain of patients with MCS and to explore the pertinent mechanism, a set of ROIs related to consciousness circuitries was selected as the targets, including occipital lobe, precuneus, supplementary motor area, angular gyrus, superior temporal gyrus, and middle frontal gyrus. The FC intensity of left middle frontal gyrus significantly decreased the post-1-week sham tDCS compared with the baseline (FDR corrected $p < 0.001$), but other brain networks showed no significant changes. In contrast, FC intensity was significantly increased in right precuneus, which was nearby the stimulated site post-2-week real tDCS compared with the baseline (FDR corrected $p < 0.001$). Importantly, FC intensity of the bilateral occipital lobe, which was distant from the left DLPFC, was also significantly increased in post-2-week real tDCS compared with the baseline (FDR corrected $p < 0.001$). Also, an increased FC intensity was also observed not only in the nearby brain regions of the stimulated site (e.g., left supplementary motor area), but also in the distant brain regions (including the right supplementary motor area, right angular gyrus, and right superior temporal gyrus) post-2-week real tDCS compared with those post-1-week sham tDCS (FDR corrected $p < 0.001$) (**Figure 2**; **Table 3**).

DISCUSSION

The findings from this study demonstrated the effect of tDCS in treating patients with MCS and explored its possible mechanism. We found the increase of CRS-R total scores and alterations of FC in rs-fMRI mediated by 2-week real tDCS in patients with MCS. Although bias may be induced due to the lack of the control group; the recovery signs of consciousness observed by comparing the clinical assessment and neuroimaging data at the baseline, post-1-week sham stimulation, and 2-week real stimulation strengthen our findings.

In this study, the behavioral assessment showed that the CRS-R total scores were improved post-real DCS compared with the scores at the baseline in patients with MCS. However, no improvement in CRS-R was observed post-sham stimulation compared with the baseline. These results were consistent with previous pieces of research (27, 28). Angelakis et al. reported the effects of 2-week tDCS over left DLPFC in patients with different degrees of consciousness disorders, in which all the patients with MCS showed increased CRS-R scores at the end of the treatment (29). Another study demonstrated that 10 tDCS sessions over precuneus could improve the signs of consciousness in patients with DoC represented by CRS-R total scores (22). In addition, the auditory and motor CRS-R subscales scores were significantly higher post-2-week real tDCS than both the baseline and sham tDCS (**Table 2**), from which we speculated that the

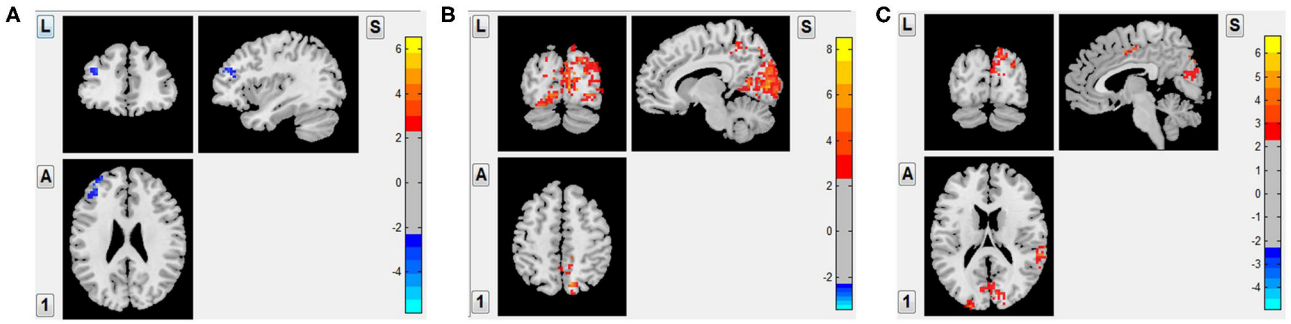

FIGURE 2 | The alteration whole brain functional connectivity of 11 patients with MCS after different tDCS protocols. **(A)**: 1-week sham tDCS vs. the baseline: decreased FC intensity in left middle frontal gyrus (*FDR corrected* $p < 0.001$); **(B)**: 2-week real tDCS vs. the baseline: increased FC intensity in right precuneus and the bilateral occipital lobe (*FDR corrected* $p < 0.001$); and **(C)**: 2-week real tDCS vs. 1-week sham-tDCS: bilateral supplementary motor area, right angular gyrus, and right superior temporal gyrus (*FDR corrected* $p < 0.001$).

TABLE 3 | Brain regions with alteration of functional connectivity (FC) after different transcranial direct current stimulation (tDCS) protocols.

Brain regions	L/R	Peak MNI coordinates (mm)			CLuster size (Voxels)	*t*-values	Trends
		X	Y	Z			
1-week Sham-tDCS VS. baseline							
Middle frontal gyrus	L	−33	51	24	34	−3.73	T1 < T0
2-week real-tDCS VS. baseline							
Occipital lobe	R	13	−92	9	990	6.1	T2 > T0
Precuneus	R	12	−75	48	59	7.59	T2 > T0
Occipital lobe	L	−9	−90	6	356	8.54	T2 > T0
2-weeks real-tDCS vs. 1-week Sham-tDCS							
Occipital lobe	R	30	−87	39	192	4.29	T2 > T1
SMA	R	9	−45	36	32	4.33	T2 > T1
Angular gyrus	R	54	−60	30	49	4.3	T2 > T1
Superior temporal gyrus	R	60	−36	18	79	4.16	T2 > T1
Occipital lobe	L	−21	−93	15	32	5.15	T2 > T1
SMA	L	0	3	48	46	4.59	T2 > T1

1. FDR corrected $p < 0.001$, cluster size > 20; R, right; L, left; T0, baseline; T1, 1-week sham tDCS; T2, 2-week real tDCS; SMA, supplementary motor area.

potential of tDCS may be related to its effect on auditory and motor functions.

Although highlighted in clinical trials that a better clinical outcome could be achieved by tDCS in DoC, little is known about its beneficial impact on neural activity and related network (30, 31). In addition, neuroimaging and electrophysiological assessments are more sensitive to identify changes caused by tDCS than a behavioral outcome (32). The FC analysis in our study showed that there was no strengthened FC but a decreased FC in left middle frontal gyrus post-1-week sham tDCS compared with the baseline. However, in post-2-week real tDCS, FC of bilateral supplementary motor area, right angular gyrus, and right superior temporal gyrus were significantly enhanced compared with that of post-1-week sham tDCS. In addition, the bilateral occipital lobe as a key node in visual network and the right precuneus as one of the key nodes in default network were all significantly activated post 2 weeks of real tDCS compared with the baseline.

Neurophysiologic and functional neuroimaging studies indicated that the recovery of the consciousness requires the participation and coordination of different brain regions in cerebrum (33). A decreased functional connectivity was found in left and right default modes, executive control, auditory, and attention networks in patients with MCS (33, 34). Previous studies in healthy participants showed that tDCS over left DLPFC could increase the FC between the left DLPFC and bilateral parietal regions (5, 35). Our findings showed that an increased FC in sensorimotor network (bilateral supplementary motor area), frontal parietal network (right angular gyrus), and auditory network (right superior temporal gyrus) post-2-week real tDCS, which provided another piece of evidence that improvement of FC in both nearby and distant of the stimulated brain regions could be induced by tDCS in patients with MCS (5, 36–39). The results of FC from rs-fMRI in our study were also in accordance with the conclusion of previous studies using electrophysiological analysis (13, 40). As to the specific

mechanism, we speculated that the anodal tDCS over the left DLPFC could simultaneously activate the stimulated brain region locally and its related brain regions distantly, owing to the residual capacity and neural plasticity in patients with MCS (36, 39).

The present study supports the effectiveness of using tDCS over the left DLPFC in treating patients with MCS. Improved CRS-R scores and enhanced FC were revealed in some patients. Our study also had some limitations. One was that the sample size was relatively small, which may reduce the statistical power. The other limitation was that no follow-up was done to assess potential long-term treatment effects. Another limitation was the lack of the control group. Although we only included the patients with same CRS-R scores on the 3 assessment sessions in 2 weeks before the enrollment, we could not completely rule out the effect of spontaneous recovery. As this could be a drawback for the study, we would carry out further randomized controlled clinical pieces of research to explore the immediate and long-term effect of tDCS in patients with MCS.

CONCLUSION

The present study demonstrated the potential of tDCS in treating MCS. Signs of consciousness in MCS could be improved through tDCS over left DLPFC, as measured by CRS-R total scores. The FC based on rs-fMRI was significantly increased in the stimulation site (left DLPFC) and distant regions mediated by tDCS.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Guangdong 999 Brain Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YP, JZ, YL, and TY designed this study. YP, JZ, XL, JD, SZ, JZ, HL, and XZ performed the experiments. Data was analyzed by YP, JZ, YL, and XW. YP, JZ, and XW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.821286/full#supplementary-material

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Robot Fully Assisted Upper-Limb Functional Movements Against Gravity to Drive Recovery in Chronic Stroke: A Pilot Study

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Background: Stroke is becoming more and more a disease of chronically disabled patients, and new approaches are needed for better outcomes. An intervention based on robot fully assisted upper-limb functional movements is presented.

Objectives: To test the immediate and sustained effects of the intervention in reducing impairment in chronic stroke and to preliminarily verify the effects on activity.

Methodology: Nineteen patients with mild-to-severe impairment underwent 12 40-min rehabilitation sessions, 3 per week, of robot-assisted reaching and hand-to-mouth movements. The primary outcome measure was the Fugl-Meyer Assessment (FMA) at T1, immediately after treatment ($n = 19$), and at T2, at a 6-month follow-up ($n = 10$). A subgroup of 11 patients was also administered the Wolf Motor Function Test Time (WMFT TIME) and Functional Ability Scale (WMFT FAS) and Motor Activity Log (MAL) Amount Of Use (AOU), and Quality Of Movement (QOM).

Results: All patients were compliant with the treatment. There was improvement on the FMA with a mean difference with respect to the baseline of 6.2 points at T1, after intervention ($n = 19$, 95% CI = 4.6–7.8, $p < 0.0002$), and 5.9 points at T2 ($n = 10$, 95% CI = 3.6–8.2, $p < 0.005$). Significant improvements were found at T1 on the WMFT FAS ($n = 11$, +0.3/5 points, 95% CI = 0.2–0.4, $p < 0.004$), on the MAL AOU ($n = 11$, +0.18/5, 95% CI = 0.07–0.29, $p < 0.02$), and the MAL QOM ($n = 11$, +0.14/5, 95% CI = 0.08–0.20, $p < 0.02$).

Conclusions: Motor benefits were observed immediately after intervention and at a 6-month follow-up. Reduced impairment would appear to translate to increased activity. Although preliminary, the results are encouraging and lay the foundation for future studies to confirm the findings and define the optimal dose-response curve.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03208634.

Keywords: stroke, upper extremity, rehabilitation, recovery of function, robotics, passive motion, reaching, task oriented training

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INTRODUCTION

The global incidence of stroke is increasing, while at the same time the incidence of death from stroke is declining (1). This means that stroke is transitioning even more into a disease of chronically disabled survivor (2). Each year, 17 million people worldwide suffer from a stroke, and approximately one-third of them present upper-limb impairment still in the chronic stage (3). Robot-assisted training is a relatively novel approach, which in patients with stroke can improve arm and hand function, arm and hand muscle strength, and ultimately their activities of daily living, but the quality of the evidence is still poor (4). Few studies evaluated robotic upper-limb rehabilitation in chronic stroke. The first study on a group of 42 patients with moderate-to-severe chronic impairment demonstrated improved motor abilities after treatment, which were sustained at a 4-month follow-up (5). A more recent study including 20 patients with severe-to-moderate impairment seems to confirm improved function is maintained at a 3-month follow-up (6). However, the added effect of robotic interventions with respect to other therapies is not demonstrated yet. Lo et al. who studied the effect of robotic therapy on 49 patients with long-term severe-to-moderate impairment, did not find significantly improved motor function at 12 weeks, as compared with usual care or intensive therapy (7). They found better outcomes over 36 weeks only compared with usual care and not with intensive therapy. A further subgroups analysis showed that improvements were not homogeneous over the group; younger age and a shorter time since stroke were associated with more significant immediate and long-term improvement of motor function (8). A recent multicentric study on 257 patients with subacute and chronic stroke demonstrated that an intervention based on the planar Massachusetts Institute of Technology (MIT)-robotic arm is not superior to an upper-limb therapy (EULT) program based on repetitive functional-task practice and to usual care (9).

New studies on patients with chronic stroke are needed to get insight into the mechanisms leading to improved motor function following robotic treatment to predict the outcome and define criteria for patients' selection and personalization of therapies. The type and intensity of the robotic intervention and the duration of the rehabilitation program, along with the patient's age, distance from the stroke, and level of impairment, are some of the factors influencing the outcome and are worthy of being studied. Two preliminary studies suggest that interventions with spatial robotic devices, which are able to assist in reaching against gravity could have an additive effect on motor recovery in patients with chronic stroke with moderate-to-severe hemiparesis (10, 11). The authors of the present study proposed a novel robotic approach based on fully assisted functional movements against gravity performed at quasi-physiological velocity. The movements are in the *real world* and cover the entire peripersonal space, moving toward and away from the body. Importantly, they are everyday gestures involving brain emotional processes, like in the case of the hand-to-mouth movement, which may recall eating. The resulting exercises are, therefore, highly engaging and stimulating. The authors found short-term-improved function in a very preliminary study on a group of 10 patients with chronic stroke with mild-to-severe impairment (12). The study reported here expands on the previous research by examining the effects of robotic rehabilitation in a larger sample of subjects with chronic stroke and by investigating on a smaller group of patients whether improved function translates to increased activity in the short term. Further, a preliminary investigation is performed to verify whether improvements in motor abilities are sustained at a 6-month follow-up.

METHODS

Study Population and Design

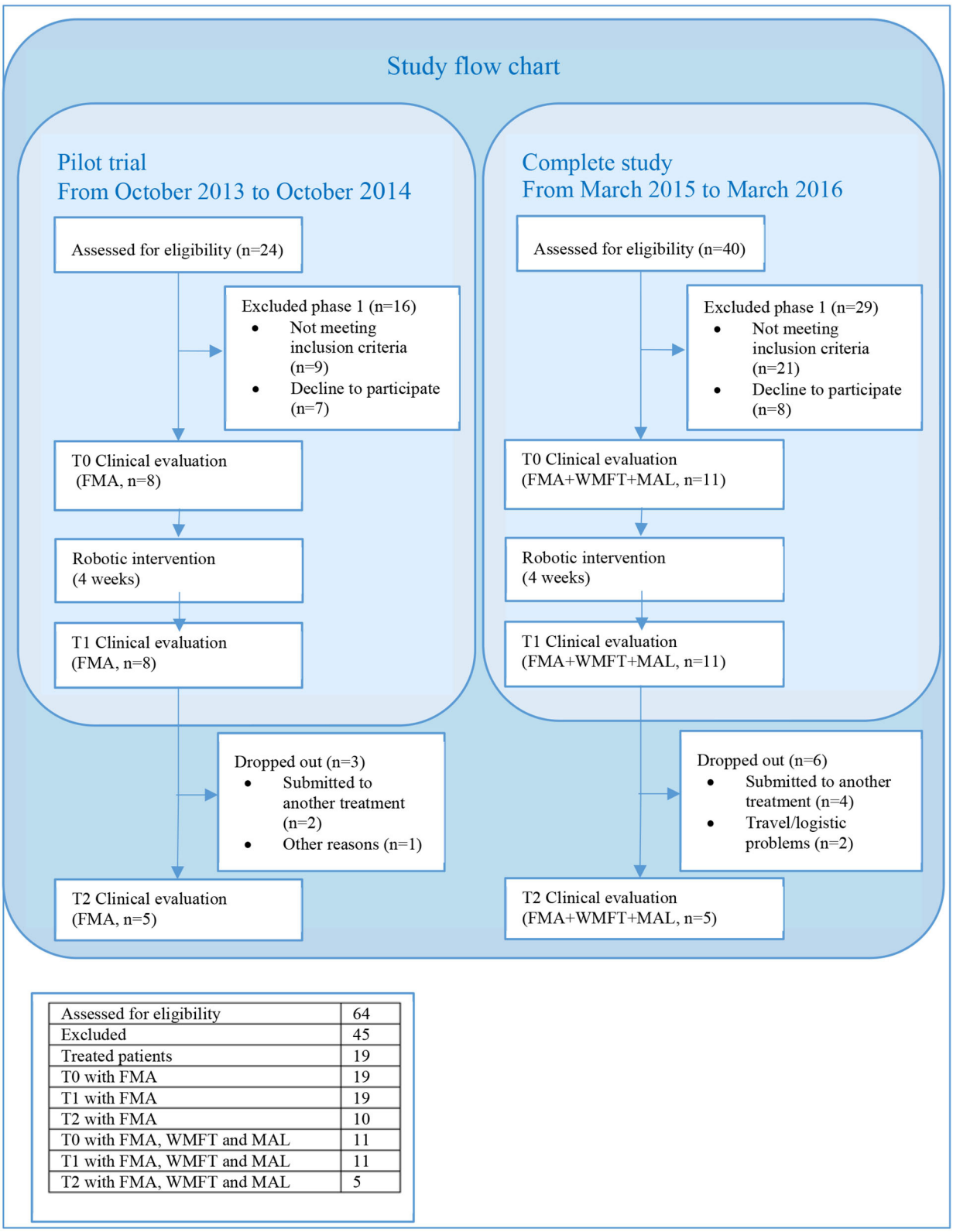
In this cohort study, a convenience sample of 19 patients with mild-to-severe upper-limb impairment, 6 months or more post-stroke, were enrolled. The inclusion criteria were: (i) hemiplegia after the first stroke; (ii) time from the stroke event >6 months; (iii) absence of severe attentive deficits; (iv) ability to perform active arm movements (shoulder flexion Medical Research Council [MRC] >1 and Active Range of Movement (AROM) >60°, elbow flexion-extension MRC >1 and AROM >90°) and able to hold the robot handle, and (vi) Modified Ashworth Scale (MAS) score ≤3 (refer to section outcome). Exclusion criteria were: (i) other concurrent upper-limb rehabilitation interventions; (ii) presence of global aphasia and/or cognitive impairments that could interfere with understanding the instructions during evaluation and treatment (Mini-Mental State Examination Test>24/30); and (iii) concomitant progressive central nervous system disorders, peripheral nervous system disorders, or myopathies.

The study was performed in two phases. A pilot trial involving eight patients aimed to verify the short-term efficacy of the robotic intervention in reducing motor impairment. Given the first positive results, the study was completed by recruiting 11 other patients to verify whether functional improvements translate to increased activity. **Figure 1** reports the flow chart of the study and a table summarizing the total number of patients who were assessed for eligibility, along with the number of patients who were excluded from the study and the ones who were treated. The local ethics committee granted the study, and all recruited participants provided written informed consent (CE 126 /2011 on 23/09/2011, and amendment CE 219/2014 on 09/10/2014). The study is registered with ClinicalTrials.gov as "Rehabilitation Multi Sensory Room for Robot Assisted Functional Movements in Upper-limb Rehabilitation in Chronic Stroke (RehaMSR)," study ID NCT03208634.

A more comprehensive summary of the study, including a detailed description of the type of assisted movements and training parameters, is presented elsewhere (12); a summary is presented below.

Intervention

The intervention was administered by a trained research therapist *via* an end-effector robot (Pa10-7, Mitsubishi, Japan), which was customized to assist 3D multi-joint functional movements against gravity performed at physiological velocity. The intervention protocol, identical in the two phases of the



Assessed for eligibility	64
Excluded	45
Treated patients	19
T0 with FMA	19
T1 with FMA	19
T2 with FMA	10
T0 with FMA, WMFT and MAL	11
T1 with FMA, WMFT and MAL	11
T2 with FMA, WMFT and MAL	5

FIGURE 1 | Study flow chart. The pilot trial took place from October 2013 to October 2014. Twenty-four patients selected from the Villa Beretta database were called over the phone and invited to participate in the study. Seventeen agreed and were screened; 5 were excluded, mainly because they were not able to hold the robot handle during one of the two movements, and 7 refused to participate. From March 2015 to March 2016, a total of 40 patients with chronic stroke who were referred to the outpatient clinic of Villa Beretta were screened; 23 were excluded because of not meeting the inclusion criteria (insufficient shoulder and elbow active ROM or inability to hold the robot handle), and 6 refused to participate. The most common reason for refusing to participate referred to difficulties in reaching the facility.

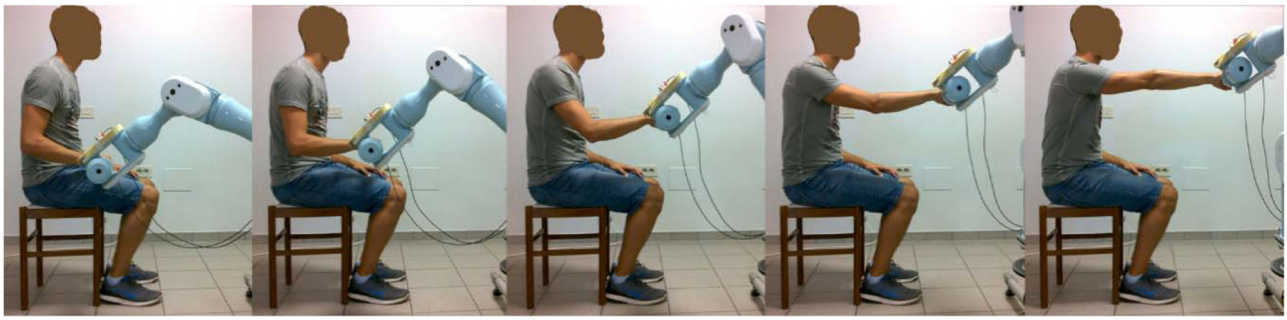


FIGURE 2 | Assisted RM: starting with the robot handle just above the thigh, the assisted Reaching Movement (RM) consisted of compound movements of shoulder flexion and elbow extension, getting as far as 90 degrees of shoulder flexion and fully extended elbow were reached.

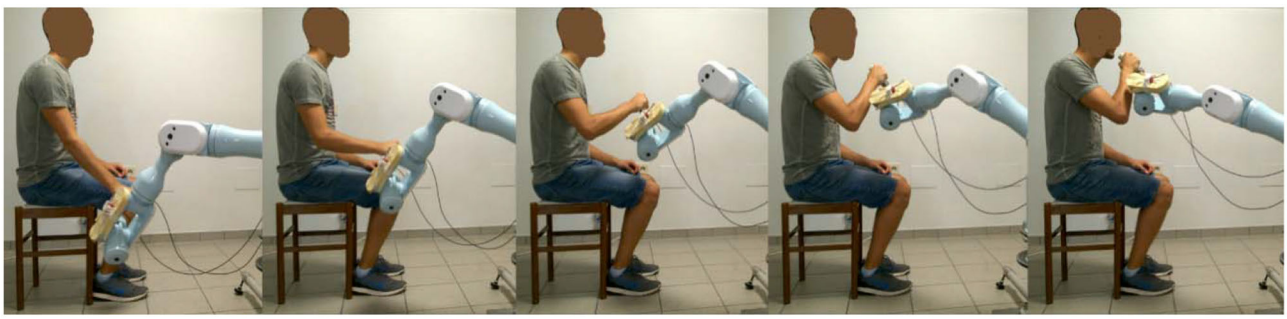


FIGURE 3 | Assisted Hand-to-Mouth Movement (HtMM): Starting with the robot handle just above the thigh, the assisted HtMM consisted in flexing the elbow (and the shoulder) to position the robot-handle in front of the mouth. Importantly, the handle was free to rotate and, therefore, the patient had to put it actively (performing wrist internal/external rotation movements) in the right position, which was with its extremity pointing toward the mouth.

study, consisted in the execution of two functional movements, namely the Reaching Movement (RM) against gravity (**Figure 2**) and the Hand-to-Mouth Movement (HtMM, **Figure 3**). Each session consisted of 20 min of robot-assisted RM and 20 min of robot-assisted HtMM. The movements were fully assisted (the robot handle moved along the path with a predefined motion law independently of the forces exerted on the handle), but the patient was explicitly asked to participate by trying to follow (slightly anticipate) the moving handle. During movement, the operator could check on a monitor the forces applied on the robot handle and encourage the patient to participate more in the movement. The movement is fully assisted because, in essence, it is performed following the preselected motion law even in the case of a plegic arm; however, the patient is free/is asked to try to perform the movement on his own. When the patient is (partially) able to perform the movement, the robot has the function to drive the patient in following the right path and perform the movement smoothly at the preselected pace.

The rehabilitation consisted of a 1-month intervention, three sessions a week performed on Monday, Wednesday, and Friday, for 12 sessions in total.

Clinical Assessment

The patients selected for the study were clinically tested at baseline (T0), just after intervention (T1), and at a 6-month follow-up (T2). The patients who underwent other interventions between T0 and T1 or T1 and T2 were excluded from the evaluation at T1 or T2, respectively. One trained physical therapist, the same for all patients, performed all outcome assessments (pretreatment as well as post-treatment and follow-up) with the supervision of the patient's referent physician. To minimize biases, the patient could not have access to and view the results of the previous sessions.

The primary outcome measure was the upper-limb motor function subdomain of the Fugl-Meyer Assessment (FMA) (14) made of the sections A-D (A shoulder and elbow, B wrist, C hand, and D coordination of the upper limb). The secondary outcome measures were the Wolf Motor Function Test Time (WMFT TIME) (15) and Functional Ability Scale (WMFT FAS) (16), and the Motor Activity Log (17) Quality of Movement (MAL QOM) and Amount Of Use (MAL AOU), which were administered to 11 out of the 19 patients, that is only in the final trial. The MRC scale for muscle strength (18) and the MAS (19) were administered to complete the patients' clinical picture. Finally, a qualitative analysis of the Draw-A-Person test (20) was performed to assess the possible deficits of the mental body representation (21).

Data Analysis

Based on the primary outcome measure results of the pilot trial, the sample size of the study was computed using the G*Power 3.1.9.2 statistical power analysis program (22). The results referred to a sample of 19 patients would allow detecting

TABLE 1 | Patients' data.

Patients	Age (years)	Sex	Affected side	Stroke type	Stroke location	Time from stroke (months)	Nr of RM	Nr of HtMM	Nr total movements
Pt 1	65	F	Left	Ischemic	Right lenticular nucleus and internal capsule	6	360	245	7,260
Pt 2	62	M	Right	Hemorrhagic	Left caudate nucleus and internal capsule	76	340	240	6,960
Pt 3	24	F	Right	Hemorrhagic	Left frontal lobe	32	337	210	6,564
Pt 4	65	M	Left	Ischemic	Right Frontoparietal lobe	11	330	230	6,720
Pt 5	76	F	Right	Ischemic	Left hemisphere	27	350	240	7,080
Pt 6	68	F	Right	Hemorrhagic	Left basal ganglia	51	330	210	6,480
Pt 7	55	M	Left	Ischemic	Right temporal lobe	32	315	245	6,720
Pt 8	65	M	Right	Ischemic	Left hemisphere	6	400	260	7,920
Pt 9	73	M	Left	Ischemic	Right basal ganglia	8	310	250	6,720
Pt 10	49	M	Right	Ischemic	Left frontoparietal lobe	19	310	212	6,264
Pt 11	74	M	Left	Hemorrhagic	Right semioval center and left frontobasal lobe	10	320	220	6,480
Pt 12	67	M	Right	Ischemic	Left thalamus	6	350	230	6,960
Pt 13	66	M	Left	Ischemic	Right hemisphere	66	218	340	6,696
Pt 14	46	F	Right	Ischemic	Left parahippocampal gyrus	168	345	205	6,600
Pt 15	64	M	Left	Hemorrhagic	Right basal ganglia	112	365	170	6,420
Pt 16	56	M	Right	Hemorrhagic	Left frontoparietal lobe	151	360	255	7,380
Pt 17	35	F	Right	Ischemic	Left frontoparietal lobe	44	400	280	8,160
Pt 18	80	M	Left	Ischemic	Right posterior internal capsule	27	340	230	6,840
Pt 19	82	M	Right	Hemorrhagic	Left Internal capsule	8	348	241	7,068
	62 ± 9	6 F	11 Right	12 Ischemic	-	45 ± 30	338 ± 24	238 ± 21	$6{,}910 \pm 304$

Nr of RM, average number of assisted Reaching Movements performed at each training session; Nr of HtMM, average number of assisted Hand to Mouth Movements performed at each training session; Nr total movements, RM + HtMM performed in total during the 12 training session.

a seven-point FMA improvement with an SD of 11.3 (medium effect size, Cohen *d*' >0.60), 80% power, and a type I error of 0.05.

For analysis, the patients were clustered in groups based on the number of evaluation sessions and the type of clinical assessments they underwent. Comparisons of the same groups' data between different evaluation sessions were performed with the Wilcoxon signed-rank test, considering the value of significance at 0.05. Because of the small size of the sample, a non-parametric test was preferred. The responsiveness of the clinical measures to the intervention was estimated using Cohen's effect size (d') (23, 24). Linear regression and Pearson's correlation and Evans' classification (25) were used for verifying and quantifying possible correlations between the FMA improvements at T1 and the age of patients, the time from the stroke, and the level of impairment at T0. For this analysis, improvements were calculated both as absolute improvements, i.e., $\Delta FMA = FMA_{T1} - FMA_{T0}$, and improvements normalized to the maximum potential recovery (26): $\Delta FMA_{NOR} = \Delta FMA/(66\text{-}FMA_{T0})$. The statistical analysis was performed using WinSTAT® ver.2012.1.0.94.

RESULTS

Nineteen patients participated in the study, 11 underwent additional WMFT and MAL, and 10 reached the evaluation at T2; their data are reported in **Table 1**. Only five patients of the group with additional WMFT and MAL reached T2 (refer to **Figure 1**); the results are not reported as an apart group in **Table 1** as the sample is too small to draw any conclusion. The mean age of the participants was 62 years ($\pm 2^*SE = 9$ years), and the time from stroke was 45 months ($\pm 2^*SE = 30$ months); six (32%) were women, 11 (58%) had right hemiparesis, seven (37%) had a hemorrhagic stroke, and all other patients had an ischemic one. At baseline, the patients had mild-to-severe impairment according to the classification of Woytowicz (27): Three were severely impaired (FMA <29), six were moderately impaired (29≤ FMA ≤42), and 10 were mildly impaired (FMA >42). The Draw-A-Person test showed heterogeneous results at T0; two thirds of the patients' drawings showed at least an anomaly; the most common anomalies were a lack or disproportion of body segments (hands, feet, and entire upper and lower limbs) and a lack of facial elements (mouth, nose, eyes, and ears). All patients were fully compliant with the treatment and could complete all 12 robotic rehabilitation sessions. In average, the patients performed 338 (218-400) RM and 238 (170-340) HtMM each session. The average number of reaching and hand-to-mouth movements performed by patients after the 1-month treatment was 6918 (6420–8160). No adverse effect was observed; the intervention is safe in this sense. Unfortunately, nine out of the 19 patients who underwent the treatment missed the clinical evaluation at T2, mainly because they received a medical treatment between T1 and T2, which could interfere with the

TABLE 2 | Means ± Double SEs for clinical results along with T1 vsT0 and T2 vsT1 Cohen's Effect Size d' and *p*-values.

Evaluation	T0	T1	T2	Immediately after intervention			Six months after intervention		
				Mean diff (95% CI)	d'	*p*	Mean diff (95% CI)	d'	*p*
(*n* = 19)									
FMA	42.8 ± 5.7	48.9 ± 5.1		6.2 (4.6–7.8)	0.55	<0.0002			
FMA SecA	25.2 ± 2.6	28.3 ± 2.4		3.1 (2.2–4.0)	0.60	<0.0005			
FMA SecB	5.3 ± 1.4	5.9 ± 1.5		0.7	0.21	ns			
FMA SecC	8.1 ± 1.9	10.1 ± 1.7		2.1 (0.9–3.2)	0.57	<0.001			
FMA SecD	3.8 ± 0.5	4.6 ± 0.5		0.8 (0.6–1.1)	0.86	<0.001			
MRC	10.2 ± 0.7	11.3 ± 0.7		1.1 (0.6–1.5)	0.36	<0.002			
MAS	3.4 ± 0.7	3.1 ± 0.8		−0.3	0.25	ns			
(*n* = 11)									
WMFT TIME	7.3 ± 1.5	6.5 ± 1.3		−0.8s	0.38	ns			
WMFT FAS	4.0 ± 0.3	4.3 ± 0.3		0.3 (0.2–0.4)	0.67	<0.004			
MAL AOU	1.46 ± 0.71	1.64 ± 0.74		0.18 (0.07–0.29)	0.15	<0.02			
QOM	1.29 ± 0.71	1.43 ± 0.72		0.14 (0.08–0.20)	0.12	<0.02			
FMA	48.0 ± 5.1	53.9 ± 4.1		5.9 (4.0–7.8)	0.88	<0.004			
FMA SecA	28.1 ± 2.2	31.1 ± 1.6		3.0 (1.9–4.1)	1.13	<0.006			
FMA SecB	5.8 ± 1.6	6.3 ± 1.9		0.5	0.14	ns			
FMA SecC	9.9 ± 1.9	11.5 ± 1.5		1.6 (0.7–2.4)	0.64	<0.02			
FMA SecD	4.2 ± 0.4	5.1 ± 0.4		0.9 (0.5–1.3)	1.36	<0.02			
MRC	11.5 ± 0.5	12.5 ± 0.5		1.0 (0.5–1.3)	0.54	<0.02			
MAS	3.7 ± 1.5	3.7 ± 1.7		0.0	0.00	ns			
(*n* = 10)									
FMA	38.4 ± 9.1	44.3 ± 7.2	48.1 ± 7.2	5.9 (3.6–8.2)	0.47	<0.005	9.7 (4.6–14.8)	0.86	<0.007
FMA SecA	23.2 ± 4.3	25.9 ± 3.6	27.8 ± 3.4	2.5 (1.2–3.7)	0.47	<0.02	4.6 (1.5–7.7)	0.86	<0.02
FMA SecB	4.4 ± 2.2	5.1 ± 1.9	5.6 ± 2.1	0.7 (0.2–1.2)	0.23	<0.05	1.2 (0.2–1.2)	0.36	<0.05
FMA SecC	6.5 ± 3.0	9.0 ± 2.8	10.3 ± 2.6	2.5 (0.6–4.4)	0.57	<0.02	3.8 (1.5–6.1)	0.92	<0.008
FMA SecD	3.3 ± 0.8	4.3 ± 0.8	4.4 ± 0.7	1.0 (0.6–1.4)	0.84	<0.02	1.1 (0.5–1.7)	0.99	<0.02
MRC	8.9 ± 1.0	9.9 ± 1.1	11.8 ± 0.7	1.0 (0.5–1.3)	0.28	<0.02	2.9 (0.6–3.9)	1.07	<0.006
MAS	3.4 ± 0.8	2.8 ± 1.1	2.6 ± 1.4	−0.6	0.47	ns	−0.2	0.09	ns

The table is in 3 parts: (1) FMA of 19 patients at T0 and T1; (2) WMFT and MAL at T0 and T1 of a subgroup of 11 patients (along with FMA to define the level of impairment) and (3) FMA at T0, T1 and T2 of a subgroup of 10 patients. MRC and MAS are shown to complete the patients' clinical picture. FMA, Upper-Extremity Fugl-Meyer Assessment (max 66 pts); SecA, Shoulder and Elbow Section (max 36 pts); SecB, Wrist Section (max 10 points); SecC, Hand Section (max 14 pts); SecD, Coordination/Velocity Section (max 6 pts); MRC, Medical research Council (max 15 points); MAS, Modified Ashworth Scale (max 15-negative points); WMFT, Wolf Motor Function Test; TIME, average duration (s) to perform items; FAS, Functional Ability Scale (max 5 pts): MAL, Motor Activity Log; AOU, Amount of Use (max 5 points); QOU, Quality Of Use (max 5 pts).

clinical evaluation results. The clinical results at T0, T1, and T2, along with the Cohen's effect size d' and *p*-values, are reported in **Table 2**.

At T1, the patients ($n = 19$) showed a statistically significant improvement in the FMA (+6.2/66, 95% CI = 4.6–7.8, $p < 0.0002$) as well as almost all the FMA subsections (the shoulder and elbow–SecA +3.1/36, 95% CI = 2.2–4.0, $p < 0.0005$; the hand–SecC +2.1/14, 95% CI = 0.9–3.2, $p < 0.001$; and the coordination–SecD +0.8/6, 95% CI = 0.6–1.1, $p < 0.001$). The improvement (+0.7/10) in section B score, the one regarding the wrist functionality, was not statistically significant ($p = 0.075$). Regression curves are plotted in **Figure 4**. There was no correlation neither between ΔFMA and the patients' age ($r = -0.06$, $p = 0.40$) nor between ΔFMA and the time from stroke ($r = -0.22$, $p = 0.18$). The same results were found when the ΔFMA normalized on the maximum potential recovery was used for regression (ΔFMA_{NOR} *vs.* "age": $r = -0.18$, $p = 0.22$; ΔFMA_{NOR} *vs.* "time from stroke": $r = -0.20$, $p = 0.21$). A moderate negative correlation was found between ΔFMA and the patients' functional level at baseline FMA_{T0} ($r = -0.45$, $p < 0.03$) but, by contrast, a moderate positive correlation was found between ΔFMA_{NOR} and FMA_{T0} ($r = 0.40$, $p < 0.05$). As regards the MRC, there was a statistically significant increase in the score (+1.1/15,95% CI = 0.6–1.5, $p < 0.002$) while the reduction of 0.3 in the MAS score was not statistically significant. Responsiveness to the intervention, according to Cohen's definition, was large for FMA SecD, moderate for FMA, FMA SecA, and FMA SecC, and small for MRC. The qualitative analysis of the drawings of the Draw-A-Person test that presented some anomalies at T0 showed heterogeneous results, ranging from no-difference to the full integration of all body segments and recovery of their proportion at T1 compared with T0. In **Figure 5**, two self-explanatory examples

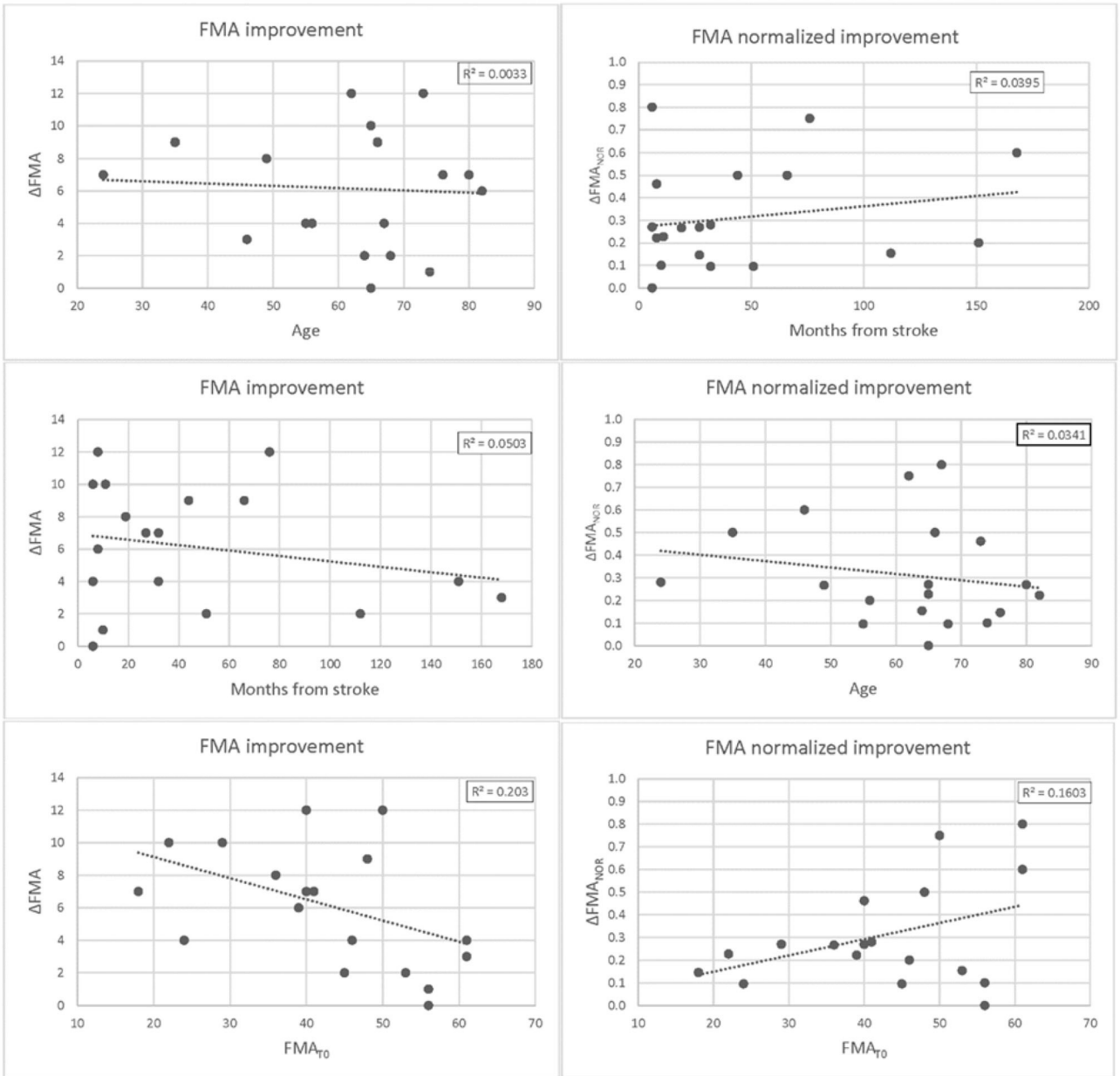


FIGURE 4 | Differences in Fugl-Meyer Assessment (FMA) at T1 vs. T0 plotted against patients' age (**upper** panel), months from stroke (**middle** panel), and FMA scores at baseline. Differences are expressed as absolute values ΔFMA = FMAT1 -FMAT0 (**left** panel) and potential recovery ΔFMANOR = ΔFMA/(66-FMAT0) (**right** panel). For each plot, the linear regression curve along with the r-squared value is also shown.

show the recovery of the facial elements, body segments, and proportions.

At T1, the subgroup of patients ($n = 11$) who underwent additional WMFT and MAL evaluation, showed a statistically significant improvement in WMFT FAS (+0.3/5, 95% CI = 0.2–0.4, $p < 0.004$) but not in WMFT TIME (−0.8s, $p > 0.05$). They showed a statistically significant improvement in the quantity (AOU, +0.18/5, 95% CI = 0.07–0.29, $p < 0.02$) as well as the quality scale (QOM, +0.14/5, 95% CI = 0.08–0.20, $p < 0.02$) of the MAL. Also, for this group, improvements in FMA total score and subsections A, C, and D were statistically significant (FMA +5.9/66, 95% CI = 4.0–7.8, $p < 0.004$; SecA +3.0/36, 95% CI = 1.9–4.1, $p < 0.006$; SecC +1.6/14, 95% CI = 0.7–2.4, $p < 0.02$; and SecD +0.9/6, 95% CI = 0.5–1.3, $p < 0.02$) as well as in MRC (+1.0/15, 95% CI = 0.5–1.3, $p < 0.02$). Responsiveness to the intervention was large for FMA total score and subsections A and D, moderate for WMFT FAS, FMA SecC, and MRC, and trivial for MAL, both quantity and quality of use.

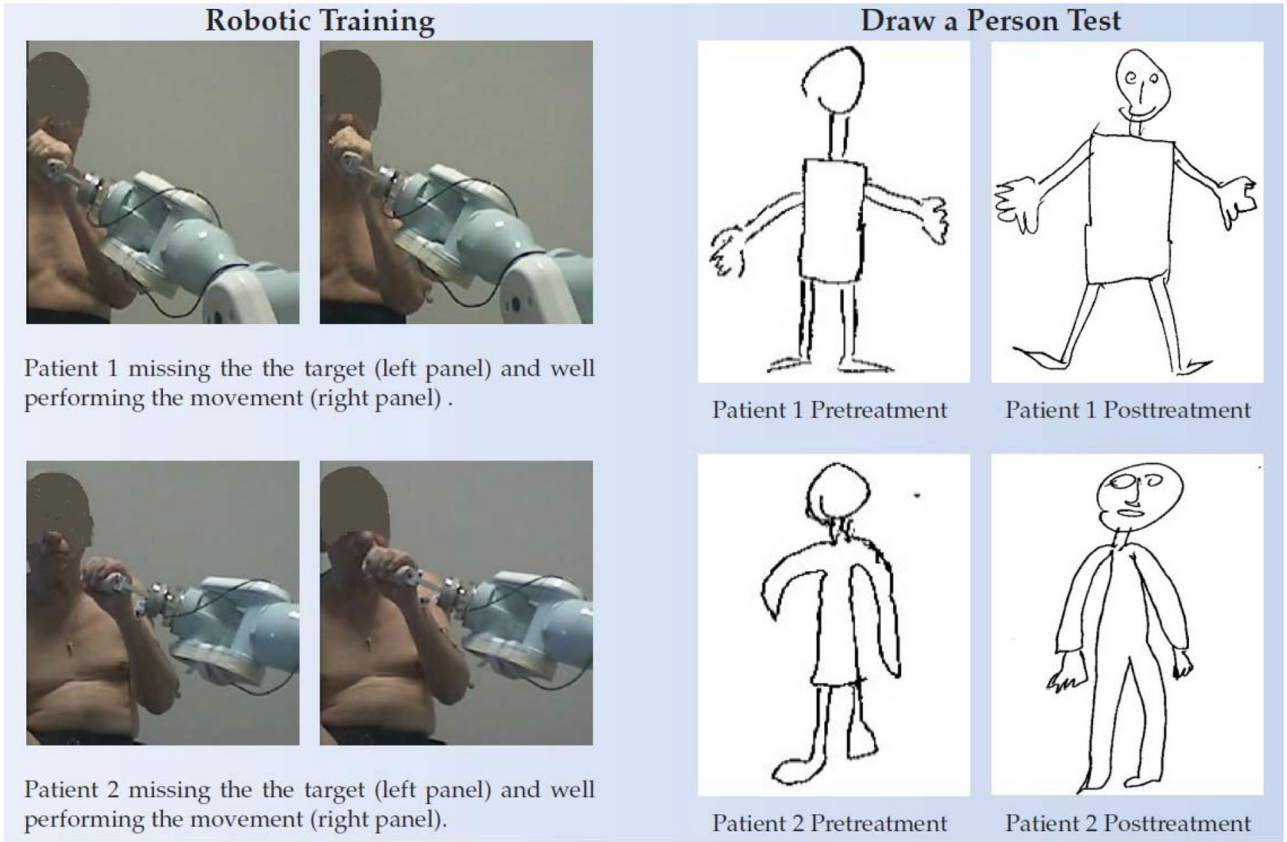


FIGURE 5 | Draw-A-Person test of two chronic patients. **Left** panel, the two patients performing the robot assisted movements (first trials very left pictures) and after some sessions of training. In the beginning, they were not able to place the robot handle in front of the mouth as requested. **Right** panel, the pre and posttreatment Draw-A-Person test.

The subgroup of patients ($n = 10$), who reached the evaluation at T2, showed statistically significant improvements at T1, in FMA total score and all subsections and MRC (FMA +5.9/66, 95% CI = 3.6–8.2, $p < 0.005$; SecA +2.5/36, 95% CI = 1.2–3.7, $p < 0.02$; SecB + 0.7/10, 95% CI = 0.2–1.2, $p < 0.05$; SecC + 2.5/14, 95% CI = 0.6–4.4, $p < 0.02$; SecD +1.0/6, 95% CI = 0.6–1.4, $p < 0.02$; MRC + 1.0/15, 95% CI = 0.5–1.3, $p < 0.02$). Comparison between T1 and T2 results showed a statistically significant improvement in MRC (+1.9/15, $p < 0.02$, responsiveness = 0.62) while improvements in FMA total score and subsections were not significant. Comparison between T0 and T2 showed statistically significant improvements in all FMA subsections (FMA +9.7/66, 95% CI=4.6-14.8, $p<0.007$; SecA +4.6/36,95% CI=1.5-7.7, $p<0.02$; SecB +1.2/10, 95% CI=0.2-1.2, $p<0.05$; SecC +3.8/14, 95% CI = 1.5–6.1, $p < 0.008$; and SecD + 1.1/6, 95% CI = 0.5–1.7, $p < 0.02$) as well as MRC (+2.9/15, 95% CI = 0.6–3.9, $p < 0,006$). The responsiveness to the intervention measured at T1 was large for FMA SecA, moderate for FMA SecD, and small for FMA total score, SecB, and SecC as well as MRC. The responsiveness to the intervention measured at T2 was large for all scales but FMA SecB, which was small.

In the last subgroup ($n = 5$), made of the subjects who underwent additional WMFT and MAL evaluation and reached T2, 2 subjects showed improvements compared with T1, while the other three showed no difference. The result is encouraging, but the sample size is too small to draw any conclusion on the patients' activity 6 months postintervention.

DISCUSSION

The present study investigated the short-term effects of a novel robotic intervention in a group of patients with chronic stroke by evaluating the impairment reduction measured through FMA and aimed to verify in a subgroup of patients whether improved function translates to increased activity by evaluating the WMFT and the MAL. Further, a preliminary analysis of the FMA was performed in the second subgroup of patients who reached the evaluation at T2 to verify whether improvement reduction is maintained at a 6-month follow-up.

The results showed improved group average overall upper-limb function following the intervention that can be considered both real and clinically meaningful for people with chronic stroke

as ΔFMA is >6 points and, therefore, beyond both the Minimal Detectable Change (MDC) and the Minimal Clinically Important Difference (MCID), which for the FMA are both equal to 5.2 points (28).

The intervention is relatively short (4 weeks) and relatively frequent (3 times a week); however, it is intense (577 movements each session, 6,918 in a month, on average). Previous studies on chronic stroke reported do differ for the duration [Fasoli et al. (5) and Posteraro et al. (6): 3 times a week for 6 weeks; Lo et al. (7): 36 1-h sessions over a period of 12 weeks; Rodgers et al. (9): 3 times a week for 12 weeks]. It is further important to recall that these results were obtained with an intervention based on fully assisted movements. Therefore, the approach neither meets the *assist as need* principle nor the *Detection of Patient Intent* (DPI) method, used in robotic rehabilitation to maximize neuroplasticity (12). However, a recent neurophysiological study by the group of Farina demonstrated that Hebbian plasticity could be induced in healthy subjects even by using a passive device, as long as motor imagery is combined (29). Our patients were explicitly asked to (try to) follow the movement of the robot handle they were grabbing during repeated RM and HtMM. So, they knew the starting time of the next movement, and similar to the study of Farina et al. they were imagining the movement just before it started and, conceivably, Hebbian plasticity mechanisms could have been enhanced. This needs further investigations as, on the one side, Farina's results were on healthy subjects and, on the other side, the veracity of the neurophysiological equivalence between his study and ours is not sure. However, there is evidence that Hebbian-type stimulation is feasible even in chronic stroke during robot-assisted wrist movement (30). In addition, and even more importantly, the hypothesis is consistent with a previous study we made in a patient with chronic stroke who was administered the same intervention; we found no organized electroencephalography activity during no-assisted HtMM performed with the affected limb and, conversely, quasi-physiological activity during fully assisted HtMM (31). A specific feature of the hand-to-mouth movement is that the subject is required to orient the handle toward the mouth actively. Therefore, implicitly, the patient is asked to focus on the whole movement and the position of the different body segments. This exercise recalls the *Cognitive Multisensory Rehabilitation,* a promising therapy for upper limb recovery in stroke, where the therapist probes the patients through questions to consciously reflect on the position of their arm and hand in space and to have a focused awareness to the multisensory processing and their movements during sensory discrimination exercises. In a recent study, the authors explained that Cognitive-Multisensory-Rehabilitation exercises target the restoration of body awareness directly, which in turn, directly and indirectly, improves body image and, thus, *Mental Body Representation* as a whole, which aids the restoration of motor function (21). At the brain function level, they found, following the intervention, increased functional connectivity in the parietal operculum between the right OP1/OP4 and 30 areas distributed across all lobes (34 areas were impaired at baseline). In conclusion, they speculated that (i) OP1/OP4 in the multimodal integration network plays a crucial role in the formation of accurate body awareness and that (ii) improvement of body awareness may activate OP1/OP4, leading to restoration of the brain connectivity that was observed. In this study, the patients were administered the Draw-A-Person test to assess mental body representation. The results showed improvements in the posttreatment tests; specifically, the persons drawn were complete with all the body segments, which also respected the proportions; face elements, such as the eyes, the nose, and the mouth, were added with respect to baseline (**Figure 5**). Even if not investigated, it is conceivable that these patients had decreased connectivity in the brain relevant for sensorimotor function. The intervention could have improved body awareness and, consequently, motor restoration, as described by Van de Winckel et al. (21). However, this hypothesis is not supported by an instrumental evaluation based on functional MRI. It would be interesting to investigate further in a group of selected patients assessing functional connectivity pre and post-intervention.

Interestingly, with the above consideration, improvements were found not only proximally, at the shoulder and the elbow (FMA SecA), but even distally, hand opening included (FMA SecC). First, this was unexpected, considering the robot did not mobilize the hand. The patients had to hold the robot handle during the execution of the assisted functional movements, and this could explain improved finger flexion but not improved hand opening. However, it is known that hand control is affected by the proximal joints position and, particularly, volitional finger extension is, in patients with stroke, affected strongly by shoulder abduction (32). A recent neurophysiological study showed that the development of abnormal joint coupling (flexion synergies) and hand impairment following stroke is correlated with structural changes in the brainstem (33). Possibly, the execution of spatial multi-joint functional movements could help to improve movement velocity, inter-joint coordination, and regaining physiological synergies; in fact, the responsiveness to the treatment was large for FMA SecD (coordination/velocity) and moderate for FMA SecA (Shoulder and elbow). Improved shoulder function and reduction of flexor synergies would explain improved hand opening in our patients. The whole mechanism could also have been enhanced by increased body awareness, as described above. Further investigations based on neuroimaging are needed to confirm these hypotheses.

Different from a previous study by Wu et al. (8), we found no correlation between ΔFMA and the patients' age. There are several possibilities explaining this inconsistency. Simply, our result could be affected by the small size of the sample, or, alternatively, differences in the level of impairment at baseline could account for the result found. In fact, in this study, 10 out of 19 patients presented mild upper-limb impairment; conversely, in the study of Wu et al., the patients had moderate-to-severe upper-limb impairment. A final possible explanation is that motor improvements following our intervention might be due to some biological mechanisms, which are actually independent of the patients' age. This would not be surprising considering that similar results were found post robotic intervention in 190 patients in the subacute phase of the stroke (34); within 6 months, the upper-limb impairment resolves by a fixed proportion of 70% of each patient's maximum possible

improvement (35). This "rule," known as "proportional recovery" holds across all ages, indicating that the motor recovery is due to fundamental biological mechanisms (26). Possibly, even in chronic stroke, other factors like the lesion size and location and involved biological mechanisms play a more critical role in the recovery process than the patients' age. In acute stroke, Byblow et al. demonstrated that 30% of patients do not fit the "proportional recovery rule" because of damage to descending motor pathways (36), and similar results were found in chronic stroke (37).

Furthermore, no correlation was found between ΔFMA and the time from the stroke. This suggests that in the chronic stage of the disease, the mechanisms leading to improved function are active even many years after the stroke. We found 2–4 points of improvement in FMA even 9 years or more after stroke, corresponding to 15–60% of the potential recovery. Finally, all patients except one gained at least 1 FMA point, and 11 patients overtook the MCID. These results are consistent with what Dobkin reported in a review, namely that many patients retain latent sensorimotor function that can be realized any time after stroke with a pulse of goal-directed therapy (38). This is a crucial finding in rehabilitation, also emerging due to the diffusion of robotics that, even more importantly, helps to understand the mechanism leading to the recovery.

The results showed a moderate negative correlation between ΔFMA and the patients' functional level at baseline FMA_{T0}; this could be due to the ceiling effect. Indeed, by contrast, a moderate positive correlation was found between ΔFMA_{NOR} and FMA_{T0}. The sample size is too low to draw any conclusion regarding a possible correlation between functional recovery and level of impairment at baseline.

About the second question, whether improved function translates to increased activity, the clinical tests seem to confirm the hypothesis. Preliminary results referred to increased activity measured on the WMFT FAS, the responsiveness of which to the treatment was large. However, although the average group improvement (+0.3/5 points) was larger than the MDC, which is 0.1/5 points for patients with chronic stroke, (39) we do not know whether the improvement can be considered clinically meaningful because the MCID is not established yet for patients with chronic stroke. The improvement in WMFT TIME (−0.8 s) was largely beyond the MDC (0.1 s) but was not statistically significant. Similarly, the self-reported arm use has improved as measured on the quantity as well as the quality scale of the MAL, but the responsiveness was trivial for both measures. We can say little about the soundness of the results, as the MDC is not established yet for MAL. It is worth recalling that the intervention was short (1 month, only) and, at T1, the patients could not have realized yet they could perform some daily life activities and, consequently, the validity of the self-reported activity could be affected. Probably, a test at 3- or 6-month follow-up could be more reliable. Unfortunately, out of the 11 patients who were evaluated for WMFT and MAL, only five reached the assessment at T2; the sample is too small to draw any conclusion.

Regarding the last question, whether improvements in motor abilities are sustained at 6-month follow-up, the results are positive. Comparison between the assessments at T1 and T2 showed improvements in FMA total score and all subsections, although they were not statistically significant. However, and even more importantly, improved function in the period T1-T2 was demonstrated by increased responsiveness, which was large for FMA total score and all subsection at T2, whereas at T1, it was moderate for FMA SecD, small for FMA total score, SecB, and SecC, and large only for FMA SecA. Recalling that no intervention was performed in the period T1-T2, it means that no continuous treatment is required, and cyclic treatment sessions can be enough. This is not surprising; probably improvements at T2 were due to increased use of the upper limb in everyday life, as demonstrated by improved MAL and WMFT at T1. This would also explain the moderate improvement in strength as shown by the comparison between the MRC results at T1 and T2 (MRC + 1.0/15, $p < 0.02$; $d' = 0.62$). To summarize, there is some evidence that the intervention improves both function and upper-limb use in everyday life that further generates a virtuous circle, whereby an increased use of the limb leads to improved function and strength, which, in turn, leads to subsequent increased use and so on. Some preliminary evidence on improved body awareness following the intervention supports this hypothesis. Immediately after the first training sessions, some patients referred the operator to be very satisfied with the intervention because they could move the arm they had not been able to move since the stroke. Although they knew they were performing RM and HtMM not autonomously but, by contrast, with the robot assistance, the movement sensation was so intense as if they were performing the movement themselves. In patients like these, the Draw-A-Person test showed improved body awareness (40). As patients become more aware of their upper limb, they begin to use it more and more in activities of daily living, thus reducing the risk for the *learned non-use* phenomenon.

A final matter to discuss regards the novelty of the approach we used. We already pointed out that the movements were fully assisted and, therefore, there is a risk of negative effects like decreased patient effort and reduced need to "solve" the problem of relearning upper-limb control (11). Conversely, assistance may also have positive effects like increased somatosensory stimulation, complete and accurate proprioceptive signals, better engagement, better ability to do tasks and, thus, receiving positive feedback about efforts. A key goal for robotic therapy device research is to increase the positive effects while decreasing the negative ones (11). In this framework, we believe that movements, highly functional, such as the HtMM may enhance the positive effects and, conversely, reduce the negative ones. The execution of movements that the patient has been repeated many times in life probably recalls intense sensations related to the accomplished task (e.g., eating and/or touching the face) with high emotive impact. In fact, all patients have been able to perform a high number of movement repetitions at each session without ever showing any sign of boredom. In the case of the HtMM, the patients had to position the robot handle in front of the mouth actively. Combining distal active movements (hand tasks) with proximal (elbow and shoulder) fully assisted

movements could further be a possible solution to increase the positive effects of robotic assistance and to avoid the negative ones. Even this specific aspect of the intervention that represents a novelty should be a matter of discussion in future studies. To the best of our knowledge, no other studies have been done on a rehabilitation approach based on robot-assisted functional movements in the peripersonal space performed at quasi-physiological velocity and, therefore, with high smoothness. Future studies may verify whether these novelties in the field of rehabilitation robotics could help to maximize the results. Particularly interesting would be to confirm the results that demonstrated increased activity, which actually is the ultimate goal of post-stroke rehabilitation. In fact, at the state of the art, the efficacy of robotic rehabilitation in increasing arm use is still a matter of discussion as no sound evidence has been found yet (4).

Limitation of The Study

There are several limitations to our study. First, the sample size is small, and there are several dropouts, particularly at the follow-up, as some patients, given the good results, started other rehabilitation programs before being tested at the six-month follow-up. Therefore, the intervention will need to be applied to a larger sample of participants to confirm the results found: significant improvements in the function of the shoulder, elbow, and hand, in movement velocity, and inter-joint coordination as measured on the upper-limb FMA scale. Second, as there was no control group, we cannot know whether patients have improved better than they could have following other therapies (*e.g.,* traditional therapy, constraint-induced movement therapy, or other robotic therapies). Anyway, this study is preliminary, and the aim was to verify the efficacy of the intervention to justify a future randomized control trial. Third, we do not know whether a more intensive and more prolonged treatment could have led to better results. However, in the field of robot-assisted therapy, this is still a general open question to be further investigated (2). Very few trials have looked into the optimum intensity and duration of a specific intervention, and the literature still lacks studies of dose-response interactions to define rehabilitations gains peak (38). Fourth, the assessor was not blinded to the treatment and, although he could not have access to the patients' previous evaluation results, he may have been led to give higher scores at T1 and T2. To reduce this risk of biases, the patient's referent physician double-checked the clinical evaluation results with the support of the patients' assessments videos; nevertheless, effect sizes might have been inflated, and they should be taken cautiously. Fifth, some hypotheses we made on neuroplasticity to explain the results obtained should be verified by imaging investigations. We made a preliminary study with electroencephalography that seems to confirm our hypotheses (31) but, indeed, further studies are needed. Sixth, our conclusions are based on clinical measures only, which are inherently subjective. The kinematic analysis could help to explain more the mechanisms underlying the recovery following the rehabilitation approach presented in this study. Notably, it could be helpful to measure the movement smoothness, which is a measure of inter-joint coordination and, therefore, an indirect measure of the motor control ability (13, 41). This is particularly important as smoothness was demonstrated to be related to brain activity (42), and its analysis could help to understand what patients exactly learn when measuring improvement in quality of motor performance (43, 44). Finally, the robot used is not commercially available for rehabilitation, and, in case the additive value of the invention would be demonstrated, transfer to clinical practice could be difficult. However, in the last 2 years, our team developed, to continue the study, the control of a new robot (UR0, Universal Robots, Denmark), which is available on the market for human-robot cooperation.

CONCLUSION

In this article, we presented a novel rehabilitation intervention based on robot fully assisted functional movements against gravity performed at quasi-physiological velocity. The compliance with the intervention was excellent. Preliminary evidence was provided in chronic stroke for reduced impairment, sustained even at 6-month follow-up. This conclusion is based on the upper-limb FMA. Very preliminary results suggested that reduced impairment translates to improved activity. This conclusion is based on the WMFT and MAL scores. In short, the results are encouraging and lay the foundation for further studies corroborated by imaging and instrumental assessments to confirm the findings, verify the potential additive value of the intervention, and define the optimal dose-response curve. This would be the first step to make attractive for companies the development of a robot enabling this intervention and, therefore, the first step toward clinical use.

DATA AVAILABILITY STATEMENT

Average groups data are reported in the tables included in the article; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interaziendale delle Province di Lecco, Como e Sondrio. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MC participated in the design of the study, data collection, data analyses, and drafted the manuscript. CG and GG participated in the design of the study, enrollment of the patients, and data collection. FM and LM participated in the design and coordination of the study. All authors have read and approved the manuscript.

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The Effects of Enriched Rehabilitation on Cognitive Function and Serum Glutamate Levels Post-stroke

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Aim: This study aimed to explore the effect of enriched rehabilitation (ER) on cognitive function and serum glutamate levels in patients with stroke.

Methods: Forty patients diagnosed with post-stroke cognitive impairment (PSCI), according to the inclusion criteria, and undergoing inpatient rehabilitation were enrolled in the study. Patients were randomly assigned to receive 8 weeks of ER treatment (ER group; $n = 20$) or conventional medical treatment (CM group; $n = 20$). In addition, 20 age-matched healthy subjects who were outpatients in our hospital during the same period formed the healthy control (HC) group. In- and between-group differences in cognitive function were assessed during pre-intervention and post-intervention based on the Montreal Cognitive Assessment (MoCA), the Symbol Digit Modalities Test (SDMT), and the Trail Making Test (TMT). The serum levels of glutamate, tumor necrosis factor (TNF), and malondialdehyde (MDA) levels were also detected pre-intervention and post-intervention.

Results: Pre-intervention cognitive function and the levels of all the serum parameters assessed significant difference between the HC group and the PSCI group (both ER and CM groups) ($p < 0.05$), but not between the two groups of patients with PSCI ($p > 0.05$). Significant improvements were observed in cognitive function in both the ER and the CM groups post-intervention compared with pre-intervention, as evidenced by the measured improvement in MoCA, SDMT, and TMT scores. Similar improvements were seen for serum glutamate, the degree of oxidative damage, and the level of inflammation in both the treatment groups ($p < 0.05$). More enhancements in cognitive function, including MoCA, SDMT, TMT scores, and the serum levels of glutamate, the degree of oxidative damage, and the level of inflammation were shown in the ER group compared with the CM group post-intervention ($p < 0.05$).

Conclusions: ER can improve cognitive function in patients with PSCI. The associated mechanism may be related to the negative regulatory effect of ER on serum glutamate, TNF, and MDA levels, which is likely to enhance synaptic plasticity and alleviate oxidative stress- and inflammation-related damage, at least to some extent.

Keywords: enriched rehabilitation, cognitive function, stroke, glutamate, synaptic plasticity, oxidative stress

INTRODUCTION

Post-stroke cognitive impairment (PSCI) is one of the most common sequelae of stroke. Over 70% of survivors have cognitive impairment in the first week post-stroke while 37% still display cognitive deficits after 6 months (1). PSCI is strongly associated with reduced quality of life and long-term survival (2–4). Pharmacological therapeutic strategies, such as the use of cholinesterase inhibitors, have shown only limited efficacy against PSCI and many side effects, highlighting the need to explore and identify non-pharmacological strategies for the treatment of this condition (4).

Enriched rehabilitation (ER), a comprehensive strategy that combines environmental enrichment and task-oriented exercises, has shown the potential to improve cognitive function in animal models of central nervous system diseases, including stroke and Parkinson's disease (5, 6). Several recent clinical studies have also demonstrated that early ER intervention in the stroke unit can effectively improve motor function after stroke (7–9). However, little is known about the effects of ER on cognitive function in PSCI or about the underlying mechanisms.

Neurotransmitters are critical in cognitive function. Glutamate is an excitatory neurotransmitter that has been implicated in cognitive function, especially in memory and learning processes. After a stroke, glutamate levels in the infarcted site were found to be up to 80-fold higher compared with its physiological level, resulting in elevated glutamate contents in the cerebrospinal fluid and blood (10). However, excessive glutamate can lead to synaptic excitotoxicity, and even neuronal death, through aggravating oxidative stress and inflammation (11, 12). Some studies have shown that high serum glutamate levels are correlated with poor cognitive outcomes (11, 13), while others have reported that physical therapy can decrease serum glutamate contents to some extent and is associated with an improvement in overall function (14). In addition, chronic neuroinflammation is an inevitable response post-stroke, which is related to functional outcomes. Tumor necrosis factor (TNF), one of the key components in neuroinflammation secreted by activated microglia, is verified to be associated with cognitive impairment. Besides, oxidative stress, mediated by reactive oxygen species (ROS)-induced damage, plays a devastating role in stroke pathogenesis. Malondialdehyde (MDA) would accelerate the chain reaction of ROS formation and is used as a biomarker of the oxidative stress level corelated with cognitive function (15).

Given that ER has been associated with improved cognitive outcome brain functions and that serum glutamate levels have been associated with cognition, in this study, we explored the effect of ER on cognitive function, serum glutamate levels, oxidative stress responses, and inflammation-related responses in patients with PSCI.

MATERIALS AND METHODS

Participants

All patients with cerebral infarction at the Yangzhou University Clinical School from January 2020 to June 2021 were assessed for enrollment in the study based on the following inclusion criteria: cerebral infarction confirmed by MRI scan due to the lesion in the internal carotid artery system; meeting the diagnostic criteria for PSCI with a Montreal Cognitive Assessment (MoCA) score between 18 and 23; the absence of sensory aphasia and having the ability to communicate with others, at least simply; primary and unilateral onset and a volume of ischemic necrosis between 20 and 40 ml as determined diffusion-weighted imaging (DWI) (13) (how the infarct volume was calculated is described in **Supplementary Materials**); 55–70 years of age; time from onset between 2 and 3 months; Brunnstrom Stages of the affected limbs (upper and lower) between grade IV and V and capable of intracommunity walking with assistance; education level greater than high school degree (>12 years of education); stable vital signs; and capable of completing 8 weeks of rehabilitation training as required. The exact exclusion criteria are listed in **Supplementary Materials**.

Among the 217 identified patients, 61 met the inclusion criteria. Of these, 12 were unwilling to participate in the study. As measured by the clinical sample size, a minimum of 20 participants was required for each group (how to measure sample size is described in **Supplementary Materials**). Forty of the remaining 49 patients were assigned either to an ER group or a conventional medical treatment (CM) group according to a random number table, with 20 patients assigned to each group. The patients were blind to the grouping. We marked each group with letters and numbers, and the patients did not know the specific grouping situation. In the follow-up study, the therapists were assigned individual tasks without knowing the specific groups of patients. Twenty age-matched healthy subjects from the outpatient department comprised the healthy control (HC) group. The termination criteria of the study were (1) a participant presenting with serious adverse events and deemed to be incapable of continuing the trial and (2) a participant withdrawing from the trial.

This study was approved by the Medical Ethics Committee of the Clinical Medical College of Yangzhou University (Ethical Approval No. 2016055). All patients signed an informed consent form. The general process of the study is shown in **Figure 1**.

Intervention

The patients in the CM group received conventional medication, including drugs for controlling blood pressure, lowering cholesterol, improving cerebral blood flow (nimodipine 20 mg two times a day), promoting cognitive function (huperzine A 100 mg twice a day), and other related medications, according to Chinese Guidelines for diagnosis and treatment of acute ischemic stroke 2018 and other guidelines for diagnosis and treatment of ischemic stroke (10, 16, 17). In the ER group, treatment was administered for 8 consecutive weeks (2 h each time, once a day, 6 days per week), in addition to conventional medication (9, 18–21). The patients in the ER group completed various enrichment activities for 2 h in specific places using computers with an internet connection, virtual reality technology, as well as other equipment, as described below. All rehabilitative activities were of mild to moderate intensity and were monitored by a wristwatch (Apple Watch Series5) during the rehabilitation sessions, which induced a target heart rate below 65–70% of the maximum heart rate (22, 23).

Sensory-Motor Stimulation

Visual Stimulation

The Internet was used to select the reading materials and images the patients were interested in for reading and viewing one time a day for 10 min each time.

Olfactory Stimulation

The patients smelled two bottles of perfume with different scents and tried to name the scents for 5 min each time.

Tactile Stimulation

Toys or objects of different shapes, sizes, and textures were placed in black cotton cloth bags such that patients could not see the objects. The patients tried to name the objects or describe their characteristics by touching them with the hand on the paralyzed side. This process lasted for 10 min each time.

Exercise Stimulation

For lower limb exercise, the patients performed activities such as field walking, mushroom picking in the forest, or skiing in the snow using virtual reality equipment and a flat treadmill. For upper limb exercise, the patients were asked to perform tasks such as painting with a brush or making different items with plasticine. The patients were required to use the paralyzed limb aided by the healthy limb. The task lasted for 15 min each time.

Cognitive Activities

Patients in the ER group were required to complete specific tasks by integrating multiple cognitive functions using virtual reality equipment or actual scenarios, including:

Supermarket Shopping

The patients were given a list before shopping and had to return the list within a specified time. The patients had to purchase the listed items in the supermarket by themselves.

Classroom Observation

Patients had to attend lectures in the room and to recite the content as much as possible, just like student activity. Stimuli

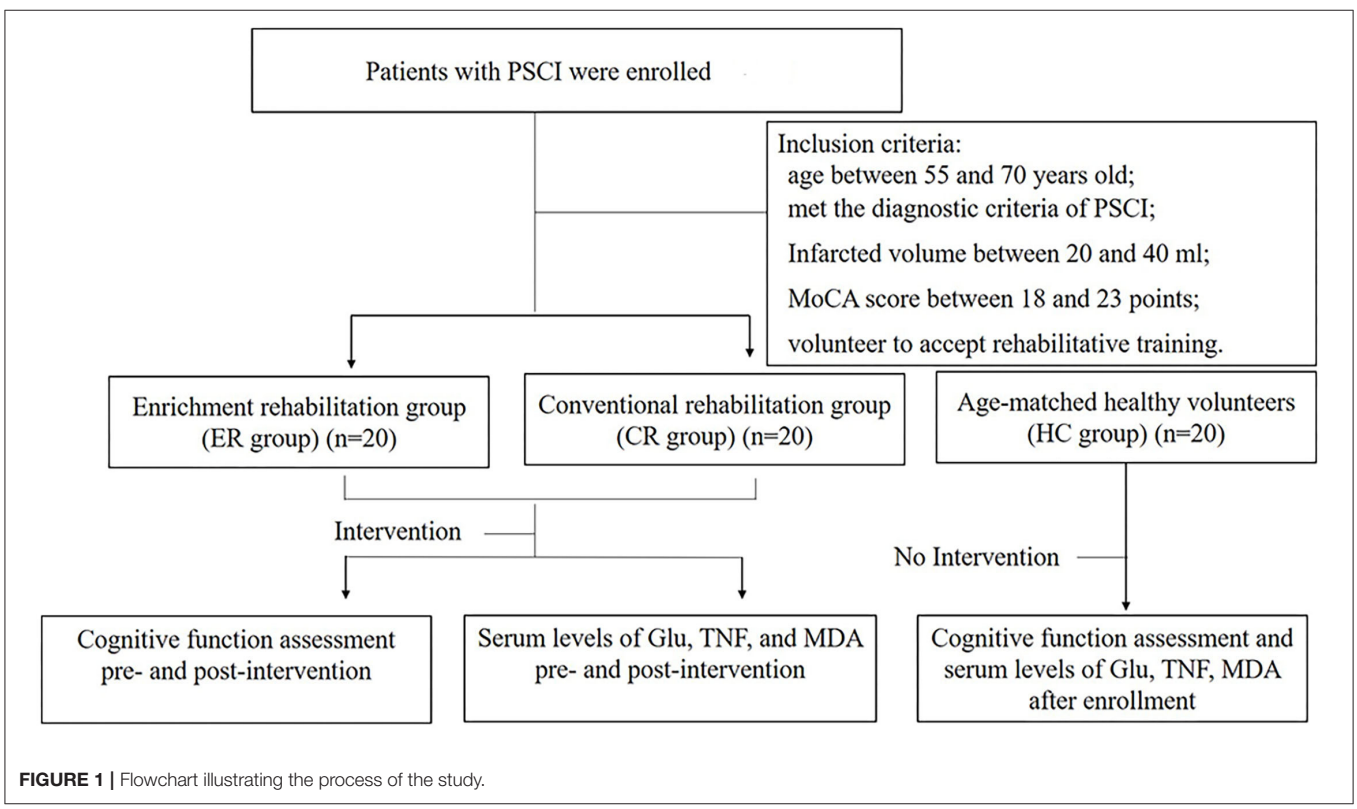

FIGURE 1 | Flowchart illustrating the process of the study.

such as noise, birds, and other people's voices were added to simulate interference during the class. Therapists asked questions after the class.

Card Games

A set of cards with different colors and graphics was used. The therapist placed three cards according to a specific rule (graphics, color, or number) and asked the patient to identify the rule and select the appropriate fourth card.

Taking the Subway

This task simulated a patient going home from the hospital. The patient was asked to complete planning the route, to choose a station to board and disembark, to enter and exit subway stations on their own, etc.

Cognitive activities were performed one time daily for a total of 40 min.

Social Activities

Participants were encouraged to communicate with each other during the entire ER training process; to play card games, chess, table tennis, and other sports involving more than one person; and to express their opinions on a hot social topic.

Social activities lasted for 40 min each time. All the above activities were undertaken under the guidance of therapists.

Outcomes and Measurement Procedures

All the patients completed the assessment of cognitive function and the measurement of serum parameters within 48 h before the first treatment and 48 h after the 8-week rehabilitation process, respectively. The HC group completed the above tests within 24 h after enrollment.

Evaluation of Cognitive Function

The overall cognitive function of patients in each group was determined based on the MoCA score. The assessment comprised eight items, including visual space and executive function, attention, naming, memory, abstract reasoning, language, delayed recall, and orientation ability, up to a maximum of 30 points, with $\geq$26 points being considered normal (24).

The symbol digit modalities test (SDMT) was used to assess attentional function. The SDMT records the number correctly entered within 90 s as the final score, excluding the number filled in during the practice (25).

The Trail Making Test (TMT) was used to evaluate the executive function, in which part A (TMT-A) is connected in sequence from numbers 1–25. TMT part B (TMT-B) is connected sequentially with numbers and letters alternating. The time spent recording TMT-A and TMT-B represented the evaluation index (26).

Serum Glutamate Level

All the patients were assessed for serum glutamate levels within 48 h before treatment, within 48 h after 8 weeks of treatment, and 12 h after fasting. In the morning, blood was drawn into a test tube without anticoagulant. Once it had precipitated at room temperature, the serum was collected and stored at −80°C. The glutamate concentration in serum was detected by high-performance liquid chromatography (13). The experimental procedure is as described in our previously published article (12). Glutamate concentration in the serum was calculated according to the standard curve (Amino acid standard reagent: Sigma, USA. Catalog number: AAS18-5ML). The concentrations of serum glutamate were expressed as μmol/L.

Serum MDA Level

The serum MDA level is a sensitive index reflecting the degree of oxidative damage in the body (27). Serum was collected as described above. The concentration of serum MDA was estimated according to the method using thiobarbituric acid reagent, and the absorbance of the supernatant was measured spectrophotometrically at 530 nm (28) (MDA Test Kit: Comin Biotechnology Co. Ltd., China. Catalog numbers: MDA-1-Y). The concentrations of MDA were expressed as μmol/L.

Serum TNF Level

The serum TNF content is a sensitive indicator that reflects the level of inflammation in the body (29). Serum was collected as described for the determination of glutamate content. The serum TNF concentration was determined by ELISA [(30); TNF ELISA Kit: Elabscience Biotechnology Co., Ltd., China. Catalog numbers: E-EL-H0109c]. All the measurements were performed according to the manufacturer's instructions. Briefly, the standard series was made by producing a series of diluted concentrations: 500, 250, 125, 61.5, 31.2, 15.6, and 7.8 pg/ml TNF to compare the differences in the gained absorbance. For the preparation of the standard addition series, we have diluted the 500 pg/ml standard 1:1 with blood serum from patients or healthy controls, resulting in 250 pg/ml recombinant human TNF standard that additionally contains extra TNF from the blood serum. Then, the absorbance at 450 nm was detected on the ELISA microplate reader (Spectra Max 190, Molecular Devices) for calculating the TNF level. The concentrations of TNF were expressed as pg/ml.

Statistical Analysis

Data were analyzed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). Results are presented as means ± standard deviation (SD) or median (quartiles) for continuous variables, depending on the normal or non-normal distribution of data. It was assessed to the normality of data by Shapiro–Wilk, and the variance homogeneity of data by one-way ANOVA test/Levene test. A chi-square test was used to analyze the between-group differences for categorical variables, such as gender and stroke site. A one-way, repeated-measures ANOVA or the Kruskal–Wallis test was performed to detect between-group differences (ER, CM, and HC groups) for continuous variables, which included MoCA, SDMT, and TMT scores as well as serum levels of glutamate, TNF, and MDA pre-intervention and post-intervention. A paired t-test or the Wilcoxon Rank Checking test was used to detect within-group differences (pre-intervention vs. post-intervention in the PSCI groups) for continuous variables. A least-significant difference test or the Mann–Whitney *U* test was utilized to compare the between-group differences post-intervention (ER

and CM groups) for continuous variables, including MoCA, SDMT, and TMT scores and serum levels of glutamate, TNF, and MDA post-intervention. The significance was set at $p < 0.05$.

RESULTS

Basic Demographic Information

In this study, the data including the scores of MoCA and TMT-A, and the serum concentration of TNF were not normally distributed nor was variance homogeneity met. There were 10 men and 10 women in the CM group, with an average age of 60.95 ± 5.70 years. The ER group consisted of 9 men and 11 women, with an average age of 61.70 ± 5.59 years. The HC group comprised 11 men and 9 women, with an average age of 61.03 ± 5.42 years. The baseline information for each group is presented in **Table 1**.

ER Enhanced Cognitive Function in Patients With PSCI

As shown in **Table 2** and **Figure 2**, significant differences in overall cognitive function, attentional function, and executive function pre-intervention ($p < 0.05$) were found between the HC group and patients with PSCI (both the CM and ER groups) but not between the two groups of patients with PSCI (CM and ER groups). After the intervention, general cognitive function, the attentional function score, and the executive function score of patients in the ER group and the general cognitive function and the attentional function score of patients in the CM group were significantly changed as compared with those before intervention ($p < 0.05$); however, those cognitive function indicators still differed significantly between the HC group and the PSCI group (both the CM and ER groups) ($p < 0.05$). Additionally, the overall cognitive function and attentional function scores were significantly higher in the ER group than in the CM group after intervention ($p < 0.05$).

TABLE 1 | Comparison of the basic demographic information for each group.

	HC group ($n = 20$)	CM group ($n = 20$)	ER group ($n = 20$)	*P*
Age (years)	61.03 ± 5.42	60.95 ± 5.70	61.70 ± 5.59	>0.05
Sex (male/female) (*n*)	11/9	10/10	9/11	>0.05
Time since onset (months)		2.46 ± 0.29	2.47 ± 0.31	>0.05
Stroke site (left/right) (*n*)		16/4	15/5	>0.05
Education (years)	14.22 ± 2.03	13.81 ± 1.89	13.75 ± 1.85	>0.05
MoCA		20.12 ± 1.58	19.95 ± 1.66	>0.05
Brunnstrom stage of the affected lower limb (IV/V) (*n*)		9/11	10/10	>0.05
Brunnstrom rating of the affected upper limb (IV/V) (*n*)		10/10	11/9	>0.05
Barthel index		69.05 ± 5.11	68.85 ± 4.73	>0.05
ASL (U/L)		30.02 ± 7.78	29.77 ± 8.28	>0.05
AST (U/L)		33.41 ± 6.98	31.11 ± 6.75	>0.05

n, number of cases; HC, healthy control; CM, conventional medical treatment; ER, enriched rehabilitation treatment; MoCA, Montreal Cognitive Assessment; ASL, alanine aminotransferase; AST, aspartate aminotransferase.

Serum Glutamate, MDA, and TNF Levels in Patients With PSCI Improved After ER Intervention

Pre-intervention, serum glutamate, MDA, and TNF levels in patients with PSCI differed significantly ($p < 0.05$) from those in the HC group; however, no differences were detected between the two groups of patients with PSCI ($p > 0.05$) for the above indicators. After the intervention, the serum levels of glutamate, MDA, and TNF in both the PSCI groups were significantly improved compared with the pre-intervention levels ($p < 0.05$). Additionally, the levels of the above indicators in the ER group were significantly better than those in the CM group ($p < 0.05$). However, post-intervention, the serum levels of glutamate, MDA, and TNF in patients with PSCI were still significantly different from those in the HC group ($p < 0.05$) (**Table 3** and **Figure 3**).

DISCUSSION

Enriched rehabilitation represents a novel therapeutic strategy that has been used to enhance neuroplasticity and improve functional outcomes in animal models with central nervous system diseases, including stroke and perinatal hypoxia–ischemia (31, 32). In the present study, we investigated the effect of ER on cognitive function in patients with PSCI as well as the associated underlying mechanisms and provided evidence for the impact of ER in a clinical setting. We found that the serum glutamate level was higher in patients with PSCI than in HCs. Our data further indicated that ER could enhance cognitive function in patients with PSCI, with the results suggesting that this effect may be related to its effect on decreasing serum glutamate levels. In addition, it was found that oxidative stress and inflammation, as indicated by the serum levels of MDA and TNF in patients with PSCI, alleviated after ER intervention.

Post-stroke cognitive impairment is a common complication in stroke survivors that requires complex treatment regimens. ER represents a non-pharmacological therapeutic strategy that combines environmental enrichment with task-oriented exercises, in which a multistimuli environment is accompanied by high-quality social and cognitive exercises. Animal studies have suggested that ER may be a viable approach for treating PSCI (32–34). Additionally, there is some clinical evidence to support that ER exerts a beneficial effect on overall function in stroke patients (9, 35). As expected, in this study, we observed that ER led to a significant improvement ($p < 0.05$) in the overall cognitive function, attentional function, and executive function in patients with PSCI, as determined by the MoCA, SDMT, and TMT scores.

Cognitive function requires the participation of a variety of neurotransmitters, which have to do with synaptic plasticity (36, 37). Glutamate, the major excitatory neurotransmitter in the central nervous system, plays an important role in synaptic

TABLE 2 | Indexes of cognitive function in each group during pre-intervention and post-intervention.

	HC group ($n = 20$)	CM group ($n = 20$)	ER group ($n = 20$)	F/χ^2	*P*
MoCA					
Pre-intervention	29(28∼29.25)[&]	19.5(18∼21)*	19.5(17∼21)*	40.12	<0.01
Post-intervention	–	24(21∼25)*[$]	26(24∼28)*[,#,$]	42.23	<0.01
SDMT					
Pre-intervention	76.95 ± 6.40[&]	44.65 ± 10.71*	45.55 ± 7.55*	95.46	<0.01
Post-intervention	–	57.75 ± 9.75*[$]	68.35 ± 11.96*[,#,$]	19.88	<0.01
TMT-A					
Pre-intervention(s)	49.78 (46.03∼54.79)[&]	58.28(52.66∼77.78)*	62.94 (43.61∼71.48)*	7.89	0.02
Post-intervention(s)	–	57.22 (49.43∼75.83)	62.27 (46.39∼71.11)	5.45	0.06
TMT-B					
Pre-intervention(s)	97.06 ± 21.85[&]	144.62 ± 31.03*	149.93 ± 36.26*	18.45	<0.01
Post-intervention(s)	–	132.85 ± 31.62*	126.86 ± 27.94*[,$]	9.76	<0.01

*Compared with the HC group, $p < 0.05$.
[&]Compared with the CM group pre-intervention, $p < 0.05$.
[#]Compared with the CM group post-intervention, $p < 0.05$.
[$]Compared with the same group pre-intervention, $p < 0.05$.
n, number of cases; HC, healthy control; CM, conventional medical treatment; ER, enriched rehabilitation treatment; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B.
F/χ^2 and P-values came from a statistical analysis of between-group differences (ER, CM, and HC groups) for continuous variables, and other values of statistical analysis are shown in ***Supplementary Materials****.*

plasticity, as well as in learning and memory processes (38, 39). However, an excess of glutamate in the brain can lead to mitochondrial damage and, consequently, the overproduction of reactive oxygen species (ROS) (40, 41). The resulting oxidative stress and inflammation may result in neuronal damage and neurological deficits (42).

The process is as follows: first, excessive glutamate can lead to the overactivation of NMDA receptors in neurons, followed by a massive influx of calcium ions into cells, resulting in mitochondrial damage (43, 44) and the overproduction of ROS (45). Through a series of cascade reactions, these ROS can generate large amounts of peroxides in the brain, such as peroxynitrite (ONOO–), leading to cell death in the central nervous system (12, 46). Second, the glutamate-mediated overactivation of NMDA receptors in neurons can also result in impaired synaptic plasticity and cognitive function (47, 48). Third, other types of receptors for glutamate, such as kainate (KA) and 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, are associated with inflammatory responses (49, 50). The activation of either receptor can promote the release of inflammatory factors. Meanwhile, excessive glutamate can also result in damage to the endothelial cells of the blood–brain barrier, which may allow the invasion of inflammatory factors from the periphery into the central nervous system (51, 52). Hippocampal pyramidal cells are among the most sensitive to the effects of inflammatory factors; accordingly, memory function can be easily impaired under conditions of inflammation (53). Fourth, oxidative stress resulting from increased glutamate levels can interact with and promote post-stroke inflammatory response. Oxidative stress induces the activation of adhesion molecules and promotes the infiltration of immune cells, which, in turn, aggravates the inflammatory reactions in the peripheral immune system and the central nervous system (54).

In addition, under physiological conditions, intracerebral nitric oxide (NO) produced by nNOS mediates communication between nerve cells. However, under inflammatory conditions, iNOS overexpression in cerebral vascular smooth muscle cells and macrophages leads to excessive NO production (55), further aggravating the inflammatory response and contributing to secondary injury after stroke (12). Therefore, it was found that a high glutamate level in the brain tissue and cerebrospinal fluid was associated with poor cognitive outcomes in stroke (13).

Metabolites can be transferred between cerebrospinal fluid and blood through meninges (56, 57). A positive correlation has been established between the level of glutamate in the serum and in the cerebrospinal fluid (11, 58). Therefore, the level of glutamate in the serum can indirectly reflect the level of glutamate in the brain. In our study, we have shown that the serum glutamate level was significantly higher ($p < 0.05$) in patients with stroke than in HCs, which is consistent with previous findings (12). However, we observed that the glutamate level was decreased in both the ER and CM groups after the different interventions ($p < 0.05$). Surprisingly, the serum glutamate level in the ER group was reduced to a greater extent than that in the CM group post-intervention ($p < 0.05$). The above results suggested that the efficacy of ER in enhancing cognitive function in patients with PSCI may be related to its effect on decreasing serum glutamate levels. However, the underlying molecular mechanisms require further investigation.

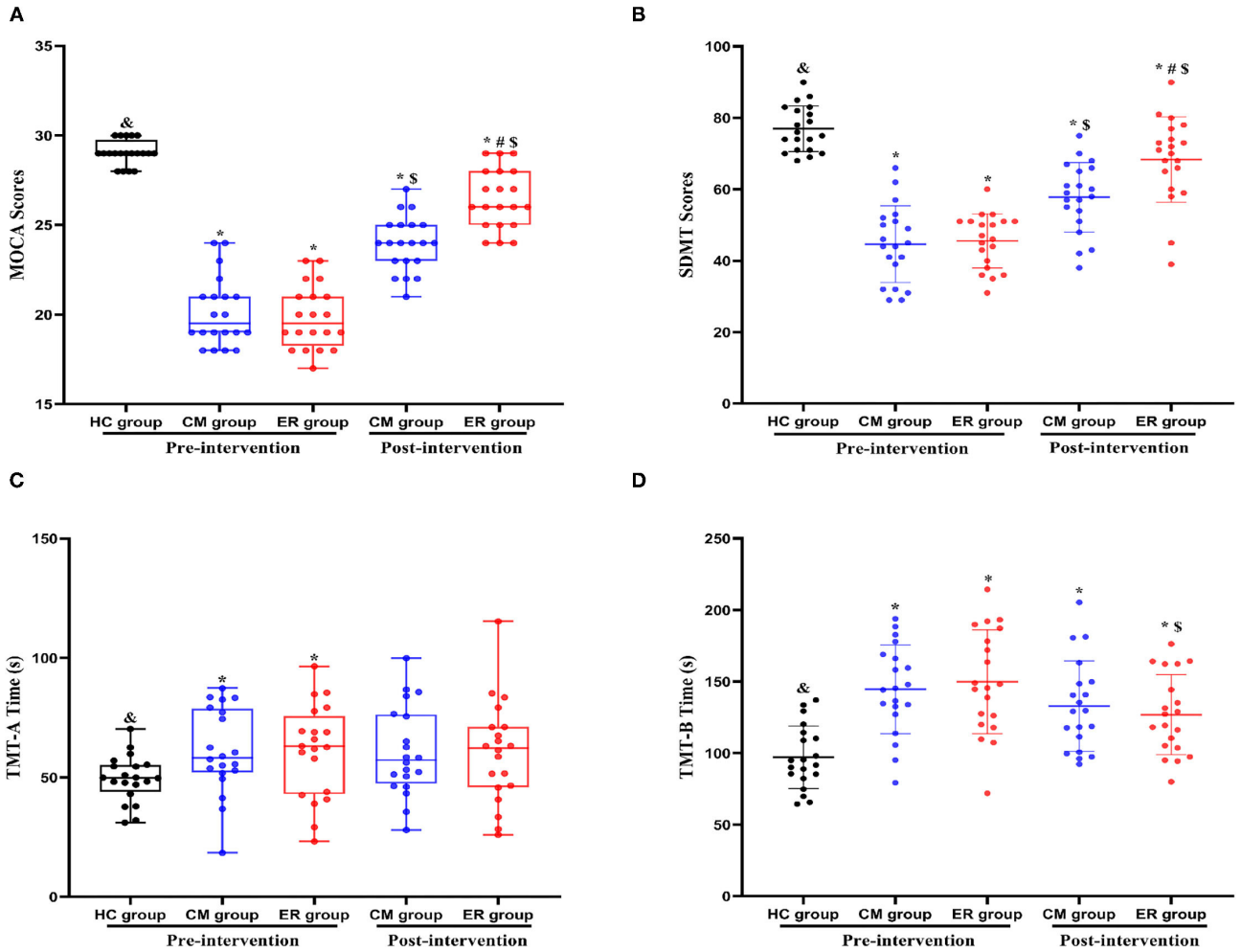

FIGURE 2 | Indexes of cognitive function in each group pre-intervention and post-intervention. *Compared with the HC group, $p < 0.05$. $^{\&}$Compared with the CM group pre-intervention, $p < 0.05$. $^{\#}$Compared with the CM group post-intervention, $p < 0.05$. $^{\$}$Compared with the same group pre-intervention, $p < 0.05$. HC, healthy control; CM, conventional medical treatment; ER, enriched rehabilitation treatment; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B. **(A)** The scores of MOCA test pre-intervention and post-intervention; **(B)** the scores of SDMT test pre-intervention and post-intervention; **(C)** the time consumption of TMT-A pre-intervention and post-intervention; **(D)** the time consumption of TMT-B pre-intervention and post-intervention.

As previously mentioned, oxidative and inflammatory mechanisms also play a pathogenic role in the process of cognitive impairment post-stroke (12, 54). In this study, we found that the serum levels of MDA, a marker of the oxidative stress response, and TNF, a marker of the inflammatory response, were significantly increased in patients with PSCI compared with those in the HC group. Additionally, in line with the changes observed in the serum glutamate levels, the serum levels of MDA and TNF in the ER group showed a more significant reduction compared with those in the CM group post-intervention ($p < 0.05$). We inferred from the above results that ER can improve cognitive function by abrogating oxidative stress and neuroinflammation induced by increased levels of glutamate post-stroke.

The strengths of our study were that, in addition to the behavioral assessment, we also analyzed serum glutamate levels in patients with PSCI during pre-intervention and post-intervention. Additionally, we investigated oxidative stress- and inflammation-related mechanisms mediated by ER through the measurement of serum MDA and TNF levels. Nonetheless, our study also had several limitations. First, this study was conducted in only one hospital and the sample size was small, which is likely to introduce bias. Additionally, due to the small sample size, we did not stratify participants based on different cognitive levels, which may mask the effect of ER. Furthermore, we could only infer the preliminary mechanisms involved in the effects of ER on PSCI; identification of the precise underlying mechanisms will be explored in a future study.

In conclusion, the present study provided clinical evidence that ER can improve cognitive function in patients with PSCI. The associated mechanism may be related to the negative regulatory effect of ER on serum glutamate, TNF, and MDA

TABLE 3 | The results of serum indexes in each group pre-intervention and post-intervention.

	HC group ($n = 20$)	CM group ($n = 20$)	ER group ($n = 20$)	F/χ^2	*P*
GLUTAMATE					
Pre-intervention (μmol/L)	73.02 ±11.35$^{\&}$	123.56 ± 20.87*	125.54 ± 21.75*	51.25	<0.01
Post-intervention (μmol/L)	–	101.46 ± 24.22$^{*,\$}$	86.98 ± 23.29$^{*,\#,\$}$	10.02	<0.01
MALONDIALDEHYDE					
Pre-intervention (μmol/L)	2.21 ± 1.01$^{\&}$	6.15 ± 1.16*	6.35 ± 1.12*	90.31	<0.01
Post-intervention(μmol/L)	–	4.78 ± 1.52$^{*,\$}$	3.32 ± 1.71$^{*,\#,\$}$	15.96	<0.01
TNF					
Pre-intervention (pg/ml)	13.12 (10.75∼14.89)$^{\&}$	30.74 (28.03∼37.01)*	30.84 (27.76∼36.45)*	39.35	<0.01
Post-intervention(pg/ml)	–	24.23 (21.77∼26.46)$^{*,\$}$	21.24 (18.34∼23.37)$^{*,\#,\$}$	31.41	<0.01

*Compared with the HC group, $p < 0.05$.
$^{\&}$Compared with the CM group pre-intervention, $p < 0.05$.
$^{\#}$Compared with the CM group post-intervention, $p < 0.05$.
$^{\$}$Compared with the same group pre-intervention, $p < 0.05$.
n, number of cases; HC, healthy control; CM, conventional medical treatment; ER, enriched rehabilitation treatment.
*F/χ^2 and P-values came from a statistical analysis of between-group differences (ER, CM, and HC groups) for continuous variables, and other values of statistical analysis are shown in **Supplementary Materials**.*

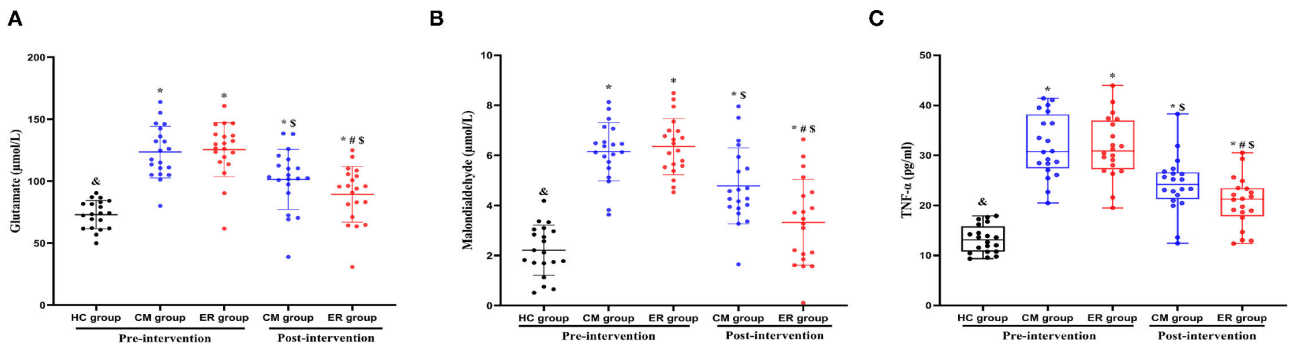

FIGURE 3 | The results of serum indexes in each group pre-intervention and post-intervention. *Compared with the HC group, $p < 0.05$. $^{\&}$Compared with the CM group pre-intervention, $p < 0.05$. $^{\#}$Compared with the CM group post-intervention, $p < 0.05$. $^{\$}$Compared with the same group pre-intervention, $p < 0.05$. HC, healthy control; CM, conventional medical treatment; ER, enriched rehabilitation treatment; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test part A; TMT-B, Trail Making Test part B. **(A)** Serum glutamate level pre-intervention and post-intervention; **(B)** serum MDA level pre-intervention and post-intervention; **(C)** serum TNF level pre-intervention and post-intervention.

levels, which is likely to enhance synaptic plasticity and alleviate oxidative stress- and inflammation-related damage, at least to some extent.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of Clinical Medical College of Yangzhou University (Ethical Approval No. 2016055). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XW, YP, and JG designed the study and wrote the manuscript. XW, YP, HZ, WD, JuW, JiW, TW, XT, and YL performed the experiments. XW, YP, HZ, WD, JuW, and JG analyzed the data. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Combining Robot-Assisted Gait Training and Non-Invasive Brain Stimulation in Chronic Stroke Patients: A Systematic Review

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Gait impairment is one of the most common disorders of patients with chronic stroke, which hugely affects the ability to carry out the activities of daily living and the quality of life. Recently, traditional rehabilitation techniques have been associated with non-invasive brain stimulation (NIBS) techniques, which enhance brain plasticity, with the aim of promoting recovery in patients with chronic stroke. NIBS effectiveness in improving gait parameters in patients with chronic stroke has been in several studies evaluated. Robotic devices are emerging as promising tools for the treatment of stroke-related disabilities by performing repetitive, intensive, and task-specific treatments and have been proved to be effective for the enhancement of motor recovery in patients with chronic stroke. To date, several studies have examined the combination of NIBS with robotic-assisted gait training, but the effectiveness of this approach is not yet well established. The main purpose of this systematic review is to clarify whether the combination of NIBS and robot-assisted gait training may improve walking function in patients with chronic stroke. Our systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Studies eligible for review were identified through PubMed/MEDLINE, Embase, Scopus, and PEDro from inception to March 15, 2021, and the outcomes considered were gait assessments. Seven studies were included in the qualitative analysis of this systematic review, with a total population of 186 patients with chronic stroke. All studies specified technical characteristics of robotic devices and NIBS used, with high heterogeneity of protocols. Methodological studies have shown a significantly greater improvement in walking capacity recorded with 6MWT. Finally, research studies have highlighted a positive effect on walking recovery by combination of robot-assisted gait training with non-invasive brain stimulation. Furthermore, future studies should identify the best characteristics of the combined therapeutic protocols.

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Keywords: robotics, transcranial direct current stimulation, chronic stroke, robot-assisted, exoskeleton, transcranial magnetic stimulation, TMS, NIBS

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INTRODUCTION

Stroke is the leading cause of disability worldwide. In Europe, in 2017, there were 1.12 million strokes (1). In the United States, more than 795,000 have a stroke each year, and about 610,000 of these are first strokes (2). Motor impairment is the most common consequence of stroke, which can be regarded as loss or limitation of function in muscle control or movement in an arm and a leg on one side of the body (3). Motor impairment of the lower limb, frequently present among patients with stroke, often results in gait disorders, hugely impacting the ability to carry out the activities of daily living and the quality of life (4, 5). Despite the efficacy of a large variety of physiotherapy interventions in improving functional outcomes in all post-stroke phases (6, 7), 6 months after stroke, more than 30% of survivors cannot walk independently (3). For this reason, it is necessary to develop novel neurorehabilitation treatments to minimize long-term disability (8).

Based on this, in recent decades, new technologies have been introduced and coupled with physical therapy with the aim of enhancing motor recovery of the lower limbs and walking ability. Among these, the use of robotic devices is emerging as promising tools for the treatment of stroke-related disabilities; robotic devices allow repetitive, intensive, and task-specific treatments that have been proved to be effective for promoting motor recovery in patients with chronic stroke (9). Robotics devices for walking rehabilitation can be classified according to the way they assist a patient's lower limbs. Morone et al. (10) distinguished two groups of these devices: exoskeletons that move the hip, knee, and ankle joints during the gait phases, and end-effector robots that move only the feet, often positioned on a support that imposes a specific trajectory, simulating the stance and swing phases during gait training.

A recent meta-analysis has shown that people who receive electromechanical-assisted gait training in combination with physiotherapy after stroke are more likely to achieve independent walking than people who receive gait training without these devices (11). Moreover, several studies have shown that robotic-assisted gait training (RAGT) led to functional improvement even in the chronic phase of stroke (12, 13). Parallelly, the potential of rehabilitation techniques has been enhanced by the use of non-invasive brain stimulation (NIBS), which facilitates neuroplasticity. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are the two most common types of NIBS, which, by modulating cortical excitability, may induce plastic changes in the brain (14). tDCS and TMS techniques seem to be effective in enhancing motor performance in patients with stroke (15–17). NIBS effectiveness in improving gait parameters has been proved by several randomized controlled trials on patients with chronic stroke (18, 19). Although tDCS in association with neurorobotics was suggested as feasible, the efficacy is currently under debate (20).

In this regard, NIBS and neurorobotics training or functional task training (21) have been combined with the aim of maximizing the enhancement of cortical plasticity. Therefore, RAGT will help improve the walking ability of patients with chronic stroke. Optimization of training protocol, promoting active participation of patients, and the use of add-on techniques, such as tDCS (22), may be considered to enhance the effects of RAGT in patients with chronic stroke. However, to date, the efficacy of NIBS, combined with robotic-assisted gait training, has not been well established. Therefore, the main purpose of this systematic review is to clarify whether the combination of NIBS and robot-assisted gait training may improve walking function in patients with chronic stroke.

MATERIALS AND METHODS

The systematic review was conducted in three steps in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (23) 1. literature search; 2. data extraction, and 3. critical appraisal. The review protocol has been registered on PROSPERO (registration ID: CRD42021244869) (International Prospective Register of Systematic Reviews).

Literature Search

An online systematic search was performed using the most popular electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science (WOS), Ebsco, and PEDro from inception to March 15, 2021. We used the combination of medical subject heading (MeSH) terms and free-text terms and were adjusted according to specification of each database. The search strategy is shown in Appendix 1 in **Supplementary Material**. The language of publication was limited to English. We selected all design studies that use NIBS coupled with RAGT. Three reviewers (B.C., L.C., and M.B.) independently and synchronously screened the titles and abstracts to identify potentially eligible articles. In case an article was only selected by one reviewer, the three reviewers discussed whether to include a study in the full-text analysis. A fourth reviewer (A.M.C.) was consulted in case a consensus between the first three reviewers was not reached. Subsequently, all the reviewers independently assessed the full text of the selected articles. After the selection of eligible studies, data were extracted, included the first author's full-name, year of publication, type of study, number of intervention and the control group, characteristics of population (e.g., mean age, prevalence of male), characteristics of stroke, type of exoskeleton and NIBS used, duration and follow-up, and outcomes used.

Data Extraction

In agreement with the PRISMA guidelines (23), we reported the results using the PICOST-DS tool, focusing on the participant, intervention, comparator, outcomes, time, setting, study design (24). The PICOST-DS model was adopted to conduct an evidence-based practice literature search and, consequently, to enhance the quality of health education interventions and programs (25) (**Table 1**).

Critical Appraisal

The methodological quality was assessed using the version two of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (26) to evaluate the quality of randomized controlled trials (RCTs).

Instead, we used methodological index for non-randomized studies (MINORS) (27) to examine non-RCTs studies. The RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Within each domain, a series of questions ("signaling questions") aim to elicit information about features of the trial that is relevant to risk of bias. A proposed judgment about the risk of bias arising from each domain is generated by an algorithm based on answers to the signaling questions. Judgment can be "low" or "high" risk of bias, or can express "ome concerns" (26). The MINORS index includes 12 items that are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate), the global ideal score being 16 for non-comparative studies and 24 for comparative studies.

TABLE 1 | The PICOTS-SD model.

P-Participants	Adult (> 18 years) Affected with chronic (> 6 months) stroke
I-Intervention	EXOSKELETON associated with Non Invasive Brain Stimulation (NIBS)
C-Comparator	Presence of a control group with characteristics comparable to the experimental group
O-Outcomes	Focus on mobility index
T-Time	No limits of time were imposed
S-Setting	Rehabilitation both inpatients and outpatients
SD-Study design	All design studies

PICOTS-SD = participant, intervention, comparator, outcomes, time, setting, study design.

RESULTS

Data Synthesis

A flow diagram of the research is reported in **Figure 1**. We found 319 records through the research method. After screening of the title and abstract, 303 articles were excluded because they did not meet our inclusion criteria (**Table 1**). Therefore, 17 articles were assessed for eligibility. After full-text reading, 7 studies were included in the qualitative analysis of this systematic review (20, 22, 28–32). The characteristics of the included studies are summarized in **Table 2**. It was revealed that studies were published between 2011 (22) and 2020 (28). Except for one retrospective clinical study (28), all the included studies were RCTs, and four of these studies were designed as pilot RCT (22, 29, 30, 32) and one as feasibility RCT (20).

Population

The studies included a total population of 186 patients with chronic stroke (72 females) aged ≥ 18 years. The sample size of the studies ranged from 8 (20) to 40 (31), and mean patients' age in the studies ranged from 61 (29) to 72 (28) years. According to the inclusion criteria, time from the stroke onset is ≥ 6 months for all selected study: mean time between the stroke onset and the

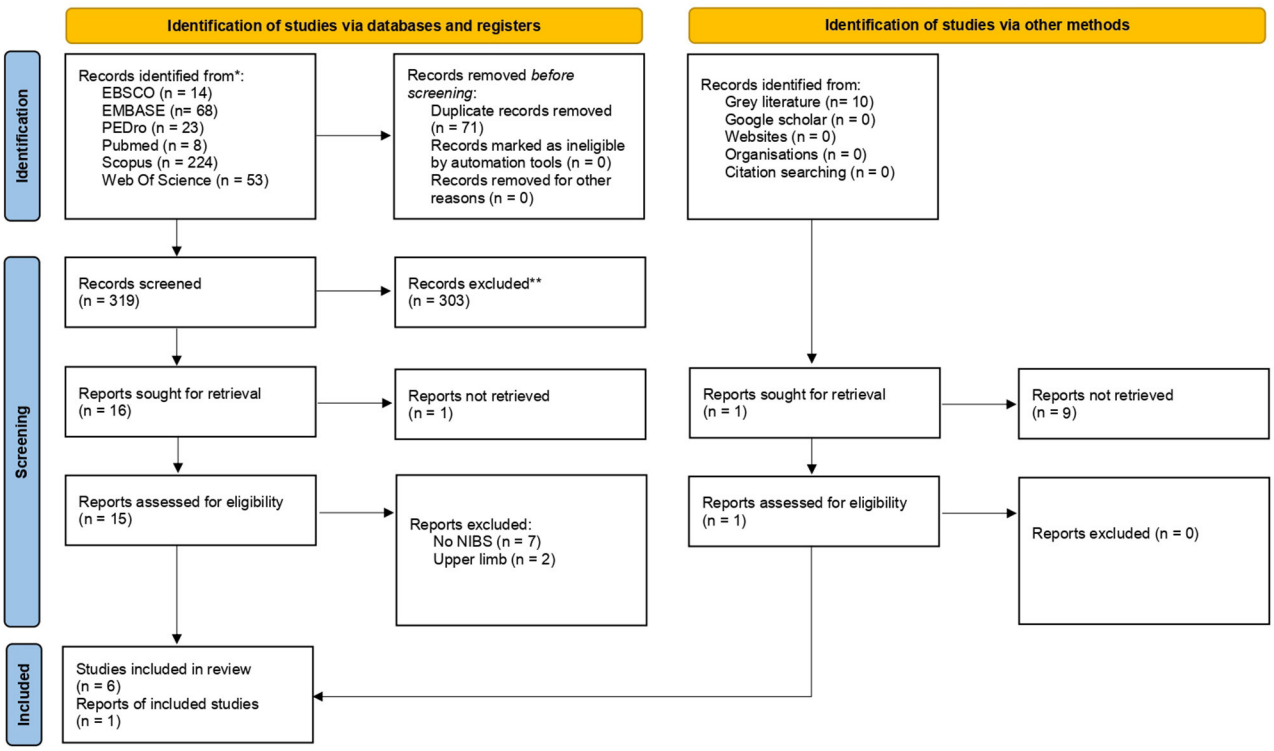

FIGURE 1 | PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. From Page et al. (23).

TABLE 2 | Characteristics of included studies.

Author	Study design	Group 1			Group 2			Group 3			Additional Therapy	Outcome	Follow-up	Drop out
		Robotic device	Type of NIBS and additional stimulation	Intervention frequency	Robotic device	Type of NIBS and additional stimulation	Intervention frequency	Robotic device	Type of NIBS and additional stimulation	Intervention frequency				
Danzl et al. (20)	Feasibility of an RCT study	Lokomat (Hocoma Inc, Zurich, Switzerland)	tDCS	3 days/week, for 4 weeks (20–40 mins)	Lokomat (Hocoma Inc, Zurich, Switzerland)	Sham tDCS	3 days/week, for 4 weeks (20–40 mins)	–	–	–	–	10MWT; BBS, FAC, SIS-16, TUG, qualitative data	After treatment, 1 month after treatment	2 during follow-up evaluation
Geroin et al. (22)	Pilot RCT	Gait Trainer GT1 (Reha-Stim, Berlin, Germany)	tDCS	5 days/week for 2 weeks (50-mins)	Gait Trainer GT1 (Reha-Stim, Berlin, Germany)	Sham tDCS	5 days/week for 2 weeks (50-mins)	–	–	5 days/week for 2 weeks (50-mins)	30 mins of LL muscle strengthening and JM	6MWT, 10MWT, FAC, MAS, MI leg subscore, R-MI, ST gait parameters	After treatment, 1 month after treatment	–
Naro et al. (28)	Retrospective clinical study	Lokomat®Pro (Hocoma Inc, Zurich, Switzerland)	bi-hemispheric dstDCS on-RAGT	6 days/week, for 8 weeks (60-mins)	Lokomat®Pro (Hocoma Inc, Zurich, Switzerland)	bi-hemispheric dstDCS post-RAGT	6 days/week, for 8 weeks (60-mins)	Lokomat®Pro (Hocoma Inc, Zurich, Switzerland)	bi-hemispheric dstDCS pre-RAGT	6 days/week, for 8 weeks (60-mins)	physical rehabilitation program (1 h) daily	6MWT, 10MWT, FAC, FIM, MI, MEP, Tinetti Scale	After treatment; 1 month and 3 months after treatment	2: 1 during treatment and 1 during follow-up evaluation
Picelli et al. (29)	Pilot RCT	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Anodal tDCS+ Sham tsDCS	5 days/week for 2 weeks (20 mins)	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Sham tDCS + cathodal tsDCS	5 days/week for 2 weeks (20 mins)	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Anodal tDCS+ Cathodal tsDCS	5 days/week for 2 weeks (20 mins)	–	6MWT, FAC, MAS, MI leg subscore, R-MI, ST gait parameters	After treatment; 2 weeks and 4 weeks after treatment	–
Picelli et al. (29)	Pilot RCT	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Cathodal tDCS on the CL cerebellar hemisphere + cathodal tsDCS	5 days/week for 2 weeks (20 mins)	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Anodal tDCS over the IL cerebral hemisphere + cathodal tsDCS	5 days/week for 2 weeks (20 mins)	–	–	–	–	6MWT, AS, FAC, MI, ST gait parameters	After treatment; 2 weeks and 4 weeks after treatment	–
Picelli et al. (31)	RCT	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Cathodal tDCS over the CL cerebellar hemisphere + cathodal tsDCS	5 days/week for 2 weeks (20 mins)	G-EO System Evolution (Reha Technology, Olten, Switzerland)	Cathodal tDCS over the IL cerebellar hemisphere + cathodal tsDCS	5 days/week for 2 weeks (20 mins)	–	–	–	–	6MWT, AS, FAC, MI STgait parameters	After treatment; 2 weeks and 4 weeks after treatment	1 during follow-up evaluation
Seo et al. (30)	Pilot RCT	Walkbot_S (Walkbot_S; P&S Mechanics, Seoul, Republic of Korea)	tDCS	5 days/week for 2 weeks (45 mins)	Walkbot_S (Walkbot_S; P&S Mechanics, Seoul, Republic of Korea)	Sham tDCS	5 days/week for 2 weeks (45 mins)	–	–	–	–	6MWT, 10MWT, BBS, FAC; FMA-LE, MRC	After treatment; 4 weeks after treatment	4 during follow-up evaluation

6MWT, 6-min walking test; 10MWT, 10-meter walking test; AS, Ashworth scale; BBS, Berg balance scale; CL, contralesional; FAC, functional ambulatory category; FIM, functional independence measure; FMA-LE, Fugl-Meyer assessment of lower extremity; IL, ipsilesional; JM, joint mobilization; LL, lower limb; MAS, modified Ashworth scale; MEP, motor-evoked potentials; MI leg subscore, Motricity index leg subscore; MRC, medical research council scale; RCT, randomized control trial; R-MI, rivermead motricity index; SIS-16, stroke impact scale 16; ST, spatiotemporal; tDCS, transcranial direct current stimulation; tsDCS, transpinal direct current stimulation; TUG, timed up and go.

start of treatment ranged between 10 (28) and 152.5 months (30) (see **Table 3**).

Intervention

The approach used in the intervention group was combined robot-assisted gait training and NIBS stimulation, with the latter performed before training (20, 28, 30), during training (22, 28, 29, 31, 32), or after training (28) (complete treatment characteristics are reported in **Table 2**).

Robotic Treatment Characteristics

All studies specified technical characteristics of robot devices (i.e., the model, the manufacturing company, and the country of production): G-EO System Evolution (Reha Technology, Olten, Switzerland) was the only one used in more than one study (29, 31, 32). Other robotic devices utilized were Gait Trainer GT1 (Reha-Stim, Berlin, Germany) (22); Lokomat (Hocoma Inc., Zurich, Switzerland) (20);; Lokomat®Pro (Hocoma Inc., Zurich, Switzerland) (26), and Walkbot_S (P&S Mechanics, Seoul, Republic of Korea) (30). Intervention frequency ranged from 3 times a week (20) to 6 times a week (28), with a mean duration session of 33 min (minimum of 20 min; maximum of 60 min); however, more than half of the training programs was carried out 5 times a week for 2 weeks, and every session lasted 20 min (22, 29, 31, 32). Two studies added a traditional therapy to the robotic one; Geroin et al. (22) associated lower limbs muscle strengthening and joint mobilization exercises with exoskeleton therapy, and Naro et al. (28) added 1 h of a physical rehabilitation program. Conventional therapy and exoskeleton therapy with sham NIBS were mostly provided for the control group. One study (30) was sponsored by the manufacturer of the gait robot. For other studies, it was either explicitly declared that the work was not supported by any grant from the public or private sector or that there was nothing to disclose financially (20, 22, 28), or information funding was not available (29, 31, 32).

NIBS Characteristics

All studies included in the systematic review used tDCS treatment, however, with high heterogeneity of protocols. All the studies set the intensity of stimulation at 2 mA with the exception of one using 1.5 mA (22). The electrode positioning area was specified for each study, following the 10–20 international EEG system (33). The cortical motor area was the most used site of stimulation, with exception of two studies (31, 32), in which the position of the electrodes varied according to the study group analyzed. Regarding electrodes, five studies (20, 22, 28–30) used a rectangular electrode, while the remaining two studies (31, 32) used circular electrodes. In addition, the Cathodal and Anodal electrodes had the same size—only Danzl et al. (20) – used an anodal electrode smaller than the cathodal one (25 vs. 35 cm^2). The duration of stimulation ranged from 7 to 20 min, five out seven studies used 20 min of stimulation, while Geroin et al. (22) used 7 min of stimulation, and Naro et al. (28) used 10 min of stimulation. The technical data of the stimulator (i.e., name, the manufacturing company, and the country of production) were available for all the studies other than Danzl et al. (20) and Naro et al. (28) (complete NIBS characteristics are available in **Table 4**).

Comparison

In the studies selected for the current systematic review, only three studies used a RCT sham controlled study design (20, 22, 30). Three studies are methodological studies, in which randomization was used to test different stimulation sites (i.e., cerebellum or spinal cord) or different types of stimulation (anodal and cathodal) (29, 31, 32). In the last study (28), a comparison was performed between the effects of NIBS delivered before, during, or after RAGT.

Outcome

In two out three studies that compared real stimulation (anodal on M1) and sham stimulation (supraorbital stimulation), a significant clinical improvement was found in the real group with respect to the sham group. Danzl et al. (20) found a statistical difference (time x group interaction) in the FAC, TUG, and SIS-16 score evaluated before and immediately after training. Seo et al. (30) found a statistical improvement in the real group in the FAC and 6MWT score at a 4-week follow-up. Geroin et al. (22) reported only a TIME effect between the two groups without time x group interaction (real vs. sham) (**Table 2**).

Methodological studies have shown a significantly greater improvement in a walking capacity recorded with 6MWT. Picelli et al. (29) find a statistical improvement in groups that underwent anodal tDCS + cathodal spinal stimulation (tsDCS) during RAGT with respect to anodal tDCS or cathodal tsDCS alone. In Picelli et al. (32), a significant improvement was found in the group undergoing a cathodal cerebellar stimulation plus cathodal tsDCS with respect to the patients that underwent anodal tDCS plus cathodal tsDCS. Differently, no difference has been reported by two different protocols of cerebellar transcranial direct current stimulation combined with transcutaneous spinal direct current stimulation on RAGT (31) and in the comparison of dual-site direct current stimulation (dstDCS) performed before, during, and after RAGT (28).

All the studies performed the clinical evaluation before, after treatment, and in the post-intervention follow-up. Time between the end of the treatment and the follow-up ranged between 2 weeks (29, 31, 32) and 3 months (28). More than half of the included studies (28, 29, 31, 32) had outcome measurements at multiple time points, up to 3 months after the intervention. All the studies used the functional ambulatories category (FAC), of which two used it as primary outcome measure (28, 30). The 6-meter walking test (6MWT) was assessed in 5 out of seven studies (22, 28, 29, 31, 32) as a primary outcome, while Seo et al. (30) used it as a secondary outcome. More than a half of the studies (22, 29, 31, 32) analyzed spatiotemporal gait parameters as a secondary outcome. Other scales that were frequently used were Motricity Index leg-subscore (22, 28, 29, 31, 32), 10-meter walking test (10MWT) (18, 20,26;, 28), and Ashworth scale (29, 31, 32). Outcomes that were less considered were Berg Balance Scale (BBS), Fugl-Meyer Assessment of Lower Extremity (FMA-LE), Medical Research Council (MRC) Scale, Modified Ashworth Scale (MAS), Rivermead Mobility Index, Stroke Impact Scale 16 (SIS-16), Timed Up and Go (TUG), Functional Independence Measure (FIM), and Tinetti Scale. Additionally, Naro et al. (28) investigated the ratio between the motor-evoked potential

TABLE 3 | Characteristics of the participants.

Study	Group 1		Group 2		Group 3	
	Characteristics of participants	**Characteristics of stroke**	**Characteristics of participants**	**Characteristics of stroke**	**Characteristics of participants**	**Characteristics of stroke**
	N.participants (F:M) Age (mean ± SD)	Type of stroke (I:H) Months after stroke (mean ± SD) Affected hemisphere (L:R) Lesion localization (%)	N.participants (F:M) Age (mean ± SD)	Type of stroke (I:E) Months after stroke (mean ± SD) Affected hemisphere (L:R) Lesion localization	N.participants (F:M) Age (mean ± SD)	Type of stroke (I:E) Months after stroke (mean ± SD) Affected hemisphere (L:R) Lesion localization
Danzl et al. (20)	4 (1:3) 64.75 ± 12.87	Chronic stroke (2:2) Months after stroke 57.3 ± 55.3 Affected hemisphere: (4:0) lesion localization: N/A	4 (3:1) 70.75 ± 9.65	Chronic stroke (4:0) Months after stroke: 26.7 ± 5.1 Affected hemisphere: (4:0) lesion localization: N/A	–	–
Geroin et al. (22)	10 (2:8) 63.6 ± 6.7	Chronic stroke (10:0) Months after stroke	10 (4:6) 63.3 ± 6.4	Chronic stroke (10:0) Month after stroke: 26.7 ± 5.1 Affected hemisphere: N/A Lesion localization: cortical 50%; subcortical 20%; mixed 30%	10 (1:9) 61.1 ± 6.3	Chronic stroke (10:0) Month after stroke: 26.9 ± 5.0 Affected hemisphere N/A Lesion localization: cortical 30%; subcortical 40%; mixed 30%
Naro et al. (28)	9 (5:4) 68 ± 4	Chronic stroke (9:0) Month after stroke: 10 ± 2 Affected hemisphere (11:4) Lesion localization: cortical 33%; large subcortical 11%; cortical-subcortical 44%; lacunar 11%	15 (9:6) 66 ± 5	Chronic stroke (15:0) Month after stroke: 11 ± 3 Affected hemisphere (11:4) Lesion localization: cortical 40%; large subcortical 13%; cortical-subcortical 40%; lacunar 7%	13 (8:5) 72 ± 4	Chronic stroke (13:0) Month after stroke: 8 ± 2 Affected hemisphere (10:3) Lesion localization: cortical 31%; large subcortical 15%; cortical-subcortical 38%; lacunar 15%
Picelli et al. (29)	10 (3:7) 64.8 ± 6.0	Chronic stroke (10:0) Month after stroke: 61.3 ± 29.3 Affected hemisphere: N\A Lesion localization: cortical 40%; subcortical 30%; mixed 30%	10 (2:8) 61.0 ± 7.2	Chronic stroke (10:0) Month after stroke: 54.8 ± 32.9 Affected hemisphere: N\A Lesion localization: cortical 40%; subcortical 20%; mixed 40%	10 (3:7) 62.8 ± 11.8	Chronic stroke (10:0) Month after stroke: 51.9 ± 41.1 Affected hemisphere: N\A Lesion localization: cortical 30%; subcortical 30%; mixed 40%
Picelli et al. (29)	10 (3:7) 62.6 ± 8.25	Chronic stroke (10:0) Month after stroke: 67.1 ± 46.75 Affected hemisphere: N\A Lesion localization: cortical 30%; subcortical 40%; mixed 30%	10 (4:6) 62.8 ± 11.81	Chronic stroke (10:0) Month after stroke: 51.9 ± 41.15 Affected hemisphere: N\A Lesion localization: cortical 40%; subcortical 30%; mixed 30%	–	–
Picelli et al. (31)	20 (10:10) 63.9 ± 10.6	Chronic stroke (20:0) Month after stroke: 66.4 ± 48.8 Affected hemisphere: N\A Lesion localization: cortical 30%; subcortical 40%; mixed 30%	20 (9:11) 65.6 ± 9.7	Chronic stroke (20:0) Month after stroke: 61.7 ± 40.1 Affected hemisphere: N\A Lesion localization: cortical 40%; subcortical 30%; mixed 30%	–	–
Seo et al. (30)	10 (3:7) 62.9 ± 8.9	Chronic stroke (8:2) Month after stroke: 152.5 ± 122.8 Affected hemisphere (2:8) Lesion localization: N\A	11 (2:9) 61.1 ± 8.9	Chronic stroke (5:6) Month after stroke: 75.5 ± 83.4 Affected hemisphere (5:6) Lesion localization: N\A	–	–

F, female; H, Hemorrhagic stroke; I, ischemic stroke; L, left; M, male; R, right.

TABLE 4 | Characteristics of NIBS.

Study	Stimulator Model (industry, country of production)	Anodal electrode Position; Size (cm^2)	Cathodal electrode Position; Size (cm^2)	Intensity	Duration (min)	Intervention in groups
Danzl et al. (20)	Not specified	CMA controlling leg; 25 cm^2	Supraorbitally 35 cm^2	2 mA	20 min Before training	Group 1: anodal+cathodal tDCS Group 2: sham anodal+sham cathodal tDCS
Geroin et al. (22)	Phyaction 787 (Uniphy, The Netherlands)	Affected CMA presumed controlling leg 35 cm^2	Controlesional orbit 35 cm^2	1.5 mA	7 min During training	Group 1: anodal+cathodal tDCS Group 2: sham anodal+sham cathodal tDCS Group 3: no NIBS
Naro et al. (28)	Not specified	Affected M1 (C3 or C4 position) 35 cm^2	Unaffected M1 (C3 or C4 position) 35 cm^2	2 mA	10 min Group 1: during training Group 2: after training Group 3: before training	Group 1: anodal+cathodal dstDCS Group 2: anodal+cathodal dstDCS Group 3: anodal+cathodal dstDCS
Picelli et al. (29)	Phyaction 787 (Uniphy, The Netherlands)	Affected M1 (C3 or C4 position) 35 cm^2	Unaffected orbit 35 cm^2	2 mA	20 min During training	Group 1: anodal tDCS+sham tsDCS Group 2: sham tDCS+cathodal tsDCS Group 3: anodal tDCS +cathodal tsDCS
Picelli et al. (29)	Starstim®, (Neuroelectrics, Spain)	tcDCS: Controlesional buccinator muscle 12,56 cm^2 tDCS: Lesioned M1, Cz position 12,56 cm^2 tsDCS:shoulder of the unaffected hemibody 23,75 cm^2	tcDCS: Controlesional cerebellar hemisphere (O1 or O2 position) 12,56 cm^2 tDCS: Ipsilesional orbit 12,56 cm^2 tsDCS: D10 spinous process 23,75 cm^2	tcDCS 2 mA tDCS 2 mA tsDCS 2.5 mA	20 min During training	Group 1: cathodal tcDCS+cathodal tsDCS Group 2: anodal tDCS+cathodal tsDCS
Picelli et al. (31)	Starstim®, (Neuroelectrics, Spain)	tcDCS:buccinator muscle 12,56 cm^2 tsDCS: shoulder of the unaffected hemibody 23,75 cm^2	tcDCS: cerebellar hemisphere (O1 or O2 position) 12,56 cm^2 tsDCS: D10 spinous process 23,75 cm^2	tcDCS 2 mA tsDCS 2.5 mA	20 min During training	Group 1: contralesional cathodal tcDCS+cathodal tsDCS Group 2: ipsilesional cathodal tcDCS+cathodal tsDCS
Seo et al. (30)	DC-Stimulator Plus (NeuroConn GmbH, Germany)	CMA presumed controlling affected leg (lateral Cz position) 35 cm^2	Forehead above the contralateral orbit 35 cm^2	2 mA	20 min Before training	Group 1: anodal tDCS Group 2: sham tDCS

CMA, cortical motor area.

TABLE 5 | Results of the studies.

	Primary outcomes	Secondary outcomes
Study		
Danzl et al. (20)	**10MWT**: no significant, but results favored the active tDCS group ($p = 0.19$)	**TUG**: significant improvement in the active tDCS group compared to the sham group ($p = 0.066$) **BBS**: no significant improvement in the active tDCS group compared to the sham group ($p = 0.919$) **FAC**: significant improvement in the active tDCS group compared to the sham group ($p = 0.028$) **SIS-16**: significant improvement in the active tDCS group compared to the sham group ($p = 0.062$)
Geroin et al. (22)	**6MWT**: significant improvement in group 1 and 2 compared to group 3 at T1 and T2. No significant difference between group 1 and 2 **10MWT**: significant improvement in group 1 and 2 compared to group 3 at T1 and T2. No significant difference between group 1 and 2	**Spatiotemporal gait parameters**: no significant differences between group 1 and 2, in both T1 and T2 evaluations. Significant difference between group 1 and 2 compared to group 3 at T1 and T2 evaluations. **FAC**: significant improvement in groups 1 and 2 compared to group 3 at T1 and T2 evaluations. No significant differences between group 1 and 2, in both T1 and T2 evaluations. **R-MI**: significant improvement in groups 1 and 2 compared to group 3 at T1 and T2 evaluations. No significant differences between group 1 and 2, in both T1 and T2 evaluations. **MI**: significant improvement in groups 1 and 2 compared to group 3at T1 and T2 evaluations. No significant differences between group 1 and 2, in both T1 and T2 evaluations. **MAS**: not reported
Naro et al. (28)	**10MWT**: no significant changes **6MWT**: significant difference between the treatmentsover time ($p < 0.001$) in relation to on-RAGTand post-RAGT **FIM**: improvement obtained over time was similar for all groups ($p < 0.001$) **Tinetti Scale**: significant difference between the treatmentsover time ($p < 0.001$) in relation to on-RAGTand post-RAGT **MI**: improvement obtained over time was similar for all groups ($p < 0.001$) **FAC**: significant difference between the treatmentsover time ($p < 0.001$) in relation to on-RAGTand post-RAGT **Ratio between the MEP of the affected and unaffected hemisphere**: MEPaff/unaff ratio was always lower than 1. MEP ratio influenced the dstDCS outcome ($F = 9.6$, $p < 0.001$) with regard to on-RAGT ($p < 0.001$).	–
Picelli et al. (29)	**6MWT**: significant differences in walking distance between the groups at the T1–T0 ($p = 0.014$) and T2–T0 ($P = 0.005$) evaluations. No significant difference between the groups at the T3–T0 evaluation ($P = 0.649$). Significant differencein group 3 vs. group 1 at T1–T0 ($P = 0.015$) and atT2–T0 ($P = 0.001$) evaluations, as well as in group 3 vs. group 2 at T1–T0 ($P = 0.010$) andT2–T0 ($P = 0.015$) evaluations. No significant difference in group 2 vs. group 1 results.	**FAC**: no significant difference between the groups at the T1–T0 ($P = 0.126$), T2–T0 ($P = 0.368$) and T3–T0 ($P = 0.342$) evaluations. **MI**: no significant difference between the groupsatthe T1–T0 ($P = 0.107$), T2–T0 ($P = 0.355$) and T3–T0 ($P = 0.715$) evaluations. **AS**: no significant difference between the groups at the T1–T0 ($P = 0.312$), T2–T0 ($P = 0.259$), and T3–T0 ($P = 0.259$) evaluations. **Cadence**: significant differences between the groups at the T1–T0 ($P = 0.003$) and T2–T0 ($P = 0.016$) evaluationsbut not at the T3–T0 evaluation ($P = 0.405$). Significant difference in group 3 vs.group 1 results at T1–T0 ($P = 0.002$) and T2–T0 ($P = 0.013$) evaluations, as well as in group3 vs. group 2 results at T1–T0 ($P = 0.005$) and T2–T0 ($P = 0.016$) evaluations. No significantdifference in group 2 vs. group 1 **Ratio between single and double support duration**: no significant difference between the groups at T1–T0 ($P = 0.512$),T2–T0 ($P = 0.416$), and T3–T0 ($P = 0.220$) evaluations
Picelli et al. (29)	**6MWT**: significant differences in walking distance between the groups at the T1–T0 ($P = 0.041$). No significant difference betweengroups at T2–T0 ($P = 0.650$) and T3–T0 ($P = 0.545$).	**FAC**: no significant difference between the groups at T1–T0 ($P = 1.000$), T2–T0 ($P = 1.000$) and T3–T0 ($P = 0.317$). **MI**: significant difference between the groupsatT1–T0 ($P = 0.017$), T2–T0 ($P = 0.045$) and T3–T0 ($P = 0.008$). **MAS**: no significant difference between the groups at T1–T0 ($P = 0.210$), T2 ($P = 0.251$) and T3 ($P = 0.644$) **Cadence**: significant differences between the groups at the T1–T0 ($P = 0.019$) but not at T2–T0 ($P = 0.650$) and T3–T0 ($P = 0.545$). **Ratio between single and double support duration**: no significant difference between the groups at T1–T0 ($P = 0.472$),T2–T0 ($P = 0.212$), and T3–T0 ($P = 0.075$) evaluations

(Continued)

TABLE 5 | Continued

	Primary outcomes	Secondary outcomes
Picelli et al. (31)	**6MWT**: no significant difference between the two groups at T1 ($P = 0.976$), T2 ($P = 0.178$) and T3 ($P = 0.069$).	**FAC**: no significant difference between the groupsat T1 ($P = 0.565$), T2 ($P = 0.538$) and T3 ($P = 0.711$) **MI**: no significant difference between the groupsat T1 ($P = 0.854$), T2 ($P = 0.854$) and T3 ($P = 0.806$) **MAS**: no significant difference between the groupsat T1 ($P = 0.720$), T2 ($P = 0.845$) and T3 ($P = 0.721$) **Cadence**: no significant difference between the groupsat T1 ($P = 0.378$), T2 ($P = 0.635$) and T3 ($P = 0.778$) **Ratio between single and double support duration**: no significant difference between the groupsat T1 ($P = 0.867$), T2 ($P = 0.715$) and T3 ($P = 0.666$)
Seo et al. (30)	**FAC**: significant greater improvement in the Anodal groupthan in the Sham group at T2 (66.7% vs. 12.5%, p = 0.024)	**10MWT**: no significant difference between T1 and T0 between the groups **6MWT:** no significant difference between T1 and T0 between the groups **BBS**: no significant difference between T1 and T0 between the groups **FMA-LE**: no significant difference between T1 and T0 between the groups **MRC**: no significant difference between T1 and T0 between the groups **MEP**: no significant difference between the groups

6MWT, 6-min walking test; 10MWT, 10-meter walking test; AS, Ashworth scale; BBS, Berg balance scale; CL, controlesional; FAC, functional ambulatories category; FIM, funtional indipendence measure; FMA-LE, Fugl-Meyer assessment of lower extremity; IL, ipsilesional; JM, joint mobilization; LL, lower limb; MAS, modified Ashworth scale; MEP, motor-evoked potentials; MI leg subscore, motricity index leg subscore; MRC, medical research council scale; R-MI, rivermead motricity index; SIS-16, stroke impact scale 16; ST, spatiotemporal, tDCS, transcranial direct current stimulation; tsDCS, transpinal direct current stimulation; TUG, timed up and go.

(MEP) of the affected and unaffected hemisphere to estimate interhemispheric balance inhibition. **Table 5** shows the results of the studies.

Methodological Quality

Methodological quality was assessed with RoB-2 (26) for all the studies except one (28). As regards to the studies that compared real versus sham stimulation (18, 20, 28), the randomization process showed some concerns in one study (20) that did not report the random generation method. All the other biases were judged as "low risk."

Differently, all the risks of bias of the methodological studies (29, 31, 32) were judged as "low risks." **Figures 2**, **3** show the assessment of the risks of bias with the selected studies.

Naro et al. (28) study was evaluated using the MINORS individual score, and its final rating was 19 over 24. "The follow-up period appropriate to the aim of the study" and "loss to follow-up <5%" did not get a maximum score, while "prospective calculation of the study size" received the minimum score. Details of the MINORS score are reported in **Table 6**.

DISCUSSION

Restoring the ability to walk is the main aim of post-stroke rehabilitation; stroke survivors commonly present reduced ability to walk and limited activities inside and outside their home. Walking has been described to have a greater chance of post-stroke recovery than hand function because it is less dependent on the post-lesion integrity of the corticospinal tract. Although it requires a lower degree of residual motor function after stroke, gait performance often persists impaired in patients with chronic stroke due to decreased dorsiflexors strength and altered interaction between different connected functional networks involved in walking (31). The present systematic review investigated the effects of combining non-invasive brain stimulation with robot-assisted therapy for gait recovery in patients with chronic stroke.

It has been shown that NIBS techniques are able to harness brain plasticity (14), and there are several neurostimulation techniques and clinical applications, both open-loop and closed-loop, which seem to support cerebral neuroplasticity (34); the most studied and used are tDCS and TMS. While researchers have shown that tDCS has the potential to improve upper extremity motor recovery following stroke if paired with intensive motor training, only a few studies have examined the effects of tDCS on lower extremity motor function (20). This systematic review suggests that tDCS of the leg area of the motor cortex in the impaired hemisphere or cerebellar transcranial direct current stimulation (tcDCS) over the contralesional/ipsilesional cerebellar hemisphere combined or not with transcutaneous spinal direct current stimulation (tsDCS) and in addition to RAGT produce an improvement in walking function, in particular regarding walking ability, as measured by FAC, and walking capacity, as measured by 6MWT.

What can be for tDCS and RAGT the correct dosage, intensity, duration, order of application, and, moreover, for tDCS, type of stimulation and the site remains the subject of further studies.

There are few studies that use NIBS in association with RAGT. tDCS is among the NIBS elective technique of neurostimulation used in all clinical trials in combination with RAGT. Five out of seven studies, included in this review, used tDCS treatment protocol, which consisted in the stimulation of the motor cortex for 20 min, 5 days a week, for 2 weeks; despite this, it has not yet been determined the best stimulation site (i.e., affected or contralesional hemisphere) and the best timing of stimulation in patients with stroke (35, 36). Indeed, there was no difference

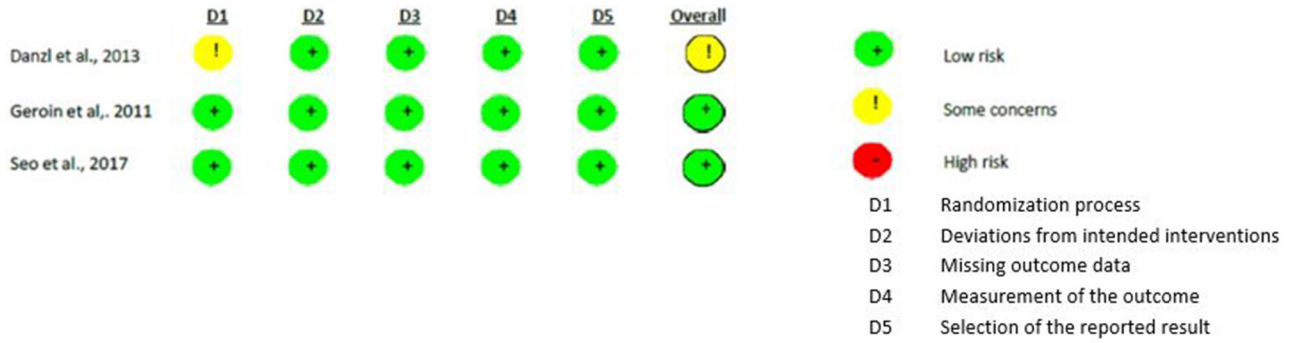

FIGURE 2 | Assessment of Risk of Bias in real versus sham studies.

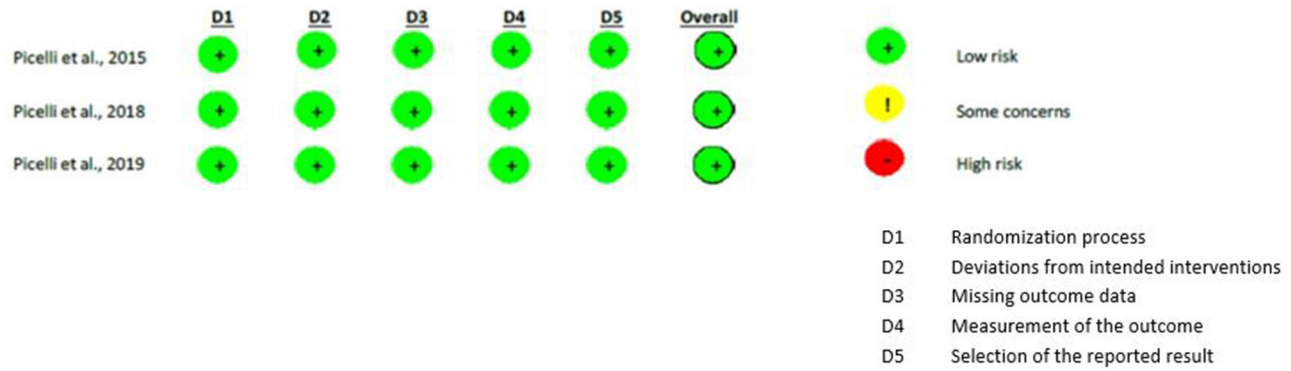

FIGURE 3 | Assessment of Risk of Bias in methodological studies.

whether tDCS was administered before, during, or after the robotic therapy (28). This contrasts with the results found in a study combining tDCS with cognitive exercises that showed improvement in the execution times of the proposed exercises only when the tDCS was performed during training execution (37). Further studies are needed to clarify what is the right timing of stimulation during RAGT.

Furthermore, this systematic review highlighted the need to clarify whether the combination of different sites of tDCS and spinal stimulation can enhance the effects of RAGT; several studies suggest that the stimulation of the nervous system at multiple sites might result in a functional improvement in patients with stroke (e.g., paired associative stimulation—PAS of peripheral and central nervous system) (34). Because the central nervous system (CNS) controls both walking pattern generation and descending control from brain, methods aimed at promoting both spinal and supraspinal activities have been recommended in patients with stroke in order to retrain walking (38). It is plausible that combined supraspinal and spinal stimulation is needed to obtain significant additional effects on RAGT. Thoracic cathodal tsDCS was found to improve motor unit recruitment in healthy people (39). Depending on the topography of spinal cells and the current direction, thoracic cathodal tsDCS should make motoneurons more responsive to synaptic activation but less prone to generate spontaneous activity that inhibits interneuronal networks (39); this could produce positive spasticity control effects, but, furthermore, neurophysiological analyses are required to clarify the effects of tsDCS on muscle overactivity (29) and to investigate both the specific timing in which it is applied and to clarify what the specific factors are that influence its effectiveness. (e.g., state of the brain and spontaneous neuronal activity) (34).

Future pieces of research will have to clarify the role of the combination of TMS with RAGT and the cerebellum implication in stroke recovery; the cerebellum is known to be strongly implicated in the functional reorganization of motor networks in patients with stroke, especially for gait and balance functions. Koch et al. (19) have demonstrated that cerebellar intermittent θ-burst stimulation promotes gait and balance recovery in patients with stroke by acting on cerebello-cortical plasticity. The patients were randomly assigned to treatment with CRB-iTBS or sham iTBS applied over the cerebellar hemisphere ipsilateral to the affected body side immediately before physiotherapy daily, during 3 weeks. The patients treated with CRB-iTBS, but not with sham iTBS, showed an improvement of gait and balance functions, as revealed by a pronounced increase in the mean

TABLE 6 | Individual MINORS score.

	Naro et al. (28)
Clearly stated aim	2
Inclusion of consecutive patients	1
Prospective collection of data	2
Endpoints appropriate to the aim of the study	2
Unbiased assessment of the study endpoint	2
Follow-up period appropriate to the aim of the study	1
Loss to follow up less than 5%	1
Prospective calculation of the study size	0
Additional criteria in the case of comparative study	
An adequate control group	2
Contemporary groups	2
Baseline equivalence of groups	2
Adequate statistical analyses	2
TOTAL SCORE	19

0, not reported; 1, reported but inadequate; 2, reported and adequate.

(SE) Berg Balance Scale score. The patients treated with CRB-iTBS, but not sham iTBS, showed a reduction of step width at the gait analysis and an increase of neural activity over the posterior parietal cortex.

From Wessel et al. (40) in pieces of research, the cerebellum provides unique plasticity mechanisms and has vast connections to interact with neocortical areas. Moreover, the cerebellum could serve as a non-lesioned entry to the motor or cognitive system in supratentorial stroke.

Finally, papers in which a robotic treatment of the lower limb is associated with non-invasive brain stimulation have been few to date for a series of considerations that arise from literature and clinical experience: (1) not all rehabilitation centers have available exoskeletal robots and non-invasive brain stimulation techniques; (2) necessary personnel trained in the use of robots and NIBS; (3) the need for time, space, and human resources; (4) the need for broad and long-term patient compliance.

It would be important to compare more homogenous rehabilitation protocols to better appreciate their beneficial effects on post-stroke recovery. Moreover, considering that each stroke patient is unique in his/her characteristics, it would be probably better to design a therapeutic intervention tailored on every single patient (34).

Given the limited number of studies, the heterogeneity in the treatment protocol and the outcome assessment techniques, it was not possible to carry out a meta-analysis to obtain a quantitative summary of the results. We have found some limitations that may present challenges for future research: sample size and few RCT studies, no neurophysiological assessment with transcranial magnetic stimulation (TMS) was performed to assess cortical excitability and brain connectivity before and after treatments, the lesion site as cortical and subcortical has not been taken into account, sometimes, it was difficult to identify the precise injury extension (heterogeneous properties of stroke), finally, generalization of the stimulation protocols (30). Moreover, no short follow-up nor comparison was done with other non-invasive brain stimulation techniques, and the studies have included only patients with chronic supratentorial ischemic stroke, and we cannot draw conclusions about the effects of the current protocols of NIBS on RAGT in patients with other conditions, as acute or subacute supratentorial ischemic stroke, hemorrhagic, or cerebellar stroke.

The studies' data support the hypothesis that anodal tDCS, combined with thoracic cathodal tsDCS, may be useful to improve the effects of RAGT in patients with chronic stroke. Moreover, cerebellum NIBS could represent a promising interventional strategy to improve residual motor functions and recovery after stroke, modulating cerebellar brain inhibition and facilitating motor skill relearning. Finally, no adverse events were recorded during the study (31).

CONCLUSION

The current systematic review showed a positive effect on walking recovery of combination of robot-assisted gait training with non-invasive brain stimulation. Specifically, the use of 20 min of tDCS (1.5–2 mA), 5 times/week for 2 weeks, can increase gait skills in patients with chronic stroke. Heterogeneity was found on the site of stimulation, the type of robot device (end effector, exoskeleton), and stimulation protocol with respect to robot-assisted therapy (before, online, or after). Future RCTs are needed to further validate the findings of these pieces of research.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

FB, MB, and GM: conceptualization. MB, FS, BC, LC, and AM: writing—original draft preparation. MB, LC, BC, and AM: methodology. BC, AM, GM, VD, FB, LZ, and SS: writing—review and editing. SS, VD, SP, LZ, and FB: supervision. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.795788/full#supplementary-material

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Psychophysiological Effects of Biographical Interventions in People With Unresponsive Wakefulness Syndrome and Minimally Conscious State

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Background: Various music interventions can evoke favorable behavioral responses or physiological reactions in people with disorders of consciousness (DOC), such as coma, unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS). However, it appears that no study thus far has investigated the effects of music on the endocrine system of people with DOC.

Objective: This explorative study aimed to investigate the effects of biographical music and biographical language on the physiological and endocrine systems of people with UWS and MCS.

Method: A cohort of 20 people with DOC (10 women, 10 men; age range 19–77) received 20 min of biographical music and biographical language. Before and afterward, they were exposed to silence. Physiological and hormonal measurements were conducted before, during, and after the interventions.

Results: Paired *t*-tests showed a significant decrease of salivary cortisol in the condition with biographical language interventions.

Conclusion: Biographical interventions can modulate reactions in the endocrine system in people with DOC. Further studies are needed to establish whether and how individuals living with DOC show psychoneuroendocrine responses to music and other arts-based interventions.

Keywords: disorders of consciousness (DOC), unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), biographical music, biographical language, cortisol, amylase, dehydroepiandrosterone (DHEA)

INTRODUCTION

Disorders of Consciousness

Unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) belong to disorders of consciousness (DOC). Most patients with DOC show signs of severely disturbed awareness (1, 2) and are unable to communicate verbally or gesture intentionally. UWS is also known as a vegetative state [VS; (3)]. People who live with this syndrome show spontaneous eye opening and a sleep-wake rhythm (4). They are able to breathe independently, but are fully dependent on assistance with activities of daily living (5). Moreover, they are unable to communicate verbally or to respond purposefully to commands (5). A considerable number of neurological patients (43%), particularly those with severe visual impairment or blindness, are misdiagnosed with UWS (6).

People with MCS show visual fixation and other physical reactions to external stimuli that are more than simple reflexes (7, 8). MCS can be divided into MCS PLUS (MCS+) and MCS MINUS (MCS–). People with MCS+ are reproducibly able to respond to commands, whereas people in MCS– are unable to do so (8, 9). UWS and MCS are not permanent states as they can change and even improve (10).

Following earlier work on diagnostic procedures and indicators to assess the severity of DOC (11, 12), state-of-the-art diagnostic tools, such as the Coma Recovery Scale Ű Revised [CRS-R; (13, 14)], and measurements of brain functions via imaging methods (15, 16) have been developed to improve the diagnosis of DOC.

Rehabilitation of People With DOC

Rehabilitation in DOC focuses on enhancing the quality of life and reducing comorbidity. Therefore, treatment strategies, which potentially elicit biographical memories as residual cognitive resources by means of multimodal perceptual stimulation [e.g., (17, 18)], non-verbal modes of communication, and social interaction, are needed (19). Sensory stimulation therapy offers olfactory, gustatory, tactile, kinesthetic, and auditory stimulation to activate patients and potentially provoke interactive responses (17, 18). Exposure to emotionally charged sounds, such as the patient's name (20), the voice of a relative (21), or music (22), has also been shown to have therapeutic value.

Effects of Music Interventions and Music Therapy for People With DOC

There are various possibilities for the use and adaption of music for people with DOC. A systematic review by Grimm and Kreutz (23) analyzed 22 quantitative studies with 329 participants with non-degenerative DOC and various musical interventions, such as music therapy, biographical music, and music combined with other interventions. The review found that music interventions may evoke favorable behavioral or (neuro-)physiological reactions in people with DOC. However, the methodological quality of the involved studies was heterogeneous. The mean number of participants was 14.95 per study. Some studies used no established diagnostic assessment, and effect sizes were not reported in most studies (23). A recent systematic review (24) included both qualitative and quantitative studies. The quantitative studies that were published since 2018 showed that music interventions led to an increase in brain connectivity (25, 26), a higher activity of the autonomic nervous system (27), or an increase in behavioral responses (28). One study (29) showed no difference in skin conductance (SC) between the music condition and the control conditions (a neutral sound and olfactory stimulation). In some studies, brain activity was higher, when the patient's name was called (30, 31).

Individual music therapy for people with DOC has been shown to lead to better conditions and significant behavioral responses when compared with environmental sounds (32). Additionally, a pilot study by Steinhoff et al. (33) documented active music therapy conducted three times per week for 5 weeks to lead to an increase in brain activity in the frontal areas, the cerebellum, and the hippocampus.

In a study conducted by Sun and Chen (34), preferred music was played for participants with DOC. Half of the 40 participants received preferred music for 4 weeks in the morning, afternoon, and nighttime prior to sleep. The control group received standard care without music intervention. A comparison of the *Glasgow Coma Scale* (GCS) showed a significantly higher score of the music group when compared with the control group. Moreover, the quantitative value of electroencephalography (EEG) differed significantly between the music group and the control group. The $\delta + \theta/\alpha + \beta$ value of the music group was decreased after the 4 weeks with music interventions. This may indicate a positive effect of the intervention on the patients' outcome as the slow wave frequency bands δ and θ are associated with a poor outcome in people with DOC, whereas the fast wave frequency bands α and δ are associated with a favorable outcome (35, 36). Puggina and da Silva (37) examined 76 participants who were sedated, comatose, or lived with UWS. A third of the participants listened to biographical music, another third listened to a message by a relative, and the last third listened to silence. During these interventions, heart rate (HR), blood pressure, body temperature, and oxygen saturation (SpO_2) were measured. Electric activity of the frontalis muscles and a hand extensor muscle was acquired by using electroneurography (ENG), and facial expressions were recorded with a video camera. The results showed that biographical music caused significant changes in the ENG signal. Biographical language produced significant changes in facial expressions. Therefore, biographical music has the potential to evoke physiological and neurophysiological effects in people with DOC.

Music can also be valuable as a diagnostic element for patients with DOC (38). Magee et al.'s (39, 40) *Music Therapy Assessment Tool for Awareness in Disorders of Consciousness* (MATADOC) combines music therapeutic and diagnostic strategies based on research findings suggesting enhanced auditory responsiveness in patients with DOC (41–43). The 14 items of MATADOC contain visual and auditory stimuli (39). These stimuli are used to evaluate motor responses and non-verbal communicative signs. Most of the stimuli consist of music, such as familiar songs. An evaluation of the MATADOC showed that this diagnostic tool is

as reliable as other diagnostics in assessing behavioral signs of consciousness (39, 44).

In summary, music interventions that include biographic music and music therapy can lead to favorable responses in people with DOC. To this date, there seems to be no study that examined the impact of music on the endocrine system of people with DOC.

Hormones and Music

Listening to music and creating music have been shown to have an impact on the endocrine system (45). Listening to music may reduce cortisol concentration in the saliva and increase the secretory immunoglobulin A [IgA; (46)]. Cortisol, a steroid that is produced by the hypothalamus-pituitary-adrenal (HPA) axis, is secreted in reaction to stress and anxiety (47, 48). Similar results were found by Linneman et al. (49). They discovered that music listening evoked a significant decrease in the cortisol concentration in saliva. The researchers measured the concentration of salivary alpha-amylase (SAA), an enzyme that breaks down carbohydrates (50). SAA concentration is an indicator of sympathetic nervous system activity (51). Linneman et al. (49) found that the change in SAA concentration was dependent on the qualities of the music being played. For instance, energetic music increased the concentration of this biomarker whereas relaxing music decreased the concentration. In a larger, randomized controlled study, 60 participants were first exposed to relaxing music, the sound of rippling water, or silence, and then to a stressful task (52). The cortisol concentration in the group, which listened to relaxing music, was highest, and the group, which listened to rippling water, had the lowest cortisol level. Alpha-amylase was decreased after the stress task more in the music group and in the silence group than in the group, which listened to rippling water. HR response showed no significant difference between the three groups (52). Kreutz (53) examined the impact of music making on different hormones. About 30 min of singing in a choir increased the concentration of oxytocin significantly, whereas this was not the case for cortisol and dehydroepiandrosterone [DHEA; (53)]. DHEA is a hormone that is produced by the HPA axis (54) and its level increases with relaxation (55, 56). Psychological stress (57) and depression (58) are associated with decreased DHEA levels. Therefore, DHEA decreases and increases opposite of cortisol and it can be an indicator for well-being.

In another study, 25 people with dementia received eight sessions of music therapy of 60 min within a 2-month period (59). Before and after the sessions, salivary IgA and alpha-amylase were collected and the participants had to fill in a mood questionnaire. The concentration of IgA and alpha-amylase was increased after music therapy, but the results were not statistically significant. Happiness scores, however, were found to significantly increase after music therapy interventions.

Aims and Hypotheses

To our knowledge, the relationship between hormones and music in people with UWS and MCS has not yet been investigated. The purposes of this explorative study were (1) to examine the impact of biographical music and biographical language on physiological responses and (2) to examine the impact of biographical music and biographical language on the endocrine system of people with DOC.

We hypothesized that biographical music and biographical language evoke more bodily reactions than silence (H1). We also assumed that the physiological responses were greater in the music condition than in the language condition (H2). The following hormones were included in the study: salivary cortisol, amylase, and DHEA. The following physiological parameters were included in the study: electromyography (EMG), blood volume pulse (BVP), SpO_2, and HR.

MATERIALS AND METHODS

Participants

Twenty-four participants with UWS and MCS were recruited at two neurological early rehabilitation departments (Department of Neurological Intensive Care and Rehabilitation, Evangelisches Krankenhaus Oldenburg and Clinic of Neurological Rehabilitation, Asklepios Schlossberg Klinik Bad König) and one long-term rehabilitation facility (Nursing Care Facility Schloss Meerholz, Area Phase F, Part A, Gelnhausen). Inclusion criteria were an age of 18 and older, an absence of dementia, no prior drug or alcohol abuse, no hearing deficit, no mechanical ventilation, and an absence of multidrug-resistant organisms in the area of the face, mouth, or tracheostomy. Between the study recruitment and study interventions, four participants were excluded due to multidrug-resistant germs ($n = 2$), meningitis ($n = 1$), or emergence from MCS ($n = 1$). Therefore, 10 men and 10 women [$M = 55.1$ years, standard deviation (SD) $= 15.09$] participated in the study. Fourteen participants lived with UWS and six with MCS (as shown in **Table 1**). Hypoxia ($n = 9$) was the most common etiology, followed by traumatic brain injury (TBI; $n = 7$), intracranial hemorrhage (ICH; $n = 2$), subarachnoid hemorrhage (SAH; $n = 1$), and tumor edema with herniation ($n = 1$). The injury's onset was 1.5 months to 30 years ago ($M = 4.64$ years, $Mdn = 3.25$ months). Three different types of assessments were conducted by physicians or trained therapists before the interventions: the *GCS* (11), the CRS-R (13), and the *Glasgow Outcome Scale* [GOS; (12)][1].

Ethics

The study was approved by the Ethics Committee of the Carl von Ossietzky University, Oldenburg [number 115/2016 (075/2016)] and was designed consistent with the principles of the Declaration of Helsinki (60). The legal representatives signed informed consent. The study is reported in the German register of clinical trials (https://www.drks.de/drks_web/setLocale_EN.do; clinical trial identifier number DRKS00010187). Each participant was anonymized to a four-digit pseudonym consisting of random numbers and letters.

Music and Language Stimuli

The legal representatives completed a questionnaire about preferred biographical music and language. This information

[1]The diagnosis of UWS or MCS is based on the best result of the three assessments.

TABLE 1 | Participants' characteristics.

Patient no.	Age (y)	Etiology	GCS total	GCS subscores (E/V/M)	CRS-R total	CRS-R subscores (A/Vi/M/O/C/Ar)	GOS	Diagnosis
1	50–55	TBI	4	2/1/1	4	1/0/1/1/0/1	2	UWS
2	65–70	TBI	5	3/1/1	8	2/2/1/1/0/2	3	MCS
3	55–60	Hypoxia	4	2/1/1	2	0/0/0/1/0/1	2	UWS
4	40–45	Hypoxia	9	4/2/3	5	0/0/1/2/0/2	2	UWS
5	70–75	Hypoxia	6	4/1/1	4	0/1/0/1/0/2	2	UWS
6	15–20	TBI	9	4/1/4	8	2/1/2/2/0/1	3	MCS
7	65–70	SAH	8	4/1/3	2	0/0/1/0/0/1	2	UWS
8	55–60	Tumor	6	2/1/3	2	0/0/1/0/0/1	2	UWS
9	75–80	TBI	8	3/1/4	7	2/1/2/1/0/1	3	MCS
10	55–60	Hypoxia	8	4/1/3	4	1/0/1/0/0/2	2	UWS
11	70–75	ICH	6	2/1/3	3	1/0/1/0/0/1	2	UWS
12	60–65	Hypoxia	10	4/3/3	8	2/1/1/2/0/2	3	MCS
13	30–35	TBI	8	4/1/3	7	2/1/1/1/0/2	3	MCS
14	55–60	Hypoxia	7	4/1/2	5	1/1/0/1/0/2	2	UWS
15	55–60	Hypoxia	7	4/1/2	5	1/1/0/1/0/2	2	UWS
16	55–60	Hypoxia	6	4/1/1	3	0/0/0/1/0/2	2	UWS
17	25–30	TBI	4	2/1/1	4	1/0/1/1/0/1	2	UWS
18	65–70	ICH	5	3/1/1	4	1/1/0/1/0/1	2	UWS
19	50–55	Hypoxia	4	2/1/1	2	0/0/0/1/0/1	2	UWS
20	45–50	TBI	7	4/2/1	8	1/2/1/2/0/2	3	MCS

TBI, traumatic brain injury; ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; y, years; GCS, Glasgow Coma Scale; E, eye opening; V, verbal response; M, motor response; CRS-R, Coma Recovery Scale Revised; A, auditory function; Vi, visual function; O, oromotor/verbal function; C, communication; Ar, arousal scale; GOS, Glasgow Outcome Scale; UWS, unresponsive wakefulness syndrome; MCS, minimally consciousness state.

was used to create individual stimuli for each participant. The biographical language stimuli consisted of audiobooks, television broadcasts, books, or newspaper articles. In cases of books or newspaper articles, the text was read out by an actor and recorded. For the music stimuli, four preferred songs were chosen. In one case, the family of a participant provided a record of a choir, in which the participant sang. The samples were edited with a program for audio editing (Audacity© 2.3; iWeb Media Ltd., Birkirka, Malta). They began with a fade-in of 5 s and ended with a fade out of 5 s. Between the songs or language pieces, a break of 1 min silence was inserted.

Design and Procedure

Prior to the start of the study, a power analysis was conducted with the program *G*Power* (61) to determine the appropriate study size. For this purpose, a two-factor analysis of variance (ANOVA) with repeated measures was utilized. The two factors represented the biographical language and biographical music of independent variables. The analysis led to a sample size of 20 participants, a significance level of $\alpha = 0.5$, a power of $\beta = 80\%$, and an effect size of 0.28.

The study took place at the bedside. The patients participated on 2 consecutive days at the same time in the music condition and in the language condition. The interventions took place at the same time as cortisol and alpha-amylase levels fluctuate with circadian cycles (47, 51). Music and language followed for each participant in a randomized order. The two conditions were assigned by drawing lots. Due to this randomization, some participants started with music and some with language on the first day. The interventions lasted approximately 20 min per condition. Before and after the interventions, baseline and post-intervention measurements were obtained for 20 min (as shown in **Figure 1**).

Data Acquisition

Data collection was performed between September 2017 and September 2019. *The NeXus-10 MKII* (62) was utilized to measure the physiological parameters. This device complies with the International Electrotechnical Commission (IEC) 60601 standard and is approved as a medical electronic device. The parameters were acquired continuously during the baseline, the intervention, and the post-measurement (as shown in **Figure 1**). HR and BVP were measured by a finger clip at the index finger of the non-dominant hand. SpO_2 was measured by a finger clip at the index finger of the dominant hand. The electrodes for the EMG were placed at the forehead at the frontalis muscle and a ground pole above the root of the nose. Saliva was collected four times per intervention. The first saliva sample was collected before the baseline (T1), the second (T2) and the third one (T3) before and after the intervention, and the last one after the post-measurement (T4). A Salivette© Cortisol (Sarstedt, Nümbrecht, Germany) with a synthetic fiber swab was used for this procedure. The biocompatible fiber roll was placed in the cheek pouches for 5 min and held tight by the experimenter. The sample was then stored in a sterile tube at −20°C.

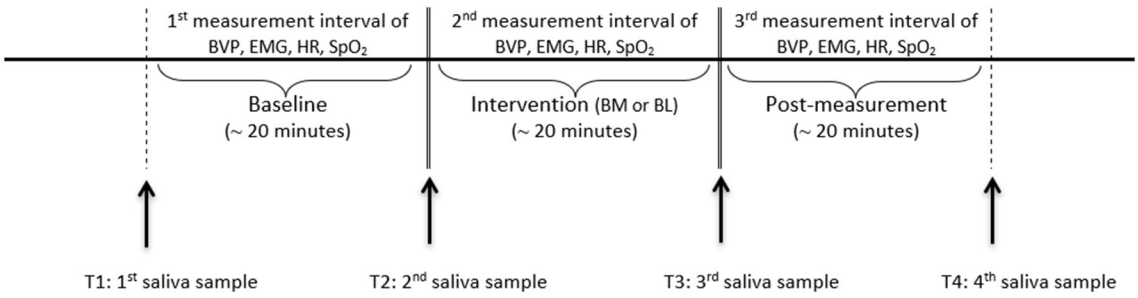

FIGURE 1 | Experimental design. BM, biographical music; BL, biographical language.

During the interventions, the room temperature was maintained between 20 and 24°C. The loudspeakers for the preferred music and language were placed at the foot side in front of the bed. The distance between the heads of the participants and the loudspeakers was maintained at 2.50 m. The volume was controlled by the sound level meter *Testo 816* (Testo, Titisee-Neustadt, Germany) next to the participant's head and was held between 60 and 65 dB. The sound level meter is approved for the frequency range from 31.5 to 8 kHz. The accuracy of the device corresponds to class 2 according to IEC 651 (DIN EN 60651) and is ±1.0 dB. Finally, a protocol was written in which confounders or special reactions were noted by the examiner.

Data Processing and Analyses

The physiological data were analyzed with *BioTrace+* (63). Artifact rejection was conducted to eliminate confounders, for example, when an electrode fell down and had to be placed at the participant again. First, the artifacts that were noted in a protocol (e.g., background noise, a loose electrode) were eliminated. In a second step, two neurologists, who were blinded to the conditions, eliminated biological and technical artifacts—such as movement artifacts—by using visual inspection. Then, the data were exported to the statistical program *IBM-SPSS Statistics* (version 26, New York, NY, USA). The mean value of the three time intervals (baseline, interventions, post-measurement) was used for statistical analysis. ANOVAs with repeated measurements and two factors were used ($\alpha = 0.5$, $\beta = 80\%$). The two factors represented biographical music and biographical language. The ANOVA's repetitions represented the measurement times (baseline, intervention, and post-measurement; T1–T3). Additionally, significance was explored based on the Student's *t*-test for dependent measures ($\alpha = 0.5$, $\beta = 80\%$).

The saliva samples were cooled and transported with dry ice to a lab. The lab was blinded to the participants and conditions. Free cortisol concentration and DHEA concentration were determined by using commercial luminescence immunosorbent assay (LUM) and commercial enzyme-linked immunosorbent assay (ELISA) from the same manufacturer (IBL International, a Tecan Group company, Hamburg, Germany), respectively. The SAA activity was measured using a kinetic colorimetric test [for details, refer to (64)] and reagents obtained from DiaSys Diagnostic Systems (Holzheim, Germany). Saliva was diluted at 1:400 using 0.9% saline solution. The reagents contained the enzyme alpha-amylase in a specified amount and alpha glucosidase, which converts the substrate ethylidene nitrophenyl to p-nitrophenol. The rate of formation of p-nitrophenol is directly proportional to the samples' amylase activity and was detected using an absorbance reader at 405 nm (BioTek Synergy HTX, BioTek Instruments, Winooski, VA, USA). Inter-and intra-assay coefficients of variation were below 10% for all analytes.

A two-factor ANOVA with repeated measurements was used for statistical analysis ($\alpha = 0.5$, $\beta = 80\%$). The ANOVA's repetitions represented the times at which the saliva was acquired (T1–T4). In addition, the mean values of the four measurement times were compared by applying the Student's *t*-test for dependent measures ($\alpha = 0.5$, $\beta = 80\%$).

RESULTS

Psychophysiological Data

The ANOVAs and the Student's *t*-tests for paired samples showed no significant changes due to biographical music or biographical language in BVP, EMG, SpO_2, and HR (as shown in **Table 2**).

Hormones

The ANOVAs showed no statistically significant effects. The Student's *t*-tests for paired samples showed that cortisol in saliva was decreased significantly in the language condition (T2–T4) {[95% CI (0.998, 7.278)] $t_{(19)} = 2.758$, $p = 0.013$, $d = -0.536$}. Between T3 and T4 in the language condition, the salivary cortisol was decreased significantly, as well {[95% CI (0.198, 6.989)] $t_{(18)} = 2.223$, $p = 0.039$, $d = -0.437$}. Biographical music led to no significant effects. Salivary cortisol was decreased after the intervention (T3) in comparison to the baseline (T2) (as shown in **Table 3**; **Figure 2**). Biographical music and biographical language led to no significant changes in salivary amylase and DHEA.

DISCUSSION

In this study, 20 participants received biographical interventions. In reaction to biographical music, salivary amylase did not

decrease significantly after the intervention in comparison to the baseline (T2 to T3) and from T3 to T4. In reaction to biographical language, salivary amylase also did not appear to significantly change. Consequently, biographical interventions had no significant effects on the production and release of salivary amylase.

Biographical music had no effect on the concentration of DHEA in saliva, which stayed at the same level during the baseline, intervention, and post-measurement. Biographical language elicited a non-significant change from T2 to T3. The SD in DHEA was in comparison to the mean value very high. An explanation for this may be that the level of DHEA decreases with age (65, 66). DHEA levels have been found to be significantly decreased when comparing people aged 50 to those aged 40 years old (65). The age of the participants included in our study was very heterogeneous with a range between 19 and 77 years. Similarly, the level of amylase is also influenced by age (50). The level of cortisol is influenced by age, but it is less affected by age than levels of DHEA (65).

Although the mean values suggested a decrease of salivary cortisol levels in the participants' saliva during listening to biographical music (T2 to T3) followed by an increase in levels after the intervention (T3 to T4), the changes were not statistically significant. During the language intervention, salivary cortisol was decreased from T2 to T4 and from T3 to T4 significantly with $p < 0.05$. This could be due to a delayed reaction. It remains unclear if this effect is in reaction to the intervention's content, the voice of the reader, or the sound of the audiobooks. Since the participants had a severe brain injury, most of them might have aphasia (4, 67) preventing them from understanding the content of the language stimuli. The decrease of cortisol in the language condition could therefore be due to the sensitivity to prosodic features of the language. Prosodic features of the native language are perceived by babies in an early stage of language development: Infants who are 6 months old are able to discriminate between the native prosody and the prosody of a language that is prosodically very different from their native language (68). This sensitivity occurs even before children are able to understand the semantic content of a language and produce the first word (69). Emotional prosody, which is not a linguistic feature but contains social information, is processed by babies from the age of 6 months onward (70, 71).

Cortisol was found to be more meaningful than amylase and DHEA in this study. Cortisol may be released in reaction to stress (72) and therefore, this can be an indication that the interventions had a calming effect. The role of cortisol differs in other studies with participants with brain injuries. Kleindienst et al. (73) measured cortisol levels in the blood of

TABLE 2 | Means (and standard deviations) of physiological responses to biographical music and language stimulation across time points.

	T1 M (SD)	T2 M (SD)	T3 M (SD)
BVP			
Music	−42.17 (71.17)	−29.97 (16.12)	−29.38 (17.23)
Language	−52.76 (79.79)	−41.05 (36.59)	−35.59 (23.11)
EMG raw			
Music	3510.65 (6743.43)	3671.60 (6,481.06)	3327.80 (6081.54)
Language	3538.20 (6240.71)	3428.29 (4090.20)	3186.48 (3310.30)
EMG (20–500 Hz)			
Music	0.0086 (0.1128)	−0.1209 (0.544)	0.0043 (0.0374)
Language	0.0263 (0.0791)	0.0479 (0.36)	0.0803 (0.3819)
HR			
Music	77.59 (14.44)	78.63 (14.49)	77.77 (14.32)
Language	75.80 (12.65)	73.96 (13.67)	74.49 (13.92)
SpO_2			
Music	93.88 (2.89)	93.72 (2.98)	93.60 (2.88)
Language	94.06 (2.85)	93.87 (2.86)	94.10 (2.62)

BVP, blood volume pulse, relative blood flow in millivolts; EMG, electromyography in microvolts (μV pk-pk); HR, heart rate in beats per minute; SpO_2, oxygen saturation measured by a finger pulse oximeter in percent.

TABLE 3 | Means (and standard deviations) of neurohumoral responses to biographical music and language stimulation across time points.

	T1 M (SD)	T2 M (SD)	T3 M (SD)	T4 M (SD)
Amylase[a]				
Music	293.07 (340.48)	320.14 (395.88)	280.61 (291.88)	237.30 (246.42)
Language	205.46 (151.00)	393.46 (617.09)	336.40 (418.21)	348.39 (392.85)
Cortisol[b]				
Music	15.58 (16.36)	13.55 (17.32)	9.70 (5.28)	10.36 (6.85)
Language	13.41 (9.77)	13.70 (9.13)	13.38 (10.83)	9.56 (5.97)
DHEA[c]				
Music	188.94 (173.29)	170.58 (135.94)	176.80 (128.15)	165.84 (141.69)
Language	179.34 (141.54)	184.08 (144.60)	228.22 (277.33)	157.57 (113.77)

[a] *sAA in U/mL.*
[b] *sCort in nmol/L.*
[c] *DHEA in pg/ml.*
DHEA, dehydroepiandrosterone.

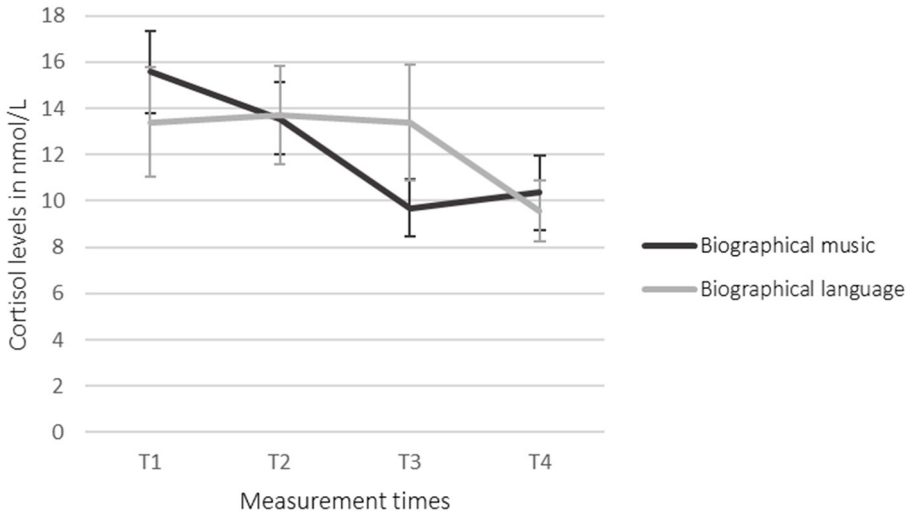

FIGURE 2 | Change in cortisol levels. Error bars represent the standard error of the mean (SEM).

71 participants with TBI in the acute phase. The blood samples were taken between 7:00 and 9:00 a.m. on days 0, 3, and 7. On the seventh day, a 24-h urine sample was taken. Patients with a moderate brain injury had a significantly higher cortisol level in the blood than patients with severe TBIs. However, in the 24-h urine sample, increased cortisol levels were found. Heinz and Rollnik (35) compared cortisol levels of patients with a poor outcome and patients with a good outcome in 93 patients with hypoxia. The mean duration of the treatment in the rehabilitation unit was 108.5 days. The results showed that there was no significant difference in cortisol levels in patients with a poor outcome (193.00 μg/l) and patients with a good outcome (194.00 μg/l). Vogel et al. (74) explored the circadian rhythm of cortisol in patients with UWS who were in the subacute and chronic rehabilitation phase. For this purpose, they measured the 24-h profiles of 11 patients with UWS and a neurologically healthy control group that consisted of 11 age and gender-matched participants. The circadian rhythm was preserved in all patients but it differed from the control group. The 24-h mean of cortisol was higher in patients than in the neurologically healthy participants. Between 16:00 p.m. and 20:00 p.m., the patients' cortisol levels were higher than those of the control group. Consequently, the role of cortisol in people with brain injuries is contradictory and might depend on the rehabilitation phase and etiology. However, the present study showed that biographical language can induce a decrease in cortisol levels in people with UWS and MCS in the subacute and chronic rehabilitation phases.

The results of this study are partly in line with the study by Puggina and da Silva (37) mentioned previously. In Puggina and da Silva's study, the participants listened to the voice of a relative in the language condition and showed significant behavioral reactions. The familiarity of the voice might be the reason for the participants' strong reactions.

In comparison to a study by Heine et al. (42), biographical language led to more physiological reactions than biographical music in our study. Heine et al. (42) used preferred music that was reported by the participants' families or loved ones. They found out that the preferred music evoked more functional connectivity in the left precentral gyrus and the left dorsolateral prefrontal cortex than in the control condition (noise from the MRI scanner). Despite the small number of five participants, the intervention showed effects of preferred music on brain regions that process cognitive functions, such as the dorsolateral prefrontal cortex (42). Moreover, the right and left gyrus precentralis showed significantly more connectivity in the music condition when compared to the control condition. Therefore, biographical music may evoke higher neural connectivity. A follow-up study conducted by the same team (25) supported these results by showing more connectivity in the frontoparietal network during the music intervention than in the control condition.

Castro et al. (75) also worked with biographical music. They presented four iterations of preferred music excerpts for 1 min to 13 participants with DOC. The control condition consisted of a continuous sound. The participants listened to these two conditions alternately. After the two conditions, an EEG measurement was conducted and during that, the participants listened to different prenames, which included their own names. The EEG response to participants' own names was higher after music interventions than after the control condition. Seven patients showed a significantly higher response to their own names in comparison to other names after they listened to music. These seven participants had a better outcome after 6 months. The remaining six participants did not show such reactions. Even though the number of participants was low, the study showed that biographical music induced cognitive processes in half of the participants.

The results of the present study and the results of previous studies suggest that biographical interventions affect emotional and cognitive function in some people with DOC. As people with

DOC cannot express themselves verbally, there will be no full certainty about how they perceive therapeutical interventions. Johnson (76) points out that such circumstances should not preclude further attempts in research or treatment that are made to enhance the quality of life for people with DOC. She calls this "ethics of uncertainty" [(76), p. 190]. Therefore, professionals have to deal with uncertainty when working with people with DOC in a rehabilitative or therapeutic setting.

Limitations

The present study was not fully blinded, as the examiner both collected and analyzed the data. Some of the participants were more in the acute state and some in a chronic state. Thus, the participants' conditions were heterogeneous. The stimuli differed in the type of genre, structure, instruments, and other features. Previous research showed that different (structural) features of music influence physiological reactions, for example, in HR, or respiratory rate (RR) in healthy populations (77, 78), and HR, heart rate variability (HRV), RR, or SpO_2 in people with DOC (79, 80).

CONCLUSION

The findings of this study are in line with previous research and add some new aspects by exploring hormones. Biographical language led to a significant decrease in salivary cortisol. This suggests that biographical interventions might reduce stress in people with UWS and MCS. The age of the participants and the time since their brain injuries, however, were heterogeneous. Therefore, the results are not generalizable. More research is needed to investigate the effects of different arts-based interventions and responses of the endocrine system in people with DOC.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article will be made available by the authors

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee, Carl von Ossietzky University, Oldenburg, Germany. The participants' legal representatives provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TG and GK conceptualized the study. TG acquired the data and wrote the first draft of the manuscript. TG, MG, and OS analyzed the data. UN provided the analysis of salivary biomarkers at his lab. All authors contributed to writing the manuscript and approved the submitted version.

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