UNDERSTANDING STROKE RECOVERY TO IMPROVE OUTCOMES: FROM ACUTE CARE TO CHRONIC REHABILITATION

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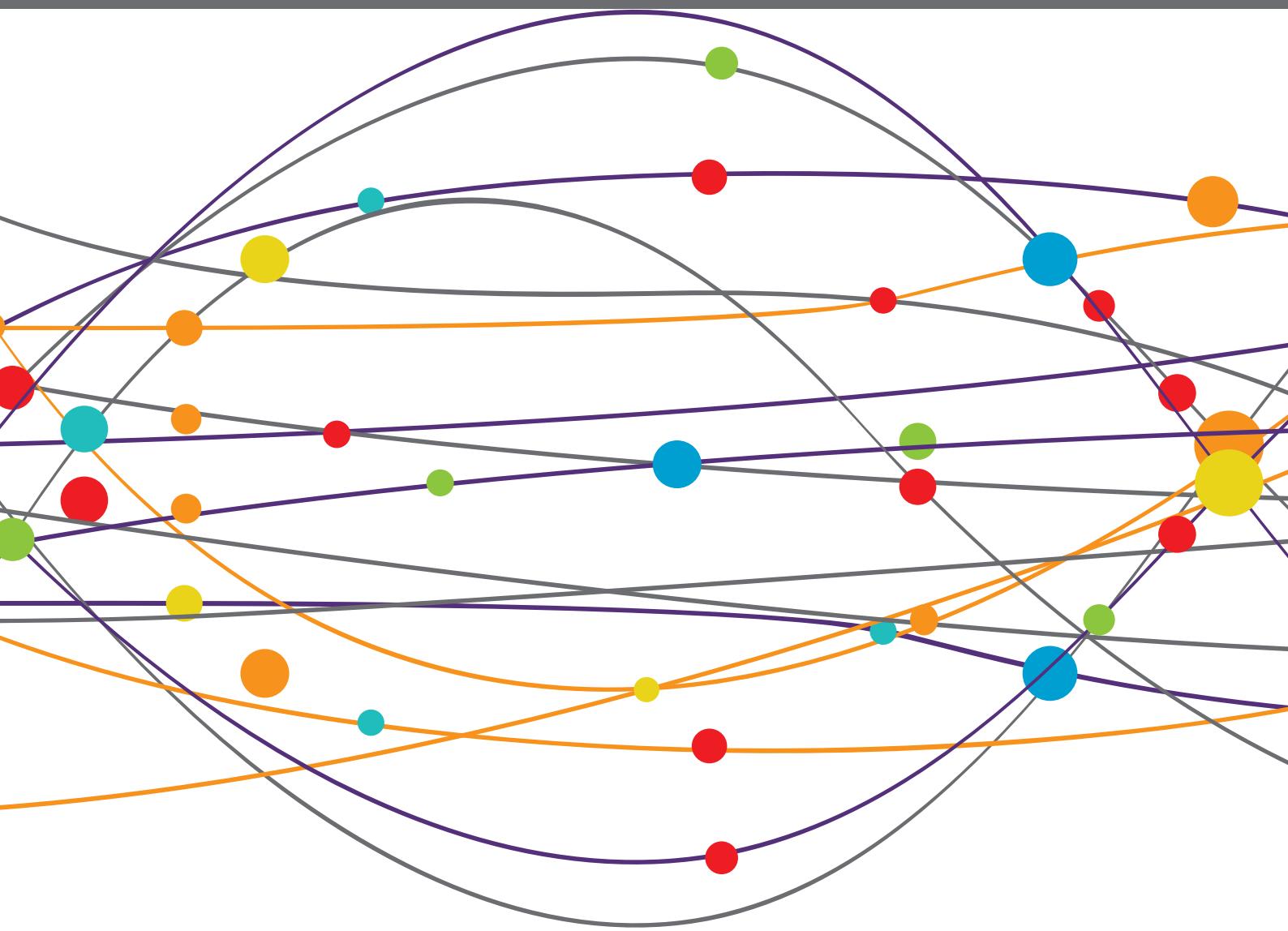

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UNDERSTANDING STROKE RECOVERY TO IMPROVE OUTCOMES: FROM ACUTE CARE TO CHRONIC REHABILITATION

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Editorial: Understanding stroke recovery to improve outcomes: From acute care to chronic rehabilitation

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Editorial on the Research Topic
Understanding stroke recovery to improve outcomes: From acute care to chronic rehabilitation

Over the past decades, stroke outcomes have improved due to advances in treatment including the implementation of reperfusion therapies such as thrombolysis and mechanical thrombectomy for acute stroke and multidisciplinary care in stroke units (1, 2). In addition, progress in research about brain function, repair mechanisms and rehabilitation interventions informed by both animal and human studies, is helping shape both research and practice (3). Yet, stroke remains a major cause of death and disability worldwide (4). The integration of data about the predictors of recovery and responsiveness to interventions, as well as the impact of psychosocial factors such as motivation and self-efficacy, has the potential to decrease the burden from this condition.

The Research Topic "Understanding Stroke Recovery to Improve Outcomes: From Acute Care to Chronic Rehabilitation" included 30 manuscripts, consisting mainly of observational studies but also of proof-of-principle randomized trials, two narrative reviews, a systematic review, a meta-analysis, a study protocol and a case report. Most of the studies addressed the prediction of outcomes or effects of specific interventions on behavioral, neurophysiological and imaging metrics.

The prediction of risks of complications in the acute phase, as well as the prognostication of long-term outcomes can influence goals of care, selection of treatment strategies as well as expectations of patients and their families. Lin et al. proposed models to predict deterioration during hospitalization and prognosis at 1-year after intracerebral hemorrhages, to be validated by prospective studies in the future. Wurzinger et al.

analyzed longitudinal data from a research database and showed that Barthel Index scores within the first 2 days after stroke predicted self-reported dependency in performance of activities of daily living, at 3 months as well as 12 months after stroke.

Shen et al. investigated risk factors and prognosis of symptomatic intracranial hemorrhage (sICH) in patients admitted within 1 week after ischemic stroke, not treated with intravenous thrombolysis or thrombectomy, and included in the Chinese Acute Ischemic Stroke Treatment Outcome Registry (CASTOR), a large multicenter, prospective study. Modified Rankin Scale (MRS) scores were assessed at 3 and 12 months after onset of symptoms. sICH occurred in 0.73% of the patients. This rate is similar to that reported in patients not treated with alteplase in the NINDS trial (0.6%) (5). Three variables were independently associated with sICH: atrial fibrillation, history of tumors, and NIHSS score at admission. SICH was associated with higher risk of poor outcome at 3 months, but not at 12 months, and with increased mortality at 3 and 12 months.

Upper limb paresis is frequent and can substantially impact disability after stroke. Pradines et al. showed in 80 stroke survivors, at a median of 9 years after stroke-onset, that chronic muscular shortening is greater in lower than upper limbs, but weakness is more prominent in the arms. In a review article, Ballester et al. condensed the evidence for a link between arm use and arm recovery: if the arm is used in daily life above a certain threshold, it is recovering through self-training creating a virtuous circle between use and recovery. If not, the opposite is triggered resulting in a vicious circle.

Three studies aimed to predict upper limb motor impairments or disability. Ueda et al. followed 60 patients and concluded that manual muscle testing of elbow flexion and active finger extension up to 72 h after stroke may be useful to predict Fugl-Meyer Assessment upper extremity motor scores and Action Research Arm Test scores, at 3 weeks. da Silva et al. combined clinical testing at admission to acute inpatient rehabilitation and MRI metrics to predict upper limb performance at a later stage after stroke. They estimated shoulder abduction and finger extension (E-SAFE) scores according to medical records, and extracted metrics of corticospinal tract (CST) lesion from routine, standard of care brain MRI, in 34 patients who completed acute inpatient rehabilitation post-stroke. CST lesion overlap was depicted by means of spatial normalization of lesion masks that were then overlaid onto a white matter tract atlas delineating CST contributions from six cortical seed regions. The authors found that upper limb performance at a median time of 3 months may be predicted by the combination of E-SAFE scores performed at a median time of 7 days, and the percentage of CST lesion overlap on MRI performed at a median of 1 day post-stroke. Interestingly, MRI metrics of CST lesion, especially those involving projections from the ventral and dorsal premotor cortices, were able to classify upper limb outcomes at a median time of 3 months, with 79.4% accuracy. The combination of clinical and MRI variables increased accuracy to 88.2%.

Neurological impairments other than upper limb paresis, but also relevant to disability, were targeted by four manuscripts. Verbeek et al. performed external validation of the Early Prediction of Functional Outcome after Stroke (EPOS) model for independent gait at 3 months post-stroke. This model was originally designed to evaluate patients between days 2 and 9, in order to predict gait independence at 6 months post-stroke. EPOS performances on days 3, 8, and 9, but not on day 1, were acceptable to predict independent gait at 3 months in mild to moderately affected patients with first-ever stroke and no pre-stroke disability. Possible next steps include the use of this model in clinical practice, in patients with a similar profile, and to test its predictive value in subjects with more severe or recurrent strokes.

Serrada et al. followed 89 patients with motor impairments up to 6 months after stroke and observed that recovery of upper limb sensation and body awareness predominantly occurred within the 1st month. In addition, sensation and body awareness were correlated not only with motor impairment and quality of life but also with self-efficacy, the belief in the capacity to achieve certain outcomes. In another manuscript, Gangwani et al. reviewed the underpinnings and the role of self-efficacy in stroke recovery, summarizing the potential for further research and development of novel interventions to improve outcomes.

Lucente et al. followed 359 subjects after acute stroke and found that fecal incontinence was present in 2% of the first-ever anterior circulation strokes. Hemorrhagic stroke and higher NIHSS scores were independently associated with the presence of fecal incontinence in the acute phase. The condition persisted in 44% of the subjects, at 3 months.

Together, these studies indicate that assessments performed early after stroke can be useful to forecast outcomes related to body structure and function, activity or participation. Not only prognostication of recovery, but also of responsiveness to rehabilitation strategies are relevant in clinical practice, so that personalized therapeutic plans can be designed. In a retrospective study, Goffredo et al. reported that a subset of kinematic parameters predicted motor impairment after upper-limb Robot-assisted Therapy in 66 subjects in the subacute phase after stroke. These parameters may hence be useful to identify patients more likely to benefit from this type of intervention.

One of the goals of rehabilitation is to positively influence recovery trajectories. Otero-Ortega et al. outlined the state of the art on the use of trophic factors, cell therapy, and extracellular vesicles to promote adaptive plasticity. Hung et al. discussed the exciting perspective of protecting the brain prior to a lesion. They proposed that pre-stroke physical activity could enhance collateral circulation, known to play a crucial role in protecting the brain against infarction during ischemia. According to this hypothesis, physical activity may limit the extent of infarction

and increase the odds of good outcomes after first-ever or recurrent ischemic strokes.

Other promising strategies to boost recovery were covered by several manuscripts. The interventions administered to achieve this goal included administration of sertraline, intensive rehabilitation, cycling combined with functional electric stimulation, acupuncture and neuromodulation interventions. Disability, upper or lower limb motor impairment/function, dysphagia, cognitive and visual outcomes were evaluated.

Pharmacological enhancement of recovery motivated several investigations over the past decades. In a prospective observational study of consecutive acute ischemic stroke patients and motor impairments ($n = 114$), Stuckart et al. reported a higher rate of favorable outcomes (mRS ≤ 2 at 3 months) in those who received sertraline at the discretion of the treating neurologist—for instance, for clinically suspected post-stroke depression or at high risk for this condition—compared to an untreated control group.

Intensity, frequency and starting time of rehabilitation may be critical to stroke outcomes. Garcia-Rodrigues et al. followed three cohorts for 6 months: patients with stroke treated with (1) intensive rehabilitation therapy or (2) conventional therapy, and control subjects without stroke. Upper limb motor impairments and functional ambulation improved earlier in patients treated with intensive rehabilitation therapy.

The definition of doses or therapeutic windows for optimal delivery of rehabilitation interventions, as successfully performed in the field of hyperacute stroke treatment (1, 2) may harness the development of game-changing interventions and inform clinical trials. Kroth et al. described the protocol of a study that intends to compare effects of repetitive peripheral sensory stimulation delivered in combination with upper limb training, delivered either at an early phase or in the chronic phase after stroke, on upper limb motor outcomes and imaging biomarkers.

In a study by Hu et al., training in the form of cycling was combined with functional electrical stimulation, in a non-controlled sample of 15 stroke survivors. The authors observed improved electromyographic recruitment that correlated with improved scores on balance and ambulation, after treatment. A different training paradigm was employed by Awosika et al. in order to improve gait. They reported that backward locomotor treadmill training (BLTT), consisting of training on an instrumented treadmill without body-weight support ($n = 39$), led to improvements in measures of spatial walking.

In a meta-analysis of randomized controlled studies comparing standard treatment plus and minus scalp acupuncture, Huang et al. found a benefit of additional acupuncture on motor function. Three months of acupuncture had a greater effect than 1 month. Which aspect of acupuncture (sensory stimulation, psychological factors) caused the effect, remains to be investigated.

Balcerak et al. systematically reviewed 41 randomized controlled trials to address dysphagia in subacute stroke. Interventions included acupuncture, physical therapy, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, transcranial direct current stimulation and repetitive transcranial magnetic stimulation (rTMS). Of these, intensive physical therapy, rTMS and pharmaceutical treatment are promising; however, further research is required.

Neuromodulation interventions are promising therapeutic treatment for addressing multiple domains of recovery after stroke. Kim et al. showed that high-frequency rTMS over the ipsilesional dorsolateral pre-frontal cortex improved Mini-Mental status exam, Functional Independence Measure-cognition subscale, and forward Digit Span compared to a sham control group in subacute stroke patients. These results varied based on the lesioned hemisphere.

The application of inhibitory rTMS to contralesional Broca's area has emerged as a promising intervention to promote language recovery after stroke. Lin et al. investigated the efficacy of inhibitory rTMS over the contralesional pars triangularis, and associated functional connectivity changes in patients with chronic poststroke non-fluent aphasia, in a randomized controlled trial. Following 10 daily sessions of rTMS, they found significant improvement in language performance in the rTMS group compared with the sham stimulation group. Using resting-state fMRI, they also demonstrated changes in functional connectivity, including increased connectivity in perilesional and spared language areas of the left hemisphere, and reduced connectivity in right hemisphere language relevant areas, in particular the right pars triangularis and pars opercularis. Interestingly, they found that specific functional connectivity changes could predict language improvements following rTMS. This study provides important insights into the mechanisms underlying language improvement with contralesional rTMS over Broca's area, supporting the theory of interhemispheric imbalance during post-stroke recovery of aphasia.

On the other hand, the role of the contralesional primary motor cortex (M1) after stroke is still highly debated. Dionisio et al. showed that continous theta burst stimulation over the contralesional motor cortex resulted in an excitatory effect in the contralesional motor cortex after stimulation, but did not report significant changes to motor behavior. Revill et al. examined whether increased contralesional M1 activation, which is consistently observed in imaging studies after stroke, is due to increasing demand due to impaired motor ability. In this fMRI study, they varied the precision requirements in a hand motor task and demonstrated that with increasing task demand, there was stronger activation of the contralesional M1 in both stroke patients and healthy age-matched controls, though patients were less likely to show a linear relationship in the contralesional M1 with increased task difficulty compared with controls. These findings highlight the importance of considering task demand in studies aimed at understanding the role of the

contralesional M1 and in the development of interventions that target this area for neurorehabilitation.

Connectivity studies can provide clues about mechanisms of reorganization as well as effects of interventions. Xu et al. investigated effects of neuromodulation in 24 patients with unilateral occipital strokes and hemianopia. Using resting-state electroencephalogram, they reported increased functional connectivity between the occipital and temporal lobes in the contralesional hemisphere after delivering cathodal transcranial direct current stimulation of the contralesional hemisphere, combined with transcranial alternating current stimulation. Huang et al. performed fMRI-based connectivity analysis and described disruptions in global connectivity after stroke as compared to the healthy brain. Connectivity in certain brain areas (occipital cortex) in right-sided stroke survivors correlated with arm impairment and its recovery (as measured using the Fugl-Meyer Assessment).

On the other hand, Boot et al. found no associations between post-stroke fatigue, known to be associated with worse functional outcomes, and imaging metrics (lesion size, site or metrics of brain network connectivity) in young patients with stroke.

Bridging the gaps between knowledge gained about mechanisms of plasticity, prediction of outcomes, relationships between behavior and neurophysiological or imaging biomarkers, and development of interventions that lead to meaningful effects from the perspective of persons affected by stroke, is a major challenge for rehabilitation science. This Research Topic combined efforts from investigators engaged across the stroke continuum of care.

Factors and pathways determining the probability of recovery from an acute stroke are acting from the same moment of stroke onset and even before (prior conditioning by exercise), so knowledge of these factors by acute stroke teams responsible for patients care during the acute phase may be essential to improve outcomes. The concept that stroke recovery should be taken care of only after hospital discharge is clearly challenged by the evidence provided in this article collection.

Further research is needed to better characterize and design the process of care combining multidisciplinary acute phase and post-acute phase interventions aimed to optimize recovery from stroke. We have a well-designed hyperacute process of care (stroke code system), with coordinated multidisciplinary effort, and probably a similar innovating effort in post-stroke process of care may be needed to obtain the best effect from the neurorepair therapeutic strategies presented in this collection.

There may be important challenges ahead to increase the level of evidence for these interventions in order to be transferred into clinical practice. One important step might be to increase awareness across the stroke continuum of care as a whole, having long-term functional outcome and quality of life as the main drivers of value for all actors in the process: patients, healthcare professionals, institutions, and ultimately society.

Author contributions

AC, S-LL, TK, AL, and JA wrote sections of the manuscript. AC wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, 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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Predictors and Prognosis of Symptomatic Intracranial Hemorrhage in Acute Ischemic Stroke Patients Without Thrombolysis: Analysis of Data From the Chinese Acute Ischemic Stroke Treatment Outcome Registry

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Background and Purpose: There is limited information on symptomatic intracranial hemorrhage (sICH) in stroke patients without thrombolysis. This study aimed to evaluate the risk factors of sICH and the association between sICH and the prognosis at 3 and 12 months in acute ischemic stroke patients without thrombolysis.

Methods: Data originated from the Chinese Acute Ischemic Stroke Treatment Outcome Registry. Univariate analysis and multivariate logistic regression were used to screen the risk factors of sICH. Multivariable logistic regression models were used to assess the association of sICH with poor outcome and all-cause mortality.

Results: Totally, 9,484 patients were included, of which 69 (0.73%) had sICH. Atrial fibrillation (odds ratio [OR], 3.682; 95% confidence interval [CI], 1.945–6.971; $p < 0.001$), history of tumors (OR, 2.956; 95% CI, 1.115–7.593; $p = 0.024$), and the National Institutes of Health Stroke Scale (NIHSS) score on admission ([6–15: OR, 2.344; 95% CI, 1.365–4.024; $p = 0.002$] [>15: OR, 4.731; 95% CI, 1.648–13.583; $p = 0.004$]) were independently associated with sICH. After adjustment of the confounders, patients with sICH had a higher risk of poor outcome (OR, 1.983; 95% CI, 1.117–3.521; $p = 0.018$) at 3 months and that of all-cause mortality at 3 (OR, 6.135; 95% CI, 2.328–16.169; $p < 0.001$) and 12 months (OR, 3.720; 95% CI, 1.513–9.148; $p = 0.004$).

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Conclusion: sICH occurred in 0.73% of acute ischemic stroke patients without thrombolysis and was associated with a worse prognosis at 3 and 12 months. Atrial fibrillation, history of tumors, and NIHSS score at admission were independent risk factors of sICH.

Keywords: ischemic stroke, symptomatic intracranial hemorrhage, risk factors, prognosis, atrial fibrillation, tumor

INTRODUCTION

Stroke is the second leading cause of disability-adjusted life years worldwide in people over 50 years of age (1), which has brought a heavy burden on society and families. Until now, intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) remains the first line treatment for patients with acute ischemic stroke. Symptomatic intracranial hemorrhage (sICH) is recognized as a devastating complication of thrombolysis treatment, which occurs in 0.4–10.3% patients depending on the varied diagnostic criteria and is consistently associated with an increased mortality and a worse functional outcome (2–16). Many studies have reported the predictors of sICH after intravenous thrombolysis, including stroke severity, age, onset-to-treatment time, baseline glucose, hyperdense cerebral artery sign, and early infarct signs on baseline imaging (2, 3, 7, 17). However, there is limited information on sICH in stroke patients without intravenous thrombolysis.

Although the incidence of sICH was lower in the patients who received placebo compared to those given t-PA in the National Institute of Neurological Disorders and Stroke (NINDS) trial (0.6 vs. 6.4%), management of acute stroke remains challenging, considering the vast number of stroke patients without intravenous thrombolysis worldwide (18). Tan et al. (19) reported that 4.4% of ischemic stroke patients without thrombolysis developed sICH. But this is a single-center study with only 406 patients included. Another study based on a multicenter registry analyzed sICH in those who did not receive any antithrombotic therapy (20), while most patients with acute ischemic stroke would receive antithrombotic treatment after stroke, of which approximately one third underwent antiplatelet therapy (APT) prior to the onset of stroke in the real world (21, 22).

The purpose of this study is to investigate the risk factors and prognosis of sICH in patients with acute ischemic stroke that did not undergo thrombolytic therapy in a large multicenter, prospective cohort in China.

METHODS

Study Design and Population

Data was obtained from the Chinese Acute Ischemic Stroke Treatment Outcome Registry (CASTOR), a multicenter, prospective, hospital-registry ($n = 80$) study conducted in 46 cities across China. The trial design and protocol were described elsewhere (23). The hospitals included in our study were required to have a neurology ward with over 100 stroke patients admitted every year. Consecutive patients from May 2015 to October 2017 were eligible for enrollment in the study if they met the following criteria: (1) age $\geq$18 years. (2) acute ischemic stroke diagnosed according to the Chinese Guideline for Diagnosis and Treatment of Ischemic Stroke (2014). (3) admitted within 1 week after onset of stroke. (4) consent to participation in this study. Patients with cerebral hemorrhage or an expected survival $<$3 months due to systemic diseases were excluded. Patients were assessed five times during the course of the study at admission, 7 ± 2 days after enrollment, discharge, and $\sim$3- and 12- months post-stroke.

This study was registered with ClinicalTrials.gov (NCT02470624) and approved by the ethics committees of Peking University First Hospital (IRB approval number: 2015[922]) and all participating hospitals. This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients or an guardian (if the patient was unable to provide it) to participate.

Data Collection

Baseline information was collected predominantly by face-to-face interviews. The details of the diagnosis and treatment strategy during admission were obtained from the medical records and interviews with patients or their proxies. The information included: (1) demographic variables, including age and sex; (2) medical history, including hypertension (patients taking antihypertensive agents or with blood pressure $>$140/90 mmHg on repeated measurements), diabetes mellitus (patients taking antidiabetic agents, with fasting blood sugar level $>$126 mg/dL or HbA1c $\geq$6.5%, or with a casual plasma glucose level $>$200 mg/dL), hyperlipidemia (patients taking lipid-lowering agents or with an overnight fasting cholesterol level $>$240 mg/dL, triglyceride level $>$200 mg/dL, or low-density lipoprotein level $>$160 mg/dL), history of stroke (previous cerebral infarction and/or hemorrhage), atrial fibrillation(AF), coronary heart disease, history of tumors; (3) medication history within 3 months prior to onset of stroke (single antiplatelet agents, dual antiplatelet agents, lipid-lowering agents, antihypertensive agents, antidiabetic agents); (4) medication administered after onset of stroke (thrombolysis, antiplatelet agents, anticoagulation agents, lipid-lowering agents, antihypertensive agents, antidiabetic agents); (5) clinical features of the index stroke, including National Institutes of Health Stroke Scale score (NIHSS), Glasgow Coma Scale score (GCS) and systolic and diastolic blood pressure on admission.

Diagnosis of sICH

Repeated brain CT/MRI was suggested when neurological deterioration occurred in stroke patients. sICH was defined as the hemorrhage confirmed by CT/MRI scans during admission with clinical deterioration or an increase of four or more points in NIHSS score or adverse events indicating clinical worsening (e.g., drowsiness, increase of hemiparesis) recorded by the investigator, according to the definitions outlined in the European-Australasian Acute Stroke Study (ECASS-II) classification (24).

Outcome Assessment

The functional outcome measured using the modified Rankin scale (mRS) was collected via face-to-face or telephone interview at 3 and 12 months after the onset of symptoms. Poor outcome was defined as a mRS score of 3–6. All-cause death was defined as death from any cause and confirmed by a death certificate from the hospital or the local citizen registry. The outcomes in our study included the proportion of poor outcome and all-cause mortality at 3 and 12 months.

Statistical Analysis

Data were expressed as median values, inter-quartile ranges (IQR) for continuous variables, and frequencies and percentages for discrete variables. The statistical significance of intergroup differences was assessed using Mann-Whitney U-test or χ^2 tests as appropriate. Multivariate logistic regression analysis was subsequently used to identify the independent risk factors from those variables with $p < 0.1$ in the univariate analysis. Calculated odds ratios (ORs) were used to measure the association between sICH and risk factors. The relationship of sICH with poor outcome and all-cause mortality was assessed using several logistic regression models. Model 1 was adjusted for age and sex; Model 2 was further adjusted for medical history (previous stroke, hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, AF, and history of tumors), medication 3 months prior to the onset of stroke (lipid-lowering agents antiplatelet agents, antihypertensive agents), and the clinical features of the index stroke (NIHSS and GCS scores on admission, diastolic pressure, and systolic pressure on admission) based on Model 1 and Model 3 was further adjusted for treatment in the hospital (antidiabetic agents, antihypertensive agents, lipid-lowering agents, antithrombotic agents) based on Model 2. A sensitivity analysis was performed that restricted the study population to those who were admitted within 48 h of stroke onset. All p-values were two-sided, with $p < 0.05$ considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics and Incidence of sICH

In total, 10,002 consecutive patients with ischemic stroke within 7 days of onset were enrolled in the CASTOR study. We excluded 518 patients for the following reasons: incorrect diagnosis ($n = 21$), withdrawal of informed consent ($n = 4$), discontinuation from the study at the choice of patients or at the decision of the researchers considering patient safety ($n = 5$), unavailability of sICH data ($n = 2$), insufficient data on admission ($n = 38$), and undergoing intravenous thrombolysis or endovascular treatment ($n = 448$). Finally, 9,484 patients (median age, 64.0 years; 65.6% males) were included in this the analysis (**Figure 1**). The median NIHSS score at admission was 4 (IQR 2–7). Among the 9,484 patients, 69 cases (0.73%; median age, 66.0 years; 66.7% males) had developed sICH during admission.

Predictors of sICH

The characteristics of patients with and without sICH are summarized in **Table 1**. Univariate analysis revealed the differences between patients with and without sICH were significant in the following features: age ($p = 0.012$), NIHSS score at admission ($p < 0.001$), GCS score at admission ($p < 0.001$),

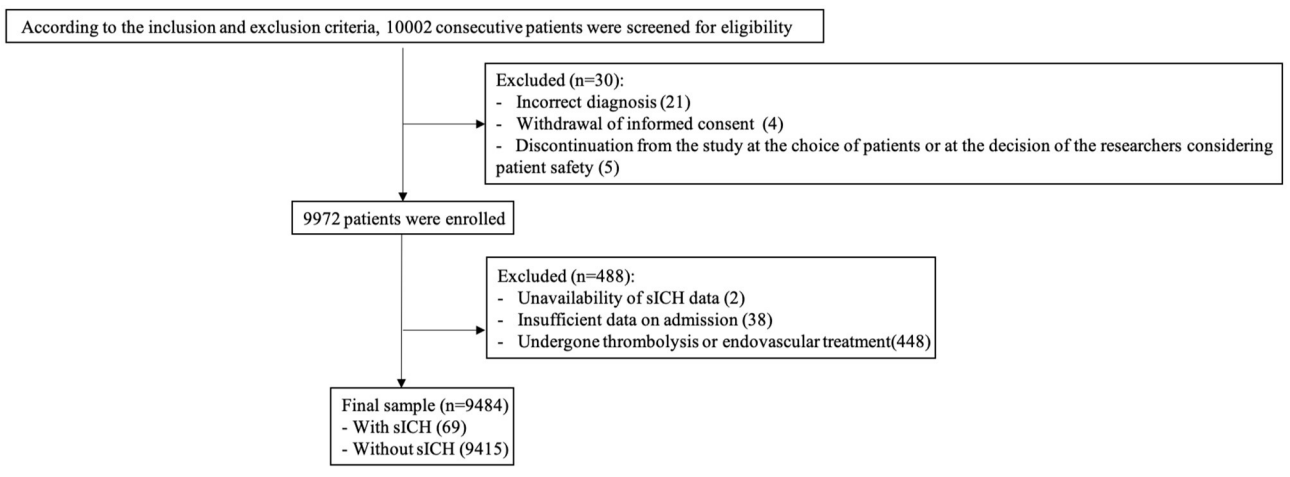

FIGURE 1 | Study patients flow chart.

TABLE 1 | Baseline characteristics of ischemic stroke patients with and without sICH ($n = 9,484$).

	All	Without sICH ($n = 9,415$)	With sICH ($n = 69$)	*P*-values
Male	6,221(65.6)	6,175(65.6)	46(66.7)	0.851
Age	64.0(55.0–72.0)	64.0(55.0–72.0)	66.0(59.5–75.0)	**0.012**
Diastolic pressure on admission	87(80–97)	87(80–97)	89(76–98)	0.943
Systolic pressure on admission	150(135–164)	150(135–164)	155(136–167)	0.259
NIHSS score on admission				**<0.001**
0–5	6,067(64.0)	6,041(64.2)	26(37.7)	
6–15	2,929(30.9)	2,899(30.8)	30(43.5)	
>15	488(5.1)	475(5.0)	13(18.8)	
GCS score on admission				**<0.001**
13–15	8,594(90.6)	8,540(90.7)	54(78.3)	
9–12	691(7.3)	683(7.3)	8(11.6)	
3–8	199(2.1)	192(2.0)	7(10.1)	
Past history				
Previous stroke	2,258(23.8)	2,243(23.8)	15(21.7)	0.685
Hypertension	6,141(64.8)	6,101(64.8)	40(58.0)	0.237
Diabetes mellitus	2,460(25.9)	2,436(25.9)	24(34.8)	0.093
Dyslipidemia	296(3.1)	294(3.1)	2(2.9)	0.915
Coronary heart disease	1,315(13.9)	1,303(13.8)	12(17.4)	0.395
Atrial fibrillation	515(5.4)	499(5.3)	16(23.2)	**< 0.001**
History of tumors	238(2.5)	233(2.5)	5(7.2)	**0.012**
Medication before admission (3 months prior to stroke)				
Lipid-lowering agents	422(4.4)	417(4.4)	5(7.2)	0.258
Antiplatelet agents	0.575			
None	8,641(91.1)	8,576(91.1)	65(94.2)	
Single antiplatelet agents	728(7.7)	725(7.7)	3(4.3)	
Dual antiplatelet agents	115(1.2)	114(1.2)	1(1.4)	
Antihypertensive agents	2,853(30.1)	2,837(30.1)	16(23.2)	0.210
Treatment in hospital				
Antidiabetic agents	2,825(29.8)	2,796(29.7)	29(42.0)	**0.026**
Antihypertensive agents	4,308(45.4)	4,275(45.4)	33(47.8)	0.688
Lipid-lowering agents	8,684(91.6)	8,620(91.6)	64(92.8)	0.721
Antithrombotic agents				**0.006**
None	409(4.3)	402(4.3)	7(10.1)	
Antiplatelet agents	7,783(82.1)	7,737(82.2)	46(66.7)	
Anticoagulant agents	133(1.4)	131(1.4)	2(2.9)	
Antiplatelet + anticoagulant agents	1,159(12.2)	1,145(12.2)	14(20.3)	

Values are reported as n (%) or as Median (interquartile range).
sICH, symptomatic intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.
p-values in bold fonts indicate significant associations.

AF ($p < 0.001$), history of tumors ($p = 0.012$), antidiabetic agents during admission ($p = 0.026$), and antithrombotic agents during admission ($p = 0.006$). The multivariate logistic regression analysis showed that AF (OR, 3.682; 95% CI, 1.945–6.971; $p < 0.001$), history of tumors (OR, 2.956; 95% CI, 1.115–7.593; $p = 0.024$), and NIHSS score on admission ([6–15: OR, 2.344; 95% CI, 1.365–4.024; $p = 0.002$] [>15: OR, 4.731; 95% CI, 1.648–13.583; $p = 0.004$]) were the independent risk factors of sICH (**Table 2**).

Antithrombotic Therapy and sICH in Patients With AF

In our study, 515 patients (5.4%) had a history of AF, of which 250 (48.5%) patients received antiplatelet therapy, 71 (13.8%) received anticoagulant therapy, 162 (31.5%) received both antiplatelet and anticoagulant therapy, and 32 (6.2%) did not receive any antithrombotic therapy during admission. In patients with AF, the development of sICH was not significantly associated with the antithrombotic regimen (**Table 3**).

TABLE 2 | Multivariate analysis to identify factors associated with sICH in patients with ischemic stroke without thrombolysis.

	OR	95%CI	*P*-values
Atrial fibrillation	3.682	1.945–6.971	**<0.001**
History of tumors	2.956	1.115–7.593	**0.024**
NIHSS score on admission			
0–5	*Ref.*		
6–15	2.344	1.365–4.024	**0.002**
>15	4.731	1.648–13.583	**0.004**

NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval. p-values in bold fonts indicate significant associations.

TABLE 3 | Antithrombotic regimens and sICH in patients with atrial fibrillation.

	All	Without sICH ($n = 499$)	With sICH ($n = 16$)	*P*-values
Antithrombotic agents				0.141
None	32(6.2)	29(5.8)	3(18.8)	
Antiplatelet agents	250(48.5)	244(48.9)	6(37.5)	
Anticoagulant agents	71(13.8)	70(14.0)	1(6.3)	
Antiplatelet + anticoagulant agents	162(31.5)	156(31.3)	6(37.5)	

sICH, symptomatic intracranial hemorrhage.

Tumor Types and sICH

In our analysis, 238 (2.5%) patients had a history of tumors, of which 10 (42%) had nasopharyngeal cancer, 35 (14.7%) had malignant tumors of the digestive system, 14 (5.9%) had lung cancer, 15 (6.3%) had breast cancer, 8 (3.4%) had liver cancer, 33 (13.9%) had reproductive system tumors, 5 (2.1%) had tumors of the hematological system, 8 (3.4%) had a combination of two types of tumors, and 110 (46.2%) had other tumors. There was no significant association between tumor types and sICH ($p = 0.251$) (**Table 4**).

Prior APT and sICH

Among the 9,484 patients without thrombolysis, 843 (8.9%) received APT within 3 months prior to stroke onset, of which 115 received dual APT treatment with aspirin and clopidogrel, and 728 received single APT (663 patients with aspirin alone, 117 with clopidogrel alone, and 5 with cilostazol alone). There was no significant difference in the risk of sICH among the three groups (0.8% in the no APT group, 0.4% in the single APT group and 0.9% in the dual APT group, $p = 0.575$).

sICH and Poor Outcome

The mRS score at 3 months was collected in 8,890 (93.7%) patients, of which 1,734 (19.5%) had a mRS score of 3–5 and 95 (1.1%) patients had died (mRS = 6). At 12 months post stroke onset, the mRS score was collected in 8,332 (87.9%) patients, of which 1,209 (12.7%) had an mRS score 3–5 and 191(2.0%) patients had died. Compared to those without sICH, the patients with sICH had a higher risk of poor outcome (45.3 vs. 20.4%, $p < 0.001$; 33.3 vs. 16.7%, $p = 0.001$, respectively) and mortality (10.9 vs. 1.0%, $p < 0.001$; 13.3 vs. 2.2%, $p < 0.001$, respectively) at 3 and 12 months. After adjusting for the confounding variables, the differences in poor outcome (OR, 1.983; 95% CI, 1.117–3.521; $p = 0.018$) at 3 months and all-cause mortality at 3 (OR, 6.135; 95% CI, 2.328–16.169; $p < 0.001$) and 12 months (OR, 3.720; 95% CI, 1.513–9.148; $p = 0.004$) remained statistically significant (**Table 5**).

TABLE 4 | Tumor type and sICH in acute ischemic stroke patients without thrombolysis.

	All	Without sICH ($n = 233$)	With sICH ($n = 5$)	*P*-values
Nasopharyngeal cancer	10(4.2)	10(4.3)	0(0.0)	0.251
Malignant tumors of the digestive system	35(14.7)	33(14.2)	2(40.0)	
Lung cancer	14(5.9)	15(6.0)	0(0.0)	
Breast cancer	15(6.3)	15(6.0)	1(20.0)	
Liver cancer	8(3.4)	7(3.0)	1(20.0)	
Reproductive system tumors	33(13.9)	33(14.2)	0(0.0)	
Hematological system tumors	5(2.1)	5(2.1)	0(0.0)	
Other tumors	110(46.2)	119(46.8)	1(20.0)	
Combined with two types of tumors	8(3.4)	8(3.4)	0(0.0)	

sICH, symptomatic intracranial hemorrhage.

Sensitivity Analysis

When we restricted the study population to those who were admitted within 48 h of stroke onset, there were 6,835 patients were included in the sensitivity analysis, of which 55 (0.8%) patients developed sICH. AF (OR, 3.432; 95% CI, 1.723–6.835; $p < 0.001$), history of tumors (OR, 3.255; 95% CI, 1.128–9.391; $p = 0.029$), and NIHSS score at admission ([6–15: OR, 2.844; 95% CI, 1.524–5.307; $p = 0.001$] [>15: OR, 5.073; 95% CI, 1.601–16.072; $p = 0.006$]) were the independent predictors of sICH (**Supplementary Tables 1–4**). Further, sICH was significantly associated with the increased risk of poor outcome at 3 months and all-cause mortality at 3 and 12 months (**Table 6**).

DISCUSSION

In this study, we found that sICH occurred in 0.73% of acute ischemic stroke patients without thrombolysis during admission and AF, history of tumors, and NIHSS score at admission were the independent risk factors of sICH. In these patients, sICH was associated with a higher risk of poor outcome at 3 months and an increased mortality at 3 and 12 months. No significant association between sICH and poor outcome at 12 months was observed.

Previous studies on acute ischemic stroke have focused on hemorrhagic transformation (HT), while the diagnosis of sICH required an imaging change and a deterioration in neurological

TABLE 5 | Relationship of all-cause death and poor functional prognosis with sICH in patients without thrombolysis.

Outcomes	OR	95%CI	*P*-values
At 3 months			
Poor outcome			
Unadjusted	3.234	1.972–5.305	<0.001
Model 1	3.019	1.824–4.997	<0.001
Model 2	2.000	1.128–3.549	0.018
Model 3	1.983	1.117–3.521	0.019
Death			
Unadjusted	12.194	5.411–27.482	<0.001
Model 1	10.069	4.337–23.377	<0.001
Model 2	6.711	2.651–16.992	<0.001
Model 3	6.135	2.328–16.169	<0.001
At 12 months			
Poor outcome			
Unadjusted	2.497	1.455–4.284	0.001
Model 1	2.284	1.307–3.989	0.004
Model 2	1.530	0.832–2.812	0.171
Model 3	1.550	0.842–2.855	0.159
Death			
Unadjusted	6.800	3.185–14.521	<0.001
Model 1	5.725	2.576–12.726	<0.001
Model 2	3.718	1.540–8.979	0.004
Model 3	3.720	1.513–9.148	0.004

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, medical history (previous stroke, hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, AF, and history of tumors), medication 3 months prior to the onset of stroke (lipid-lowering agents, antiplatelet agents, antihypertensive agents), and the clinical features of the index stroke (NIHSS and GCS scores on admission, diastolic pressure and systolic pressure on admission).
Model 3: adjusted for variables in model 2, plus treatment in the hospital (antidiabetic agents, antihypertensive agents, lipid-lowering agents, antithrombotic agents).
OR, odds ratio; CI, confidence interval; mRS, modified Rankin scale.

TABLE 6 | Sensitivity analysis.

Outcomes	OR	95%CI	*P*-values
At 3 months			
Poor outcome			
Unadjusted	3.632	2.091–6.310	<0.001
Model 1	3.449	1.966–6.053	<0.001
Model 2	2.185	1.159–4.121	0.016
Model 3	2.148	1.138–4.053	0.018
Death			
Unadjusted	11.678	4.830–28.237	<0.001
Model 1	9.923	3.967–24.823	<0.001
Model 2	5.671	2.038–15.783	0.001
Model 3	5.285	1.813–15.403	0.002
At 12 months			
Poor outcome			
Unadjusted	2.818	1.565–5.073	0.001
Model 1	2.626	1.430–4.822	0.002
Model 2	1.661	0.857–3.218	0.133
Model 3	1.688	0.869–3.279	0.122
Death			
Unadjusted	6.990	3.083–15.849	<0.001
Model 1	5.927	2.484–14.140	<0.001
Model 2	3.786	1.455–9.851	0.006
Model 3	3.756	1.417–9.961	0.008

Patients admitted within 48 h after the onset of stroke were included in the sensitivity analysis (n = 6,835).
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, medical history (previous stroke, hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, AF, and history of tumors), medication 3 months prior to the onset of stroke (lipid-lowering agents,antiplatelet agents, antihypertensive agents), and the clinical features of the index stroke (NIHSS and GCS scores on admission, diastolic pressure and systolic pressure on admission).
Model 3: adjusted for variables in model 2, plus treatment in the hospital (antidiabetic agents, antihypertensive agents, lipid-lowering agents, antithrombotic agents).
OR, odds ratio; CI, confidence interval; mRS, modified Rankin scale.

function. In our study, the incidence of sICH in patients without thrombolysis was similar to that noted in NINDS trial (0.73 vs. 0.6%) (18). Several studies have reported a higher incidence of sICH in patients without thrombolysis. A systematic review showed that the incidence of sICH was 1.5% (4), which may be attributed to differences in patient selection criteria, the diagnostic criteria of sICH, the time interval between stroke onset and admission, and stroke treatment. Two studies from West China Hospital reported that the incidence of sICH was 1.3% in 2010–2011 and 4.4% in 2002–2005, respectively (15, 19). There were more patients with mild stroke in our cohort, which may explain this discrepancy. In addition, the sample sizes of these two studies were relatively small, and the patients were recruited from a single center.

We found AF was associated with an ∼4-fold increase in the risk of sICH in the patients without thrombolysis. A similar result was reported by Tan et al. (19) In patients with thrombolysis, AF was also recognized as an independent risk factor of sICH with the OR ranging from 2.5 to 7 (25). Patients with cardiogenic stroke usually have rapid occlusion of arteries, less developed cerebral collateral circulation, small penumbra and large core infarction, which increases HT (26, 27). Most patients with AF may receive anticoagulant therapy, but previous trials have shown that anticoagulation could increase the risk of intracerebral bleeding in ischemic stroke patients (28). However, Lee et al. (29) reported that the incidence of sICH did not increase in patients with cardiogenic embolism who received early anticoagulation therapy within 1 week from stroke onset. Similarly, our analysis did not find a significant association between the antithrombotic regimen during admission and sICH in patients with AF, either. The risk in those with anticoagulation was not higher than that with antiplatelet medication. This finding was also consistent with those of several other studies (30–32), and this indicated that it was AF not the accompanying anticoagulation therapy which caused the increased the risk of sICH.

In this study, a higher NIHSS score at admission was associated with sICH in patients with acute ischemic stroke who did not undergo thrombolysis. Similar results were noted in

those with ischemic stroke after thrombolysis (3, 25, 33, 34). In previous studies on patients without thrombolysis, although univariate analysis showed that patients with higher NIHSS score were more prone to HT, NIHSS score was not an independent risk factor for HT (2, 19, 20). This is perhaps explained by the smaller sample sizes of previous studies and the fact that previous studies only investigated the relationship between HT and NIHSS score at admission rather than the relationship between sICH and NIHSS score at admission. Severe ischemic stroke usually manifests as extensive brain tissue damage, including vascular damage, which is prone to bleeding.

Previous studies found that antithrombotic medications before acute ischemic stroke might increase the risk of sICH after intravenous thrombolysis (35, 36). In our study, although patients with prior APT were older and more likely to have vascular risk factors which may increase the risk of sICH, pre-stroke APT did not increased the risk of sICH, which suggests that prior use of APT did not increase the risk of sICH in stroke patients without thrombolysis. Similar results were reported in some other studies (2, 20). A study that included 12,415 patients without thrombolysis found no correlation between APT and HT, although reported a higher proportion of pre-stroke APT (17.54%) (20). The variations in the doses of pre-stroke antiplatelet therapy and the issue of patient compliance were not addressed in our study. Therefore, further research is needed.

Interestingly, we found an association between the history of tumors and sICH in acute ischemic stroke patients without thrombolysis, which had not been reported previously. Several studies investigated the relationship between a history of tumors and sICH after thrombolysis and their results varied greatly. The overall risk of hemorrhagic stroke occurrence in patients with cancer is significantly higher than that in the general population (37). Whether brain hemorrhage is directly or indirectly caused by cancer is not clear. In our study, the initial brain imaging before enrolment could exclude those patients with typical lesions of primary brain tumors or metastatic tumors. However, we could not rule out the possibility that some patients with atypical lesions of tumor had been included in the study and then had hemorrhagic transformation. Other studies indicated severe thrombocytopenia and coagulopathy may be a mechanism of cerebral hemorrhage related to tumor (37). Thus, further research is needed to investigate the mechanisms of sICH in acute ischemic stroke patients with history of tumors. Although in the latest acute ischemic stroke management guidelines, the American Heart Association and the American Stroke Association provided with some suggestions for patients with a history of tumors, such as intravenous thrombolysis is contraindicated in cases of intra-axial intracranial neoplasms and gastrointestinal malignancy, and recommended in cases of extra-axial intracranial neoplasms and systemic malignancy with reasonable (>6 months) life expectancy, the guidelines admitted that the efficacy and safety of the treatments in stroke patients with malignant disease are still unclear (38). With aging and the improvement in tumor therapy, there will be more tumor survivors who are also vulnerable to stroke. Our study showed a higher risk of sICH in stroke patients with a history of tumors, which indicated that there would be some different characteristics in these patients and warranted further research on the management of stroke in patients with history of tumors.

There was a relatively lower mortality (1.1% at 3 months and 2.0% at 12 months) in our study, which was similar to the results based on the Third China National Stroke Registry (1.3% at 3 months and 2.9% at 12 months) (39). Andrade et al. (40) reported a mortality of 6.9% at discharge and Paciaroni et al. (2) reported a mortality of 11.5% at 3 months in stroke patients. This difference may be due to the lower average age of patients and the lower median NIHSS score at admission in our cohort.

A prospective cohort study showed that post-thrombolytic sICH contributed to an increased risk of poor outcome and mortality. According to the different definitions of sICH used, the ranges of OR were 1.3–1.7 and 1.5–4.8, respectively (3). Another multicenter prospective cohort study showed that sICH could increase the risk of poor outcome by 3.57 times (7). Our findings suggested that patients with sICH had a higher risk of poor outcome at 3 months. Additionally, the patients with sICH still had a higher mortality rate at 3 and 12 months and it revealed sICH in stroke patients without thrombolysis was a serious problem in management of stroke since most patients did not receive thrombolysis in the real world. We speculated two possible reasons that would contribute to the worse prognosis. One was the direct influence of sICH, and the other reason was that the withdrawal of antithrombotic therapy at the early stage of treatment due to sICH increased the recurrent ischemic stroke. In our study, patients with sICH had a higher incidence of poor outcome at 12 months than those without sICH (33.3 vs. 16.7%, $p = 0.001$). However, the difference became insignificant after adjustment of the baseline characteristics and treatment during admission. Considering the mRS score was not collected in 1,152 patients at 12 months, we could not rule out the possibility of selective dropout.

The strengths of our study include a relatively large sample size and a multicenter design. However, our study has several limitations that need to be addressed. First, this study was an observational investigation, we adjusted for a series of identified confounding variables. However, due to the nature of observational studies, certain unmeasured or residual confounding effects were unavoidable. Therefore, we cannot conclude a causal relationship between sICH and poor outcome. Second, repeated brain imaging was often performed when the symptoms of stroke patients worsen in clinical practice, which may underestimate the risk of ICH, especially in the patients with asymptomatic or mild symptoms. However, our study focused on the patients with sICH, who had a deterioration in neurological function accompanying with ICH. So we think the risk of underestimation was limited in our study. Third, some information such as glucose level at admission, blood pressure during admission, details of brain imaging including radiographic classification of HT, and number of cerebral microbleeds were not collected in the database. So our study propably missed to elucidate the responsible mechanisms and potential protective measures of sICH. Fourth, the exact time of sICH was not recorded in our database. While sICH occurring at different timepoints may be due to varied pathological

mechanisms. Fifth, although we found an association between history of tumors and sICH, the limited sample with tumor needed the further confirmation. Sixth, we did not include the patients who underwent endovascular treatment although thrombectomy treatment had been recommended in the current guidelines. Considering there were only 23 patients who received endovascular treatment in our study and the significant difference in the risk of bleeding, we focused on those who only received medication treatment. Seventh, the CASTOR study recruited the patients who were admitted within 7 days of onset from acute ischemic stroke, which indicates a possible heterogenous population, and those who had developed sICH at early stage would not be included in this registry, which may underestimate the incidence of sICH. However, in the sensitivity analysis which only included those admitted within 48 h, the results were similar to that of our main analysis. Finally, all the patients were recruited in China. The rate of receiving intravenous thrombolysis and endovascular treatment, as well as the mortality were relatively lower than other studies in the western countries (2, 41–44). Hence, caution is needed when generalizing our results to other populations.

CONCLUSIONS

In a large, multicenter cohort of acute ischemic stroke patients, sICH occurred in 0.73% of patients without thrombolysis and was associated with a worse prognosis at 3 and 12 months post stroke. AF, a history of tumors, and NIHSS score at admission were the independent risk factors of sICH.

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 Peking University First Hospital (IRB approval number: 2015[922]) and all participating hospitals. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WeipS and YH: conceptualization, methodology, supervision, and writing—review and editing. ZS and YL: data curation. HJ, WeiS, RL, FL, JS, LT, GL, HC, GZ, LZ, XS, JQ, and YW: investigation. ZS: writing—original draft. All authors have read and agreed to the published 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.2021.727304/full#supplementary-material

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Sertraline for Functional Recovery After Acute Ischemic Stroke: A Prospective Observational Study

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Background: Neuroprotective and neurorestorative effects have been postulated for selective serotonin-reuptake inhibitors (SSRI). We hypothesized that sertraline, which is characterized by less severe adverse effects and more stable pharmacokinetics than classic SSRI, is associated with improved functional recovery in acute ischemic stroke patients with motor deficits.

Methods: Prospective observational study of consecutive acute ischemic stroke patients who received sertraline for clinically suspected post-stroke depression (PSD) or at high risk for PSD. Eligibility comprised acute motor deficit caused by ischemic stroke (≥2 points on NIHSS motor items) and functional independence pre-stroke (mRS ≤1). Decision to initiate treatment with SSRI during hospital stay was at the discretion of the treating stroke physician. Patients not receiving sertraline served as control group. Favorable functional recovery defined as mRS ≤2 was prospectively assessed at 3 months. Multivariable logistic regression analysis was used to explore the effects of sertraline on 3-months functional recovery. Secondary outcomes were frequency of any and incident PSD (defined by BDI ≥10) at 3 months.

Results: During the study period (03/2017–12/2018), 114 patients were assigned to sertraline ($n = 72$, 62.6%) or control group ($n = 42$, 37.4%). At study entry, patients in sertraline group were more severely neurologically affected than patients in the control group (NIHSS: 8 [IQR, 5–11] vs. 5 [IQR, 4–7]; $p = 0.002$). Also, motor NIHSS scores were more pronounced in sertraline than in control group (4 [IQR 2–7] vs. 2 [IQR 2–4], $p = 0.001$). After adjusting for age and baseline NIHSS, multivariable regression analysis revealed a significant association between sertraline intake and favorable functional outcome at 3 months (OR 3.10, 95% CI 1.02–9.41; $p = 0.045$). There was no difference between both groups regarding the frequency of any depression at 3 months (26/53 [49.1%] vs. 14/28 [50.0%] patients, $p = 0.643$, BDI ≥10). However, fewer incident depressions were observed in sertraline group patients compared to patients in control group (0/53 [0%] vs. 5/28 [17.9%] patients, $p = 0.004$).

Conclusions: In this non-randomized comparison, early treatment with sertraline tended to favor functional recovery in patients with acute ischemic stroke. While exploratory in nature, this hypothesis needs further investigation in a clinical trial.

Keywords: stroke, outcome, functional recovery, motor recovery, SSRI, sertraline, post-stroke depression, neuroplasticity

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INTRODUCTION

Stroke is the most common cause of acquired disability in adulthood (1). While acute stroke care has undergone major therapeutic achievements in recent years, only a few pharmaceutical agents eventually showed promising clinical results from a neuroprotective perspective (2–4). Both neuroprotective and neurorestorative effects are postulated for selective serotonin-reuptake inhibitors (SSRI) (5–7), which were suggested to promote functional recovery after stroke by modifying ischemia-associated hyperexcitation, post-stroke inflammation, and hippocampal neurogenesis. Moreover, SSRI may augment cerebral blood flow and counteract evolution of the infarct core (6–11). Animal studies have further suggested that hippocampal expression of neurotrophins such as brain-derived neurotrophic factor (BDNF), an important mediator of cerebral plasticity and neurogenesis, is stimulated by SSRI (7, 8, 12–14).

The randomized controlled fluoxetine for motor recovery after acute ischaemic stroke (FLAME) trial, published in 2011, examined the effect of the SSRI fluoxetine on motor outcome in patients with ischemic stroke. There was an improvement in motor deficits and overall functional outcome compared to placebo after 90 days in patients receiving fluoxetine (5). Meanwhile, three larger multicenter randomized controlled trials concluded that single daily intake of fluoxetine for a period of 6 months has no beneficial effect on functional outcome in patients with ischemic stroke (15–17). However, previous clinical research has mainly focused on the SSRI fluoxetine, despite promising results from the pre-clinical setting with other SSRI (18). In any case, the use of fluoxetine in stroke patients appears debatable. On the one hand, it has a higher potential for detrimental interactions with the cytochrome P450 isoenzyme system compared with other SSRI bearing a high risk of adverse drug effects especially in the elderly and in patients exposed to polypharmacy (19). On the other hand, fluoxetine is the only SSRI considered to be unsuitable for geriatric patients (20). Lastly, fluoxetine seems to be inferior to other SSRI in terms of effectiveness in the treatment of depression (21), an entity frequently found in stroke survivors (21, 22). Almost one-third of all stroke patients develops a post-stroke depression at any time after stroke and its presence is associated with unfavorable outcome regardless of stroke severity and degree of disability (23). Pharmacotherapeutic approaches using antidepressants continue to play an important role in prevention and therapy of PSD (22).

In view of the former considerations, we aimed to explore the effects of sertraline on functional outcome and development of PSD in patients with acute ischemic stroke. As clinical data on potential effects of sertraline on motor recovery in ischemic stroke are limited (18), the results could serve as basis for sample size estimation for a randomized controlled trial.

METHODS

Study Design and Participants

This was a prospective, non-interventional observational study that enrolled consecutive patients with acute ischemic stroke at a tertiary care stroke center. Patients were eligible if they were ≥18 years, had an imaging-confirmed diagnosis of acute ischemic stroke with a corresponding motor deficit (defined as ≥2 points in the motor items of the National Institutes of Health Stroke Scale [NIHSS] score) and a new prescription of sertraline following the index event. Patients with no corresponding prescription served as the control group. Indications for sertraline grounded on routine clinical practice and comprised treatment of patients with clinically suspected PSD and patients at high risk of PSD (e.g., severe motor deficit, functional dependency, history of depression). The ultimate decision to prescribe sertraline was at the discretion of the treating stroke neurologist and independent of study-specific procedures (i.e., results from the depression instruments). Patients were not eligible for this observational study, if they had no or only mild motor deficit, a premorbid modified Rankin Scale (mRS) score ≥2 or co-morbidities likely associated with limited participation in follow-up tests (e.g., aphasia or severe dementia [defined as Mini Mental State Exam [MMSE] <10]).

As standard-of-care, patients were prescribed sertraline 50 mg daily following admission paralleled by physical therapy. Patients who met the above-mentioned study criteria, but for whom sertraline was not prescribed for clinical reasons, were assigned to the control group. Reasons for clinical decision against prescription of sertraline were: (1) lack of clinical indication as judged by the treating stroke neurologist; (2) denial of sertraline medication by the patient; (3) medical contraindications for sertraline. Patients in the control group received the same in-hospital stroke care standards but no antidepressant medication.

Study Procedures

At study entry, patient-related (such as demographic information, previous comorbidities, medication) and stroke-related (such as onset of symptoms, etiology, localization, acute reperfusion therapies) data were recorded. Neurological and functional status (NIHSS, pre-morbid mRS), depressive symptoms (Beck Depression Inventory [BDI]) and neurocognitive function (MMSE) were evaluated. At discharge, NIHSS and mRS scores were obtained by assessors blinded to group assignment. A structured telephone interview was done at 3 months (90 ± 14 days) to evaluate the primary endpoint of this study (mRS). During the interview, further questions were asked about behavior of taking sertraline since discharge and, if applicable, the date and reason for its discontinuation. Any new vascular events that occurred in the meantime, such as stroke, transient ischemic attack (TIA), or myocardial infarction, were documented. Each patient was informed that a survey for re-evaluation of a depression including BDI and the Patient Health Questionnaire (PHQ-9) would be sent by mail. If the

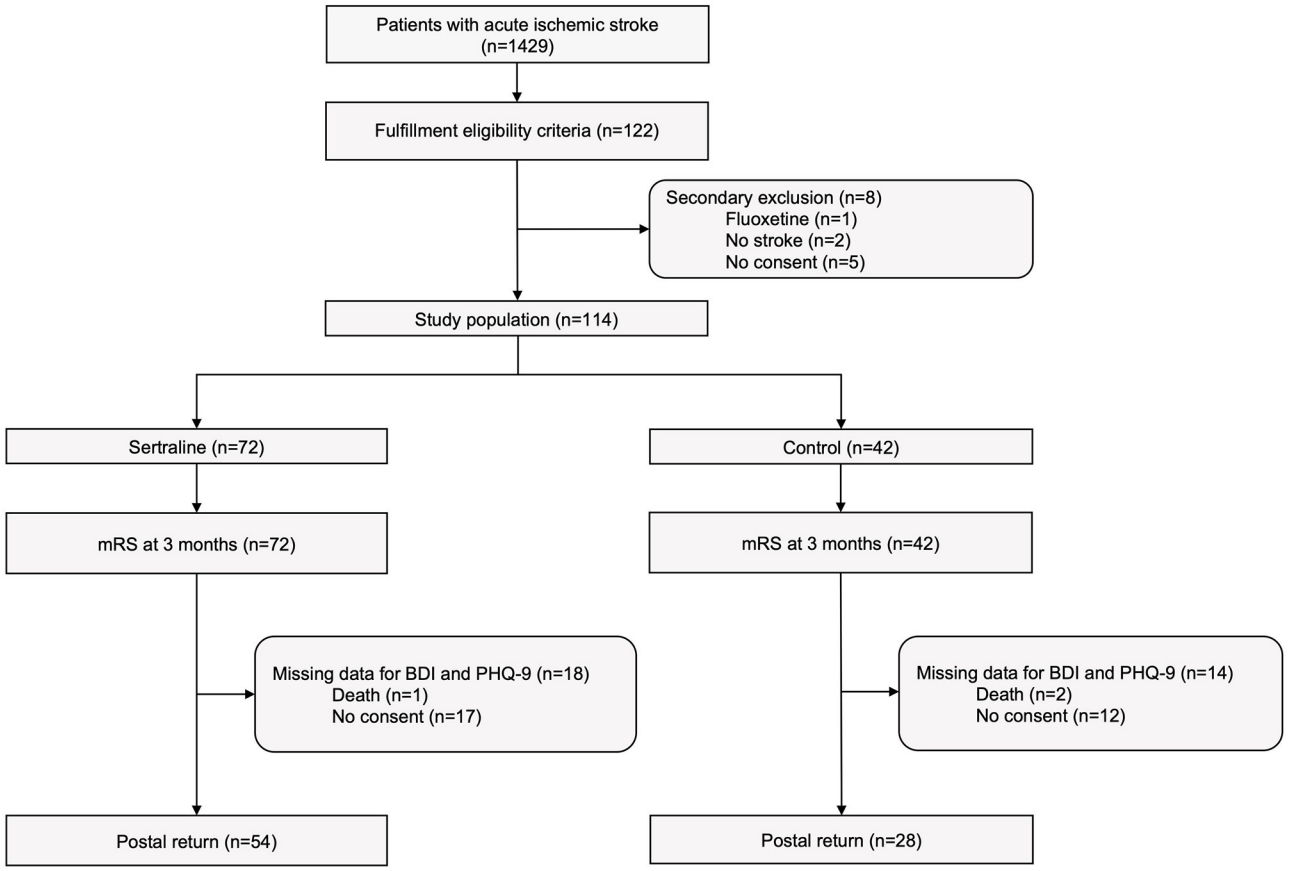

FIGURE 1 | Study flow chart.

survey was not returned within 2 weeks, a reminder call was undertaken, which was repeated every 2 weeks. The surveys received were evaluated and the completion date recorded. The same number of study visits and interviews were accomplished at pre-specified time points for all patients, regardless of their group assignment.

Outcome Measures

The primary outcome measure was favorable functional status at 3 months (90 ± 14 days) defined as an mRS score ≤2. Secondary outcome measures comprised frequency of any PSD (defined by BDI ≥10 or PHQ-9 ≥10 points) and incident PSD (defined as *de novo* increase of BDI ≥10 or PHQ-9 ≥10 points) at 3 months. Moreover, safety outcomes including recurrent ischemic or hemorrhagic stroke, recurrent TIA, myocardial infarction, and death were assessed at 3 months.

Statistical Analysis

STATA software was used for statistical analysis (Version 12.1, StataCorp, College Station, TX). Non-parametric continuous data were identified by the Shapiro-Wilk test and presented as median (interquartile range, IQR). Categorical data were summarized using frequencies and percentages. Wilcoxon rank sum test was used for between-group comparisons for differences in age, time intervals, premorbid mRS, baseline NIHSS, BDI, and MMSE scores as well as follow-up PHQ-9 and BDI scores. Pearson's chi-square test or Fisher's exact test (when expected values were <5) were used for comparing sex, comorbidities, antidepressant premedication, acute stroke therapies, stroke etiologies, and presence of any depression at baseline and follow-up as well as safety and functional outcomes at 3 months among both groups. The McNemar's test was applied for within-group comparisons of differences in favorable functional outcome and the presence of any PSD between discharge and follow-up. Adjusted odds ratio (OR) including its 95% confidence interval (95% CI) was calculated by multivariable regression analysis to describe the effect of sertraline on favorable functional outcome and PSD at 3 months. Independent predictor variables entered into the final model were identified using the backward stepwise elimination method with removal set for variables with p-value >0.2. The significance level was set at $\alpha < 0.05$. Available case analysis was applied where data were missing.

RESULTS

Between March 13th, 2017, and December 28th, 2018, 1429 patients with acute ischemic stroke were treated at the

TABLE 1 | Baseline characteristics of the study cohort.

	Sertraline ($n = 72$)	Control ($n = 42$)	p
Demographics			
Age, years, median (IQR)	69.5 (19.5)	71 (21)	0.95
Female, *n* (%)	29 (40.3)	19 (45.2)	0.61
Premorbid mRS, *n* (%)			
0	64 (88.9)	40 (95.2)	
1	8 (11.1)	2 (4.8)	0.32
Comorbidities/patient history			
Risk factors, *n* (%)			
Arterial hypertension	57 (79.2)	31 (73.8)	0.51
Hyperlipidemia	40 (55.6)	18 (42.9)	0.19
Arterial fibrillation	22 (30.6)	8 (19.1)	0.20
Depression	4 (5.6)	3 (7.1)	0.71
Diabetes mellitus	21 (29.2)	18 (42.9)	0.14
Current nicotine abuse	20 (27.8)	12 (28.6)	0.93
Sleep apnea	1 (1.4)	0 (0)	1.00
Previous stroke/TIA	10 (13.9)	4 (9.5)	0.57
Dementia	0 (0)	1 (2.4)	0.37
Antidepressant premedication, *n* (%)	3 (4.2)	3 (7.1)	0.67
Stroke-related data			
NIHSS, median (IQR)			
Total NIHSS score	8 (6)	5 (3)	0.002
Motor items of NIHSS	4 (5)	2 (2)	0.001
Acute therapy, *n* (%)	39 (54.2)	18 (42.9)	0.24
Intravenous thrombolysis	20 (51.3)	6 (33.3)	
Endovascular therapy	7 (17.9)	7 (38.9)	
Combinatory treatment	12 (30.8)	5 (27.8)	0.21
Stroke etiology, TOAST-classification, *n* (%)			0.53
Large-artery atherosclerosis	24 (33.3)	13 (31.0)	
Cardio embolism	24 (33.3)	13 (31.0)	
Small-vessel occlusion	7 (9.7)	5 (11.9)	
Stroke of other determined etiology	0 (0)	2 (4.8)	
Stroke of undetermined etiology	17 (23.6)	9 (21.4)	
ESUS, *n* (%)	15 (20.8)	9 (21.4)	0.94
Interval between admission and study entry, days, median (IQR)	4 (4.25)	3.5 (3.75)	0.039
Questionnaires			
Depression, BDI			
Median (IQR)	9 (9)	6.5 (10)	0.052
Any depression (BDI $\geq$10), *n* (%)	32 (44.4)	15 (35.7)	0.36
Mild depression (10 $\leq$ BDI $\leq$ 19)	23 (31.9)	11 (26.2)	0.69
Moderate depression (20 $\leq$ BDI $\leq$ 29)	9 (12.5)	4 (9.5)	0.77
MMSE, median (IQR)	24 (9)	25 (8)	0.33

mRS, modified Rankin Scale; TIA, transient ischaemic attack; NIHSS, National Institutes of Health Stroke Scale; TOAST, trial of ORG 10172 in acute stroke treatment; ESUS, embolic stroke of undetermined source; BDI, Beck Depression Inventory; MMSE, Mini Mental State Exam.

Department of Neurology at the University Hospital Dresden of whom 122 met study criteria and agreed to participate in this observational study. Major reasons for non-eligibility were premorbid functional dependency (mRS $\geq$2), lack of qualifying motor deficit, and limited ability to participate in the study (e.g., due to aphasia). Eight patients were excluded after study enrollment leaving a final study population of 114 patients, of whom 72 patients were assigned to sertraline group and 42 patients to control group. Reasons for secondary study exclusion were (1) prescription of fluoxetine ($n = 1$), (2) non-stroke diagnosis ($n = 2$), (3) withdrawal of consent to study participation ($n = 5$). The study flow chart is depicted in **Figure 1**.

Baseline characteristics were well-balanced between the two groups except for NIHSS that was higher in the sertraline than

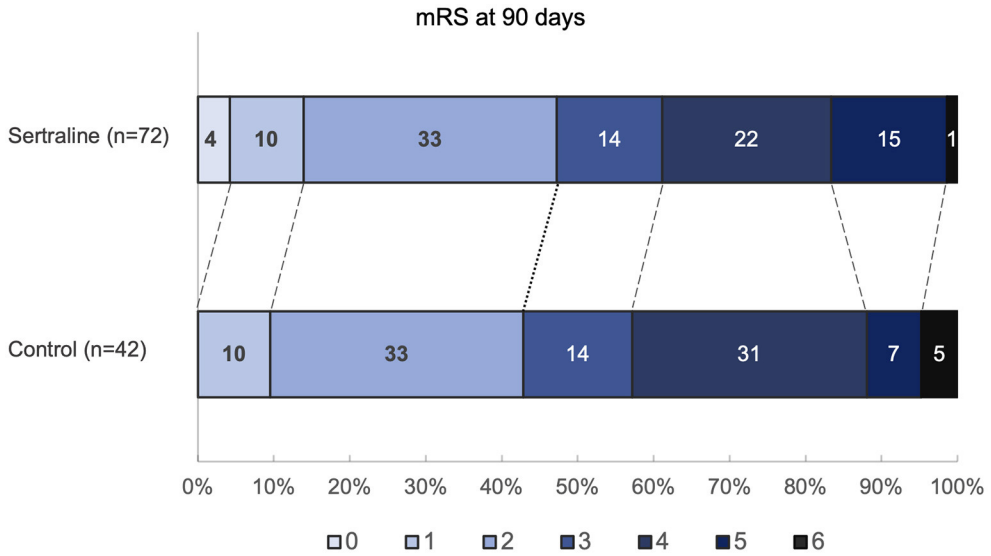

FIGURE 2 | Distribution of mRS scores at 90 days. Values within each colored region correspond to the percentage of patients with the corresponding mRS outcome. mRS indicates modified Rankin Scale.

in the control group (8 [IQR 5–11] vs. 5 [IQR 4–7]; $p = 0.002$). Likewise, the motor items on NIHSS were more pronounced in the sertraline than in the control group (4 [IQR 2–7] vs. 2 [IQR 2–4], $p = 0.001$). The median age of patients at baseline was 70.5 (IQR 58–79) years, 48 (42.1%) patients were women, and all patients were previously functional independent. Elapsed time between symptom onset and first intake of 50 mg sertraline was 4 (IQR 3–7) days. Due to depressive symptoms, the dose of sertraline was modified during hospitalization to 75 mg ($n = 1$) or 100 mg ($n = 5$). No difference regarding the presence of depressive symptoms at study inclusion (BDI ≥10 points) was evident between both groups (32/72 [44.4%] vs. 15/42 [35.7%]; $p = 0.936$). Baseline characteristics are shown in **Table 1**.

Median duration of sertraline intake was 82 days (IQR 64–90). Of 72 patients in the sertraline group, 46 patients (63.9%) continued sertraline intake until the telephone interview, whereas 25 patients (34.7%) stopped taking sertraline prematurely. One patient (1.4%) could not provide any information on medication. Most frequent reasons for premature termination were adverse effects ($n = 8$) including changes in personality ($n = 3$), seizure ($n = 1$), hyponatremia ($n = 1$), dizziness ($n = 1$), and cognitive disturbances ($n = 1$) as well as medication change by the treating general practitioner ($n = 5$), and unspecified reasons ($n = 8$).

The mRS scores at 3 months were available in all patients. At 3 months, median mRS scores were comparable between both groups (3 [IQR 2–4] vs. 3 [IQR 2–4]; $p = 0.67$) (**Figure 2**). Likewise, the frequency of favorable functional outcome did not differ between patients treated with sertraline and controls (34/72 [47.2%] vs. 18/42 [42.9%]; $p = 0.65$). However, a higher proportion of patients improved to a favorable functional status (mRS score of ≤2) between discharge and follow-up in the sertraline group as compared with controls (19/72 [26.4%] vs. 5/42 [11.9%] patients; $p < 0.001$). After adjusting for age and baseline NIHSS, multivariable regression analysis revealed an association between sertraline intake and favorable functional outcome at 3 months (OR 3.10, 95% CI 1.02–9.41, $p = 0.045$). The full model is shown in **Table 2**. When we added PSD (defined by a BDI ≥10) at follow-up to the model, its presence led to a 65% lower chance of achieving a favorable functional outcome compared to patients without PSD (OR 0.35, 95% CI 0.13–0.97, $p = 0.043$). In this *post-hoc* model, sertraline still showed a trend toward improved favorable functional outcome as compared with controls (OR 3.06, 95% CI 0.99–9.49, $p = 0.052$).

TABLE 2 | Multivariable regression analyses of favorable functional outcome and post-stroke depression at 3 months.

Variable	Comparison	OR (95% CI)	*p*
Sertraline	yes vs. no	3.10 (1.02–9.41)	0.045
Age	per 1-year increase	0.88 (0.84–0.93)	<0.001
NIHSS at baseline	per 1-point increase	0.74 (0.63–0.86)	<0.001

Favorable functional outcome defined as mRS ≤2 constitutes the dependent variable. Variables entered into the model comprised age, baseline NIHSS at study entry, group assignment, and acute therapy. The variable acute therapy was removed from the final model at p = 0.596 (p > 0.2). mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; CI, confidence interval.

There were no differences between the two groups with regard to median PHQ-9 score (5 [IQR 3–8] vs. 6 [IQR 3.5–10], $p = 0.399$) or median BDI score (9 [IQR 5–13] vs. 10 [IQR 5.5–15], $p = 0.57$) at 3 months. Also, there was no difference between the presence of depression (BDI ≥10) after 3 months (26/53 [49.1%] vs. 14/28 [50.0%] patients, $p = 0.643$). Neither there was a difference when PHQ-9 cutoffs were considered ($p > 0.05$). In multivariable regression analysis adjusted for group assignment, age and baseline NIHSS, there was no association between sertraline intake and the presence of PSD at 3 months, neither

TABLE 3 | Secondary patient outcomes at 3 months.

	Sertraline ($n = 72$)	Control ($n = 42$)	p
Safety outcomes			
TIA, *n* (%)	0 (0)	0 (0)	1.00
Stroke, *n* (%)	3 (4.2)	0 (0)	0.30
Acute coronary events, *n* (%)	0 (0)	0 (0)	1.00
Death	1 (1.4)	2 (4.8)	0.55
Questionnaires			
Return of questionnaires, *n* (%)			
No return	18 (25.0)	14 (33.3)	
Return	54 (75.0)	28 (66.7)	0.28
Complete	46 (83.6)	23 (82.1)	
Elapsed time between phone interview and completed questionnaires, days	$n = 54$	$n = 26$	
Median (IQR)	11 (24)	19.5 (62)	0.22
PHQ-9	$n = 54$	$n = 28$	
Median (IQR)	5 (5)	6 (6.5)	0.40
Presence of depression (PHQ-9 $\geq$ 10), *n* (%)	10 (18.5)	9 (32.1)	0.18
BDI	$n = 53$	$n = 28$	
Median (IQR)	9 (8)	10 (9.5)	0.57
Presence of any depression (BDI $\geq$10), *n* (%)	26 (49.1)	14 (50.0)	1.00
Incident depression (BDI $\geq$10), *n* (%)	0 (0)	5 (17.9)	0.004

TIA, transient ischemic attack; PHQ-9, Patient Health Questionnaire; BDI, Beck Depression Inventory.

with PHQ-9 (OR 1.35, 95% CI 0.28–6.4, $p = 0.708$) nor with BDI (OR 0.99, 95% CI 0.37–2.61, $p = 0.980$). Taking into account incident depression at 3 months, however, none of the patients assigned to the sertraline group developed a PSD while five patients in the control group were diagnosed with incident PSD (according to BDI), which corresponds to an increase of 17.9% ($p = 0.004$). Further secondary and safety outcomes are detailed in **Table 3**.

DISCUSSION

The major result of this non-interventional study was that early intake of sertraline might favor functional recovery as measured by the mRS in patients with acute ischemic stroke. Moreover, less patients receiving sertraline developed incident depression at 3 months suggesting a potential role for this agent in severely affected stroke patients who are at high risk for PSD.

As opposed to the recently published FOCUS, AFFINITY, and EFFECTS trials, patient eligibility criteria in the present study resembled those applied in the FLAME trial that solely enrolled patients with ischemic stroke (5, 15–17). In pre-clinical studies, potential neuroprotective and neuroplastic effects of SSRI on post-stroke recovery were largely attributed to modification of pathogenic mechanisms following ischemic stroke, such as ischemia-associated hyperexcitation, inflammatory processes in the post-acute phase, augmentation of cerebral blood flow, as well as enhancement of BDNF-expression and stimulation of adult neurogenesis in the subependymal zone and in the hippocampal dentate gyrus (4–10, 12–14). Thus, the predominant inclusion of this stroke subtype may ensure high internal validity in studies on neuroprotective effects of SSRI and stroke. The recent fluoxetine trials, in turn, additionally included patients with intracerebral hemorrhage (ranging from 12 to 15%), who, aside from the aforementioned pathophysiologic considerations, naturally have worse functional prognosis than ischemic stroke patients (15–17, 24).

Although we did not find an absolute difference in the unadjusted analysis of favorable functional outcome at 3 months between both study groups, one should notice that a high proportion of control patients were already functionally independent at discharge leaving less potential for improvement in this group. On the other hand, more than one-fourth of sertraline patients showed substantial improvement in mRS over the first weeks following discharge despite more severe baseline deficits as reflected by both overall and motor NIHSS scores, while no such effects were seen in the control group. Considering these differences in baseline stroke severity, sertraline was associated with a more than 3-fold probability of achieving a favorable functional outcome after 3 months, which is in line with results from a *post-hoc* analysis of the FLAME trial (mRS 0–2 at 3 months: fluoxetine, 26% vs. control, 9%) (5). Although hypothesis generating, sertraline might therefore have a particular effect on motor deficits as previously suggested for fluoxetine by the FLAME but rejected by the FOCUS, AFFINITY, and EFFECTS trials (5, 15–17). However, the median NIHSS scores in the FOCUS and AFFINITY (6 points) as well as in the EFFECTS (3 points) trials indicate a predominance of mild strokes at inclusion, especially in comparison with patients studied in the FLAME trial (12.8 points in the fluoxetine group) (5, 15–17). While patients in our study and in the FLAME trial

were functionally independent at baseline, up to 8% of patients in the fluoxetine RCTs trials suffered from functional dependence prior to the index stroke (5, 15–17). The results of these trials might therefore be limited by an insufficient delimitation of patients potentially susceptible to a beneficial effect of SSRI.

According to mechanistic considerations derived from animal experiments, sertraline intake should started as early as possible after the neurologic index event to mediate a neuroprotective effect on cerebral hemodynamics and impede evolution of penumbra into core (8–10, 25, 26). Thus, sertraline was started in our study at a median of 4 days after stroke onset (with almost one-third of patients treated within 3 days from stroke onset) that is far below the corresponding interval in the FLAME trial (mean 8.9 days) (5). The FOCUS, AFFINITY, and EFFECTS trial even defined a much wider treatment interval with a maximum of 15 days after stroke onset (15–17). However, early initiation of SSRI treatment is challenging in the acute phase of stroke. There is general notion that SSRI should not be used routinely to promote recovery after stroke, and depression currently appears the only indication that justifies early treatment with SSRI in stroke patients (18, 22). In the acute phase of stroke, however, depressive symptoms might by obscured by neurological deficits complicating its recognition and the focus is rather on stroke treatment and rehabilitation than evaluation of PSD. The necessity of a fasting phase in acutely treated stroke patients and dysphagia after stroke may also delay initiation of SSRI treatment in acute stroke (27). As potential neuroprotective effects of SSRI appear to be frontloaded in ischemic stroke, future trials need to ensure its early initiation in the hyperacute phase of stroke when vulnerability to irreversible injury is the highest.

One-third of patients discontinued sertraline intake prior to 90-days follow-up, whereas most reasons for premature termination were not necessarily due to pharmacological undesirable effects (except epileptic seizure and hyponatremia in each case). According to available literature data, bone fractures, epileptic seizures and hyponatremia may occur in up to 4% of patients treated with fluoxetine (15–17). Respective data for sertraline in stroke patients are lacking, although similar risks can be assumed for its utilization.

A large fraction (>40%) of patients in this study showed any depressive symptoms at study inclusion (according to a BDI $\geq$10 points), which might have distorted our negative results regarding a potential preventive effect of sertraline on PSD. This contrasts with numerous studies from the literature that showed preventive effects of certain SSRI on both prevention and treatment of PSD (21, 28, 29). However, when we considered incident depression as the variable of interest, fewer patients taking sertraline were found having incident PSD at 3 months compared with controls, which was seen for fluoxetine in a similar manner in the recent FOCUS and EFFECTS trials (15, 17).

Our study has several limitations. First, as group allocation was not random, our findings might be influenced by selection bias and further potential shortcomings associated with the non-randomized design. Although consecutive sampling was applied in our study, the eventually low number of control patients might be a particular indicator of sampling bias in our study. On the other hand, selection bias might have rather deviated the results toward false negativity as severely affected stroke patients were more likely to be treated with sertraline in our study than less affected patients (as reflected by different NIHSS scores at study entry). A beneficial effect of sertraline, if any, therefore needed to be strong to become apparent in our study. Nonetheless, a potential placebo effect in those treated with sertraline should be considered when interpreting our study results. Second, the high proportion of patients suffering from any degree of depression at study entry complicates the differentiation between potentially neuroprotective effects of sertraline on stroke recovery and its natural antidepressant effect that might have enhanced patients' motivation and cooperation during rehabilitation. Any depressive symptoms at study entry might have increased the odds of having PSD and unfavorable functional outcome at 3 months (22). Nonetheless, the observation that any depressive symptoms were similarly distributed among both groups may have minimized this source of bias in our study. When we adjusted for PSD, sertraline was no longer significantly associated with favorable functional outcome suggesting that adverse effects of PSD might have outweighed potentially beneficial effects of sertraline on functional outcome post-stroke. Consequently, future trials should focus on stroke patients absent of any depressivity at study baseline to explore the sole impact of early sertraline on stroke-recovery. Third, we did not apply psychiatric interviews for depression diagnosis, and the use of self-assessment instruments instead could have deviated the true frequency of PSD in our study, especially when completion of the survey was supported by relatives or others (30). Lastly, our data only allow conclusions to be drawn on the SSRI sertraline. Except fluoxetine that remains the only SSRI tested for clinical efficacy in a large randomized trial, other SSRI such as citalopram showed also promising results on motor outcome in stroke patients and could therefore represent an option for future clinical trials evaluating neuroprotective or neurorestorative therapies (31). The strengths of our study comprise the prospective approach, the well-characterized study population with stroke-associated motor deficits and the completeness of follow-up data concerning the primary endpoint.

CONCLUSIONS

Early intake of sertraline was associated with a tendency toward improved functional recovery from acute ischemic stroke and prevention of incident PSD in these patients. Although limited by its observational nature, our data might form the basis for a confirmatory phase II randomized control trial.

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 was approved by the Ethics Committee (EK) of the Technische Universitaet Dresden (EK 501122016). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS and KB: conceptualization and supervision. KB: methodology and resources. IS and KB: statistical analysis. IS and CH: data curation. IS: writing—original draft preparation. IS, TS, L-PP, CH, JB, HR, VP, and KB: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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ORIGINAL RESEARCH
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Reorganization of Brain Functional Connectivity Network and Vision Restoration Following Combined tACS-tDCS Treatment After Occipital Stroke

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Objective: Non-invasive brain stimulation (NIBS) is already known to improve visual field functions in patients with optic nerve damage and partially restores the organization of brain functional connectivity networks (FCNs). However, because little is known if NIBS is effective also following brain damage, we now studied the correlation between visual field recovery and FCN reorganization in patients with stroke of the central visual pathway.

Method: In a controlled, exploratory trial, 24 patients with hemianopia were randomly assigned to one of three brain stimulation groups: transcranial direct current stimulation (tDCS)/transcranial alternating current stimulation (tACS) (ACDC); sham tDCS/tACS (AC); sham tDCS/sham tACS (Sham), which were compared to age-matched controls ($n = 24$). Resting-state electroencephalogram (EEG) was collected at baseline, after 10 days stimulation and at 2 months follow-up. EEG recordings were analyzed for FCN measures using graph theory parameters, and FCN small worldness of the network and long pairwise coherence parameter alterations were then correlated with visual field performance.

Result: ACDC enhanced alpha-band FCN strength in the superior occipital lobe of the lesioned hemisphere at follow-up. A negative correlation ($r = -0.80$) was found between the intact visual field size and characteristic path length (CPL) after ACDC with a trend of decreased alpha-band centrality of the intact middle occipital cortex. ACDC also significantly decreased delta band coherence between the lesion and the intact occipital lobe, and coherence was enhanced between occipital and temporal lobe of the intact hemisphere in the low beta band. Responders showed significantly higher strength in the low alpha band at follow-up in the intact lingual and calcarine cortex and in the superior occipital region of the lesioned hemisphere.

Conclusion: While ACDC decreases delta band coherence between intact and damaged occipital brain areas indicating inhibition of low-frequency neural oscillations, ACDC increases FCN connectivity between the occipital and temporal lobe in the intact hemisphere. When taken together with the lower global clustering coefficient in

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responders, these findings suggest that FCN reorganization (here induced by NIBS) is adaptive in stroke. It leads to greater efficiency of neural processing, where the FCN requires fewer connections for visual processing.

Keywords: brain networks, vision recovery, stroke, neuron rehabilitation, tACS, tDCS

BACKGROUND

The potential to restore visual fields following central visual system damage has attracted some attention during the last few decades (1–8). Occipital stroke, for example, leads to homonymous hemianopia whereby a quarter or half of the visual field in both eyes is lost following damage (9). This impairs visual functional abilities and quality of life (10), increasing the risk to fall or having difficulties in reading, with secondary deficits such as depression and social isolation (10–14). While visual training can improve visual fields well after the initial spontaneous recovery phase (2, 3, 15), additional recovery of vision can take many months of daily exercises.

To overcome this limitation, efforts were made to use non-invasive brain stimulation (NIBS) as a new therapeutic approach. NIBS was already used for the rehabilitation of different neurological diseases affecting the motor system, memory, language, or cognition (16). NIBS includes different protocols of low-intensity transcranial alternating current stimulation or transcranial direct current stimulation (tACS, tDCS) known to alter brain excitability (17). Especially tDCS was applied to treat different neurological and neuropsychiatric dysfunctions (18, 19). In tDCS, current flows from the anodal to the cathodal electrode, where the anode is thought to enhance (excite) and the cathode reduce (inhibit) neuronal activities (20–22). In contrast, the direction of current flow in tACS alternates between both electrodes and is able to modulate periodic oscillations (17), which can, in turn, entrain endogenous brain oscillation in a frequency- and phase-specific manner (23, 24). With tACS, it is therefore possible to enhance the power, shift the peak, and change the electroencephalogram (EEG) oscillations phase by applying the ACS at a frequency identical or close to those oscillations (25). tACS was already shown to increase parieto-occipital alpha activity and to synchronize cortical oscillations with entrainment of specific frequencies (26), and this impacts the endogenous alpha oscillation with long-lasting "after-effects" (27). When stimulating the brain in the alpha frequency range, for example, this increases alpha power, reflecting neuroplasticity changes rather than entrainment (28). NIBS can also be used to purposely modulate neuron's excitation and inhibition in many neurological diseases with a potential to induce recovery of function (29).

With regard to visual system damage, tACS was shown to enhance recovery following visual cortex or optic nerve damage (30–35). Here, a 10-day treatment course improved visual field size and visual acuity, and it reduced reaction time (RT). The proposed mechanism of action of tACS is that it can modulate synchronization of neuronal network firing of partially damaged "areas of residual vision," which managed to survive the injury, possibly involving the strengthening of synaptic transmission along the visual pathway and enhancing blood flow. For review, see (36). Indeed, tACS-induced visual improvements significantly correlated with neuronal synchronization changes (5, 34, 37) and enhanced alpha-band activity or power (28, 38).

Concerning tDCS, visual cortex damage leads to hyperactivity of the intact hemisphere, presumably inhibiting the lesioned side (39, 40), and a dual-mode tDCS can reduce visual neglect symptoms (41). That tDCS can improve visual functions was also shown both in normal subjects and in patients with visual system damage. For example, combining tDCS with visual training can improve hemianopic visual fields (42), and in healthy subjects, anodal tDCS of the occipital poles significantly reduces psychophysical surround suppression (43) and enhances occipital blood flow (44). However, little is known about possible frequency-specific neural-plastic mechanisms for vision recovery after occipital stroke, and only few studies explored the potential of NIBS to induce recovery of visual functions in patients suffering from a unilateral occipital stroke (45). Therefore, a better understanding of the neurophysiological mechanism of tACS and tDCS is needed to understand, and eventually maximize, their potential to improve visual fields after occipital stroke.

To learn more about the mechanisms and effects of tACS and tDCS in occipital strokes, we now used both protocols alone or in combination. Specifically, we hypothesized that cathodal tDCS might inhibit the intact visual cortex, reduce its hyperactivity, and thus lower the associated cross-hemispheric inhibition of the damaged visual cortex. Treatment with tACS, on the other hand, might induce endogenous neuronal oscillations on the whole-brain level. Therefore, we now studied both methods alone and in combination. Specifically, we expected that a "double-punch" approach of combined tACS/tDCS would be most effective, because it would simultaneously reduce cross-hemispheric inhibition and enhance excitability of the tissue at or near the lesion site.

To test this hypothesis, we used EEG recordings rather than functional magnetic resonance imaging (fMRI), because the EEG can measure synchronization patterns of the functional connectivity network (FCN) with high (theoretically infinite) time resolution. Indeed, as reported elsewhere, in a similar study, no consistent fMRI-activation changes were observed after NIBS (35). Therefore, the EEG may be the more sensitive and more direct measure of FCN synchronization states and their dynamics. Furthermore, the EEG can

detect even physiological alterations independent of energy consumption (46). Here we studied the neurophysiology of brain FCN plasticity in hemianopic stroke patients and describe how FCN reorganization correlates with visual field recovery.

A detailed analysis of visual field recovery was already reported elsewhere (35).

MATERIALS AND METHODS

Demographics

Unilateral occipital stroke patients ($n = 24$) suffering from hemianopia were recruited as previously described (45) and randomly assigned to one of three groups (**Figure 1A**): tDCS/tACS group (ACDC, $n = 8$, age: mean ± SD = 53.45 ± 14.18), sham tDCS/tACS group (AC, n = 8, age: mean ± SD = 58.25 ± 9.54), and sham tDCS/sham tACS group (Sham, $n = 8$, age: mean ± SD = 63.87 ± 5.38). Their EEG results were compared to 24 healthy subjects (age: mean ± SD = 57.4 ± 10.5) (see **Table 1** for details of patients and controls). The study was conducted with the guidelines of the International Conference on Harmonization of Good Clinical Practice and the applicable national legislation in agreement with the Declaration of Helsinki. All participants had signed consent form. The study was approved by the institutional review board of the University Magdeburg. The patient's group identity was known only to the experimenter who performed the stimulation. The participants were informed about their stimulation protocol after completion of follow-up diagnostics at 8 weeks (45).

Our patients' hemianopia was caused by ischemic ($n = 19$) or hemorrhagic ($n = 5$) stroke. Their age range was 18–75 years, and lesion age was >6 months. Diagnostic results showed that patients had stable visual field defects across repeated baseline measurements. We found no significant correlation of lesion age with FCN pre–post difference of the two most important parameters ("strength" and "centrality") on the alpha band, showing that lesion age had no impact on our FCN parameters (see below). It confirms our assumption that network plasticity does not depend on lesion age. In any event, subjects with spontaneous fluctuations and recovery of vision were not entered in the trial. All patients had corrected visual acuity of at least 0.4 (20/50 Snellen) or better. The presence of residual vision and detectable gradual transition between the intact and the blind part of the visual field was confirmed according to the clinician's evaluation. Patients were excluded if they had at least one of the following symptoms: malignant brain tumor, eye or other central nervous system diseases, electric or metallic implants in the eyes or head, expected low compliance, history of epileptic seizures within the last 10 years, or use of antiepileptic or sedative drugs during the recruiting process. On admission to the study, the medical history was collected and assessed by a neurologist. A comprehensive examination, in particular of visual dysfunction, was carried out. The possibility of further participation in the study depended on the results of this preliminary investigation. The patients had to have some residual visual performance, evident by a gradual transition between the blind area and the visual field's intact area.

Experimental Design

tDCS/tACS

The tACS and cathodal tDCS stimulation was delivered with conductive-rubber electrodes placed in saline-soaked sponges and connected with a NeuroConn MC8 stimulator. The tACS stimulation electrode (5 × 7 cm) and a reference electrode (10 × 10 cm) were placed at Fpz and at the right upper arm, respectively, according to 10–20 system EEG recordings. Stimulation started with a 5-Hz burst, and then frequency increased in steps of 1–30 Hz using a 48-s-long "rtACS block." The tACS stimulation was given for 20 min per day with a maximum current of 1.5 mA (peak-to-peak), which was well above the phosphene threshold (47). The block was repeated for 20 min. In the tDCS condition, the cathode was positioned above the intact hemisphere, and stimulation was done for 10 min immediately before rtACS and set at 1 mA using one electrode placed at either O1 or O2 position (3 × 3 cm) with anode at Fpz. The impedance was kept below 10 kΩ.

Sham Design

Sham patients had the identical electrode montage and stimulation duration. The tACS sham condition was designed to induce (short-lasting) phosphenes that patients could subjectively report (47); that is, it was a minimal stimulation. In addition, occasional current bursts were given to create short but presumably therapeutically ineffective phosphenes (45) involving one 5-Hz burst/min with individual amplitude for phosphene perception as used in a previous study where none of the subjects could tell to which group they belonged (45). In contrast, the tDCS sham-condition was designed to elicit only cutaneous sensations that gradually disappear because of habituation (48). Here, the current was ramped up for 30 s, then stopped, and at the end of the session ramped down for another 30 s as shown in **Figure 1A** (45). Through this design, we ensured that all patients felt their skin comparable in degree and duration with the active tDCS. The combined tDCS/tACS stimulation was designed to indicate whether prior cathodal tDCS on the intact hemisphere (a kind of conditioning) could enhance rtACS effects compared to sham stimulation and rtACS without preceding tDCS (45). Here, cathodal tDCS was applied to reduce the interhemispheric imbalance by inhibiting the visual cortex of the intact hemisphere (**Figure 1B**). All sham patients had been offered to receive stimulation treatment after the final follow-up evaluation. The stimulation parameters were kept unchanged for 20–30 min per day during the 2 weeks' treatment (**Figure 1C**). Of note: for all stimulation conditions, the default setting of the neuroConn stimulator gives short pulse of 50 Hz at 0.5 μAmp every 2 s to monitor the skin resistance.

Safety of Electrical Current Stimulation

The relatively large surface area of electrodes during stimulation limited the maximum threshold of current densities compared with other studies. The maximum current density was 42 $\mu A/cm^2$ below AC stimulating electrodes and 15 $\mu A/cm^2$ below the reference electrode. In the case of tDCS, it was 111 $\mu A/cm^2$ below the stimulating electrodes, which corresponded to a total charge density lower than 0.1 C/cm^2, which was below the safety

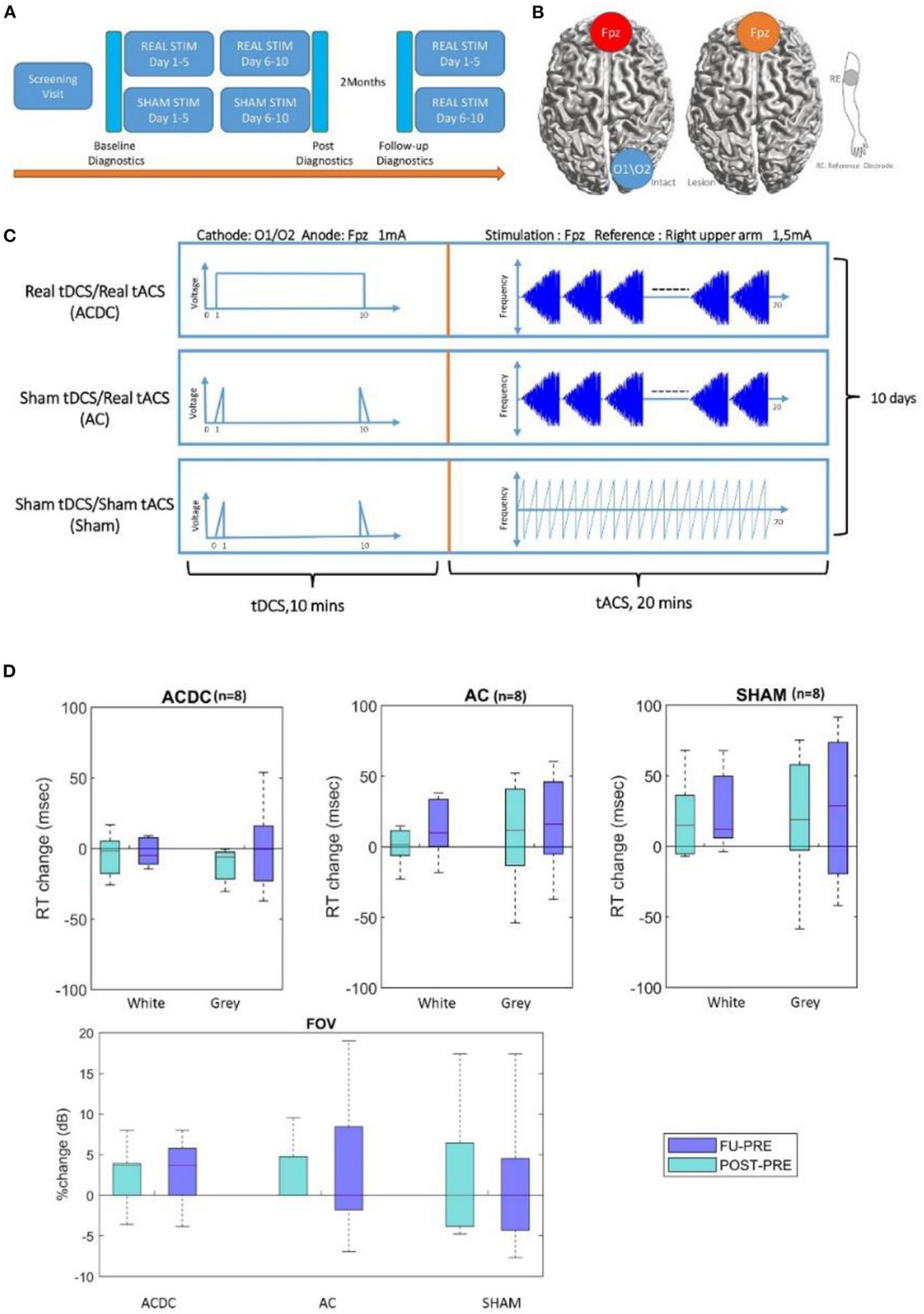

FIGURE 1 | (A) The pipeline for experiment time schedule and postdiagnostic, 5 min rsEEG, and visual parameters were recorded before the experiment as a baseline, after 10 days of stimulation, and 2 months later at follow-up. Moreover, all sham patients were offered to receive stimulation treatment after the final evaluation. **(B,C)** Therefore, three treatment groups were compared: tDCS/tACS (ACDC), sham tDCS/tACS (AC), and sham tDCS/sham tACS (SHAM). **(D)** Boxplot of White and gray areas' reaction time in visual field: the percentage change of the reaction time in ACDC decreased while in the two groups it increased. RT, reaction time (unit: millisecond). The bottom part shows the percentage changes in each group, the median of percentage changes of ACDC was positive both in POST and FU. In contrast, AC and SHAM group remains zero. From both high-resolution perimetry and visual field, the ACDC group shows a more promising visual performance improvement than the other two groups. FOV, visual field (unit: dB).

TABLE 1 | Demographics of patients and controls.

			Patients																		Controls	
ID	**Group**	**Lesion age (mo)**	**HRP_Pre**			**HRP_Post**			**HRP_FU**			**RT_Pre**		**RT_Post**		**RT_FU**		**Field of vision (dB)**			**Gender**	**Age (y)**
			Black	**Gray**	**White**	**Black**	**Gray**	**White**	**Black**	**Gray**	**White**	**Gray**	**White**	**Gray**	**White**	**Gray**	**White**	**Pre**	**Post**	**FU**		
1	2	45	181	29	231	182	28	231	180	33	228	0.50	0.43	0.49	0.43	0.53	0.42	24	25	25	M	24
2	2	61	109	41	291	112	36	293	117	23	301	0.52	0.41	0.52	0.43	0.43	0.42	26	26	25	M	44
3	0	20	60	5	376	56	14	371	55	13	373	0.44	0.35	0.38	0.34	0.42	0.35	26	26	26	M	55
4	0	45	145	65	231	123	92	226	122	85	234	0.47	0.42	0.52	0.46	0.52	0.46	21	20	20	F	75
5	1	19	208	71	162	214	69	158	205	60	176	0.55	0.48	0.55	0.48	0.60	0.48	26	26	26	M	65
6	2	28	125	24	292	115	33	293	110	33	298	0.50	0.39	0.49	0.39	0.50	0.38	28	27	28	M	53
7	1	117	194	8	239	188	16	237	191	23	227	0.49	0.39	0.52	0.39	0.48	0.43	28	28	27	M	61
8	1	29	98	48	295	103	51	287	92	79	270	0.49	0.40	0.48	0.42	0.50	0.43	27	27	27	M	56
9	0	25	149	13	279	150	13	278	149	19	273	0.50	0.38	0.53	0.38	0.46	0.38	27	27	27	M	68
10	1	156	176	19	246	176	15	250	177	16	248	0.51	0.42	0.49	0.41	0.50	0.42	24	27	27	M	51
11	1	21	133	109	199	133	117	191	157	73	211	0.48	0.43	0.53	0.40	0.54	0.41	23	23	24	M	66
12	2	11	198	14	229	198	7	236	193	18	230	0.53	0.48	0.53	0.48	0.53	0.49	27	28	29	M	62
13	0	49	170	79	192	179	39	223	180	56	205	0.45	0.39	0.51	0.41	0.54	0.45	23	27	27	F	48
14	0	27	164	128	149	138	141	162	162	123	156	0.55	0.44	0.54	0.45	0.53	0.45	26	25	25	F	55
15	2	25	186	21	234	176	31	234	177	27	237	0.51	0.37	0.50	0.36	0.51	0.37	28	29	29	F	60
16	2	19	151	34	256	133	45	263	145	32	264	0.60	0.46	0.54	0.43	0.57	0.44	24	24	24	M	50
17	0	12	48	120	273	16	91	334	47	76	318	0.50	0.42	0.50	0.41	0.56	0.43	26	29	26	M	68
18	1	43	199	30	212	202	21	218	200	27	214	0.53	0.36	0.48	0.36	0.50	0.36	21	23	25	F	54
19	2	93	170	16	255	170	6	265	172	4	265	0.52	0.44	0.49	0.38	0.58	0.39	25	27	27	M	67
20	1	6	282	28	131	283	26	132	287	25	129	0.52	0.47	0.56	0.48	0.56	0.49	26	26	26	M	53
21	0	106	194	19	228	191	14	236	193	19	229	0.62	0.53	0.63	0.56	0.63	0.54	22	24	24	M	59
22	1	9	203	12	226	199	10	232	206	9	226	0.55	0.45	0.60	0.45	0.57	0.48	29	29	27	M	57
23	0	7	227	58	156	246	59	136	248	54	139	0.66	0.65	0.74	0.72	0.75	0.72	26	25	24	F	72
24	2	10	159	68	214	177	88	176	160	88	193	0.55	0.42	0.54	0.43	0.54	0.43	27	28	28	M	54
Mean (SD)	0 Sham 1 AC 2 ACDC	40.95 (39.21)	163.70 (51.68)	44.12 (35.92)	233.16 (54.46)	160.83 (57.55)	44.25 (37.25)	235.91 (58.64)	163.54 (54.59)	42.29 (30.98)	235.16 (56.31)	0.51 (0.05)	0.42 (0.06)	0.52 (0.06)	0.42 (0.08)	0.53 (0.07)	0.43 (0.07)	25.41 (2.22)	26.08 (2.18)	25.95 (1.96)	18 M/6 F	57.37 (10.56)

Gender: M, male; F, female; lesion age: the months since stroke happened; RT, reaction time; Pre, before treatment; Post, after treatment; FU, follow-up; ACDC, rtDCS/rtACS; AC, sham/rtACS; Sham, sham/sham.

limits as described in the previous study (22). Safety guidelines for direct current applied to the human brain were reported (16, 22, 49).

The following undesirable events had been observed immediately after each stimulation session and the following day before the next stimulation session: rare cases of headache, dizziness, fatigue/drowsiness, skin sensation, blurred vision immediately after stimulation, and others. Patients were not asked to perform a visual task during stimulation sessions but just kept their eyes closed while sitting down.

EEG Recording and Pre-processing

High dense array EEG was recorded using a HydroCell GSN 128-channel net and Net Amps 300 amplifier (EGI Inc., Eugene, OR, USA) with sampled frequency 500 Hz. Impedance was ascertained to be <50 kΩ throughout the recording. Patient's resting-state EEG was recorded at three time points (before treatment: Pre, after 10 days of treatment: Post, follow-up after 2 months: FU). During the recording, patients were instructed to keep relaxed, with their eyes closed, for at least 5 min. There was no significant difference in patient's age in the three group after a Kruskal–Wallis test ($p > 0.05$), ACDC (mean ± SD = 53.45 ± 14.18), AC (mean ± SD = 58.25 ± 9.54), and sham (mean ± SD = 63.87 ± 5.38).

EEG signals were analyzed with MATLAB version 2019a and Fieldtrip (50). A digital 1–145-Hz bandpass filter was applied as well as a 50-Hz notch filter, and the data were down-sampled to 250 Hz and then referenced by the common average reference method. Five-min-long EEG recordings for both groups were segmented into 2-s-long epochs with 0.5-s overlapping. Components of eye blinks and cardiac activity were removed by an independent component analysis algorithm. The frequency was decomposed in seven frequency bands: Delta (1–3 Hz), Theta (4–7 Hz), Alpha1 (8–10 Hz), Alpha2 (11–13 Hz), Beta1 (14–21 Hz), Beta2 (22–30 Hz), and the whole alpha band as (8–13 Hz).

Source Construction

The forward model was calculated using the symmetric boundary element method (51); inverse model was calculated with a beam-forming method using the partial canonical correlation method (52), which implements dynamical imaging of coherent sources (53) algorithm for computing the spatial filters for each dipole location in the source model. The estimation of noise was projected with option cfg.projectnosie = "yes" in Fieldtrip toolbox to remove the center of the head bias with a regularization parameter λ = 5%. The Automated anatomical labelling-Volume-of-Interests atlas is an automatic anatomical labeling result (54) of spatially normalized, single-subject, high-resolution T1 MRI data set provided by the Montreal Neurological Institute (MNI) (55), which includes 120 structure definitions, only 90 subareas were used in this study.

Functional Connectivity Estimation

Brain functional connectivity was assessed by calculating the statistical synchronization to quantify the interaction between different brain region pairs (56, 57). Functional connectivity was estimated with imagery part of coherence at the anatomical level. Coherence can be used to quantify how the brain regions synchronize neural oscillation among each other (58). This method is insensitive to false connectivity arising from volume conduction to measure the functional connectivity with resting-state EEG data (59). Both the sensor level and anatomical level were defined as follows:

$$icoh_{(f,t)} = |im(\frac{\sum_{n=1}^{N} S_1^n(f,t) S_2^{n^*}(f,t)}{\sqrt{\sum_{n=1}^{N} |S_1^n(f,t)^2| \sum_{n=1}^{N} |S_2^n(f,t)^2|}})|$$

where $S_1^n(f,t)$ and $S_2^{n^*}$(f,t) are the frequency-decomposed EEG data from two specific regions for every subject and condition. Coherence between all pairs of dipoles were parcellated with the AAL atlas with the imaginary part of coherence for each subject per frequency band to obtain a parceled connectivity matrix (90 × 90). Coherence was segmented into short (local) and long (global) range, and the local coherence was determined within each lobe of interest; the long-range coherence was from left or right occipital (LO or RO) compared to the rest of the brain regions [RO] to [RT, RF, RP, LT, LF, LP, LO] or [LO] to [RT, RF, RP, RO, LT, LF, LP].

In our analysis, we used graph theory, which was developed to analyze complex network structures. It is a method now widely used to explore brain functional connectivity (FCN) changes (60, 61). Graph theory describes important properties of brain networks by quantifying typologies of their respective network measures by anatomical tracts or by functional associations (62). According to graph theory, brain areas are referred to as "nodes" or "vertices," and edges represent the connections between the nodes. The term "node degree" is used for the number of links connected to a center node, and strength is the sum weights of links connected to the center node. The clustering coefficient is the fraction of triangles around the center node (61). Node betweenness centrality is the value of all shortest paths that pass through a given node. Nodes with high values of centrality involve a large number of shortest paths. The key features of a network structure are the clustering coefficient and the path length of its connections. While a high cluster coefficient is a sign of a rather stable network, a short path length is less stable but more flexible. Brain network structures are typically somewhere in between these two poles. It is a compromise of both poles, stability and flexibility, and is called a "small world" network. The network structure was defined by different as now described.

Characteristic Path Length

In the graph theory, the shortest path length is the short distance from one node to another node, which related to network efficiency and information transfer rate (61); the characteristic path length (CPL) is the average shortest path length of all nodes in the network with a definition:

$$L = \frac{1}{n} \sum_{i \in N} L_i$$

where l_i is the average path length of between node i and all other nodes.

Clustering Coefficient

The clustering coefficient is the fraction of triangles around a node and is equivalent to the fraction of the node's neighbors that are neighbors of each other (63).

$$C = \frac{1}{n}\sum_{iN} C_i = \frac{1}{n}\sum_{iN} \frac{2t_i}{K_i(K_i-1)}$$

where C_i is the clustering coefficient of node i ($C_i = 0$ for $K_i < 2$).

Visual Field Diagnostic

Visual field parameters (visual field: FOV, high-resolution perimetry [HRP]) were assessed in patients to quantify the visual impairment in different phase. The contralateral eye's FOV was measured by OCULUS Twinfield®. HRP demonstrates the visual field charts generated by high-resolution computer-based perimetry developed by the Sabel laboratory (1).

Data Analysis and Software

Data analysis was conducted with MATLAB, 2017a (64). EEG was preprocessed and resourced in Fieldtrip (50), the functional connectivity measures were calculated by the brain connectivity toolbox (61), and the long coherence was visualized by BrainNetViewer (65). Pearson correlation was performed between the behavior data and brain network measures at each frequency band. Because our study was explorative, no adjustment was made for multiple comparisons (66).

Visual fields were analyzed with respect to absolute change in HRP and percentage change in FOV after NIBS per group. A repeated-measures analysis of variance (ANOVA) test was performed (three groups: ACDC, AC, and Sham, and two time periods: post–pre and FU–pre). *p*-value was corrected by the Tukey–Kramer test in the *post-hoc* analysis.

RESULTS

Visual Field Recovery

A detailed description of visual field recovery is published elsewhere (35). However, to explore the functional meaning of brain network changes, here we report detection performance in the visual fields and the RTs.

Visual field: There was no significant main effect ($F_{(1,21)} = 0.002$, $p = 0.9$) and no interaction effect ($F_{(1,21)} = 0.46$, $p = 0.63$) in visual field detection performance. However, as shown in **Figure 1D**, the ACDC group's FOV increased after treatment, and this was maintained at follow-up. In contrast, the other two groups' median FOV remained unchanged after treatment and at follow-up. This suggests that visual functionality of the ACDC group had a trend of an enhancement at a group level compared with baseline, which was not observed in the other two groups.

Reaction time: No significant interaction effect was observed [$F_{(1,21)} = 1.49$, $p = 0.24$] on white and gray RT percentage shown in **Figure 1D**. However, there was a trend of ACDC RT decrease (which is an improvement) in both Post and FU in the intact sector of the visual field. In contrast, both AC and Sham groups' RT increased in Post and FU compared with baseline. As for the gray area, there was neither significant interaction [$F_{(1,21)} = 0.006$, $p = 0.99$] nor a main effect for the group interactions [$F_{(1,21)} = 0.84$, $p = 0.37$]. However, RT of ACDC decreased, while the RT of AC and Sham increased comparing with baseline in Post and FU. This indicates the ACDC group has a greater visual acuity percentage change than the other two groups.

Brain Network After Brain Stimulation

We performed a two-way 3 (stimulation group: ACDC, AC, and sham) × 3 (time: Pre, Post, and FU) mixed-design ANOVA with repeated measures on the time variable of local node strength and long coherence (**Figure 2A**). A compound symmetry assumption was checked before statistical analysis was performed. The regular *p*-value calculations in the repeated measures were reported if the theoretical distribution of the response variables was of the same variance. *p*-value calculations were corrected with Greenhouse-Geisser approximation. The *post-hoc* test was estimated with a significant sign ($p < 0.05$) after a mixed-design ANOVA test, and the family-wise error rate was controlled by the Tukey–Kramer test after estimating homogeneity of variances.

To explore the role of brain functional network reorganization as potential mechanisms of recovery, we calculated the two global parameters CPL and "global clustering coefficient" using a 30% threshold of the connectivity matrix (67).

Between-Group Analysis

There was no significant interaction effect on the alpha band in the occipital lobe.

Within-Group Analysis

A significant main effect of strength was observed in the ACDC group with repeated time measures on occipital_sup of the lesioned hemisphere [$F_{(2,42)} = 5.31$, $p = 0.009$]. We ascertained that the assumption of sphericity was not violated ($W = 0.97$, $p = 0.74$). Thus, in the ACDC group, the strength of three treatment time points on occipital_ sup_LH differed significantly. *Post-hoc* analysis showed that FU strength on occipital_sup _LH was significantly higher than Pre (median ± SEM = 0.84 ± 0.32, $p = 0.044$).

The significant main effect of strength in Sham group was observed with repeated time measures on occipital_mid of the lesioned hemisphere [$F_{(2,42)} = 4.486$, $p = 0.017$] and occipital_sup of lesioned hemisphere [$F_{(2,42)} = 5.31$, $p = 0.009$]. The assumption of sphericity was not violated ($W = 0.99$, $p = 0.98$; and $W = 0.97$, $p = 0.74$, respectively). This shows that if we only consider the sham group's treatment, the strength of three time points on occipital_mid_LH and occipital_sup_LH significantly differed. *Post-hoc* analysis showed that the node strength of occipital_mid_LH after Sham treatment was significantly higher than before treatment (median ± SEM = 1.01 ± 0.42, $p = 0.050$) and follow-up (median ± SEM = 1.35 ± 0.39 $p = 0.007$). Moreover, the occipital_sup_LH node strength after Sham treatment was also observed to be significantly lower than follow-up (median ± SEM = 1.30 ± 0.41, $p = 0.011$) (**Figure 2A**, right part).

Global Small World Networks

According to graph theory, a network structure can be characterized by two opposing poles: a high cluster coefficient

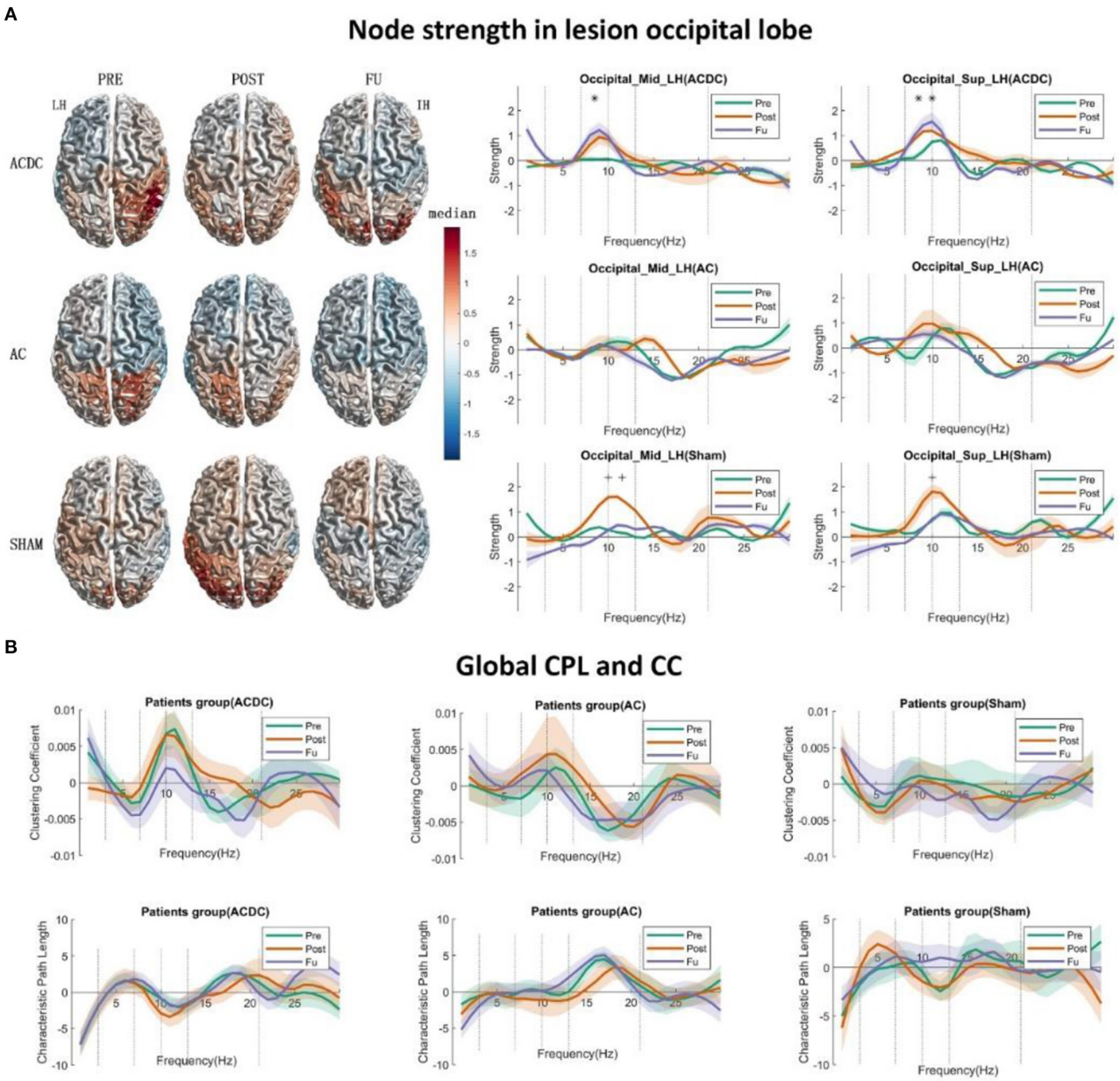

FIGURE 2 | (A) The left side displays the surface plot of the median node strength per group in the alpha band. Baseline (PRE): ACDC and AC groups have stronger connectivity than the SHAM group in the intact hemisphere (parietal and occipital), after treatment (POST): ACDC and AC groups have lower node strength than the SHAM group (parietal and occipital). Follow-up (FU): ACDC has stronger connectivity than the AC and SHAM group. Right part: Line plot of the single occipital lobe from 1 to 30 Hz with control baseline corrected. In ACDC, the middle and superior occipital regions have greater strength at POST and FU than PRE ($p < 0.05$). Meanwhile, the AC group shows a similar pattern for a three time points ($p > 0.05$) in the above two ROIs. The SHAM group's node strength was significantly enhanced after treatment and then dropped down to the original level. **(B)** This shows the global clustering coefficient and CPL for three groups. The ACDC group had decreased CC at follow-up, indicating that information transfer in the whole brain needed to pass fewer nodes than baseline (i.e., it is more efficient). Here, the connections are more ordered or less diffuse. No significance was observed in the other groups. *$p < 0.05$.

with long path length (an "ordered" network) and a low clustering with short path length (a "random" network). If the network is in between those two poles, it has a proper balance between "stability" and "efficiency." Then it is called a small world network. Patterns of anatomical connectivity in neuronal networks are sometimes characterized by high clustering and a small path length (63). We calculate the global CPL and CC using the 30% threshold of connectivity matrix as a criterion for three treatment groups to identify the small world network dynamic changes. Using these network parameters, we performed a

two-way 3 (group: ACDC, AC, and sham) × 3 (time: Pre, Post, and FU) mixed-design ANOVA with repeated measurements on the time variable. The compound symmetry assumption was checked before statistics was performed. The regular *p*-value calculations in the repeated measures were reported if the theoretical distribution of the response variables had the same variance, provided the compound symmetry assumption was not violated; *p*-value calculations were corrected with the Greenhouse–Geisser approximation, and the *post-hoc* test was estimated with a significance level of $p < 0.05$ after a mixed-design ANOVA test. The family-wise error rate was controlled by the Tukey–Kramer test following estimation of the homogeneity of variances. No significance was observed for the global CPL and CC (**Figure 2B**). However, a trend was noted in that the global CC of ACDC was decreased in FU, whereas the global CPL remained at the same level as before, a clear sign of a more efficient small-worldness network after ACDC treatment.

Correlation Between Brain Network Measure and RT

The functional meaning of the network dynamics can be explored with correlation analyses. We found a negative correlation between the intact visual field and CPL (global CPL), which was significantly different at post ($r = -0.80$, $p = 0.017$) in the ACDC group (**Figure 3A**); this indicates that a larger visual field is associated with lower CPL after treatment. Furthermore, a positive correlation was observed between RT in areas of residual vision and CPL at Pre ($r = 0.70$, $p = 0.049$), suggesting that slower RT of the residual visual field was associated with higher CPL.

The correlation between brain network measures at subregions of occipital lobe and RT in intact VF shows a trend of a treatment effect as well. Node strength correlated negatively with both the intact and the lesioned hemisphere (**Figure 3B**), indicating that better visual function is supported by higher node strength in the brain. As for centrality, which is a measure to quantify how many shortest path length go through one node, the results show that after treatment and follow-up better visual function is supported by a state where brain has a higher capacity to compensate spontaneously.

The centrality of cuneus ($r = -0.88$, $p < 0.01$) and lingual ($r = -0.73$, $p < 0.01$) in the intact hemisphere was significantly correlated with the RT (**Figure 3B**), demonstrating that ACDC may have long-lasting modulation effect than the other two groups (see follow-up). ACDC enhances both hemispheres' brain connectivity, and especially, we could assume that "silent" neurons were reactivated, more functional connectivity could be rescheduled and transferred around the lesion part.

Global Brain Connectivity

The connection coherence from lesion occipital and intact occipital to other brain regions was calculated, as shown in **Figure 3C**. A two-way mixed-design ANOVA test was conducted on brain network measures between group (ACDC, AC, sham) and time (before treatment: Pre, after treatment: Post, and: FU). The *post-hoc* analysis has been performed for the pairwise comparison with a significant level of $p < 0.05$; the family-wise error rate was adjusted.

A significant coherence was observed between the lesioned occipital (LH) and the intact occipital (IH) region in three measurements ($F_{(2,42)} = 6.509$, $p = 0.003$), and the neural correlation in the delta band was significantly declined between the lesion occipital and intact occipital lobe after ACDC. *Post-hoc* analysis indicates that coherence after Post was lower than the Pre (MD ± SEM = -0.014 ± 0.005, $p = 0.036$), with a trend at FU (MD ± SEM = -0.016 ± 0.007, $p = 0.069$).

A significant coherence was also observed between intact occipital (IO) and intact temporal (IT) in three measurements ($F_{(2,42)} = 6.16$, $p = 0.004$). The coherence between IO and IT was enhanced after Post and significantly declined at follow-up in the ACDC group in the low beta band. *Post-hoc* analysis indicates that the coherence of FU was lower than at Post (MD ± SEM = -0.017 ± 0.006, $p = 0.018$). And there was a trend of coherence enhancement after Post when compared with Pre-treatment (MD ± SEM = -0.018 ± 0.007, $p = 0.054$).

Comparing Responders With Non-responders

To further clarify the role of brain FCN reorganization in vision recovery and validate the meaning of our correlation results, we compared responders and non-responders. To this end, we used the contralateral visual field as obtained by standard Oculus perimetry as a criterion to classify each patient as either a responder or non-responder, irrespective of which treatment they received. Therefore, here we calculated only the correlation between FOV and EEG measures to compare responders and non-responders.

As shown in **Figure 4A**, patients above the zero line were considered responders ($n = 10$) and all other non-responders ($n = 14$). We performed a two-way ANOVA test (group: responder and non-responder, time: Post vs. Pre, FU vs. Pre) to investigate HRP changes that were not, but the Mann–Whitney *U*-test revealed that the FOV was greater in the responders ($z = 4.17$, $p < 0.001$) at **Figure 4B** (right part). Of note, this difference was the result of the definition of responder and confirms that both groups are, in fact, different. It does not demonstrate treatment efficacy.

Local Brain Network Dynamics Changes

To compare the local node strength and centrality changes in responders with non-responders, we performed a two-way repeated ANOVA (groups: responder and non-responder, time: baseline and FU). In the lesioned hemisphere, the low alpha-band node strength in calcarine ($F_{(1,22)} = 6.42$, $p = 0.018$) and lingual lobes ($F_{(1,22)} = 7.38$, $p = 0.012$) was significantly different between responders and non-responders during follow-up. The *post-hoc* test showed in responders higher node strength in calcarine (MD ± SEM = -1.56 ± 0.57, $p = 0.013$) and lingual area (MD ± SEM = -1.68 ± 0.49, $p = 0.002$) (**Figure 4C**). In the intact hemisphere, both low alpha band node strength in calcarine ($F_{(1,22)} = 9.60$, $p = 0.005$) and lingual lobes ($F_{(1,22)} = 5.76$, $p = 0.025$) was significantly different between both groups during follow-up. *Post-hoc*, they were higher in responders for node strength in calcarine (MD ± SEM = -1.56 ± 0.65, $p = 0.026$) and lingual (MD ± SEM = -1.503 ± 0.427,

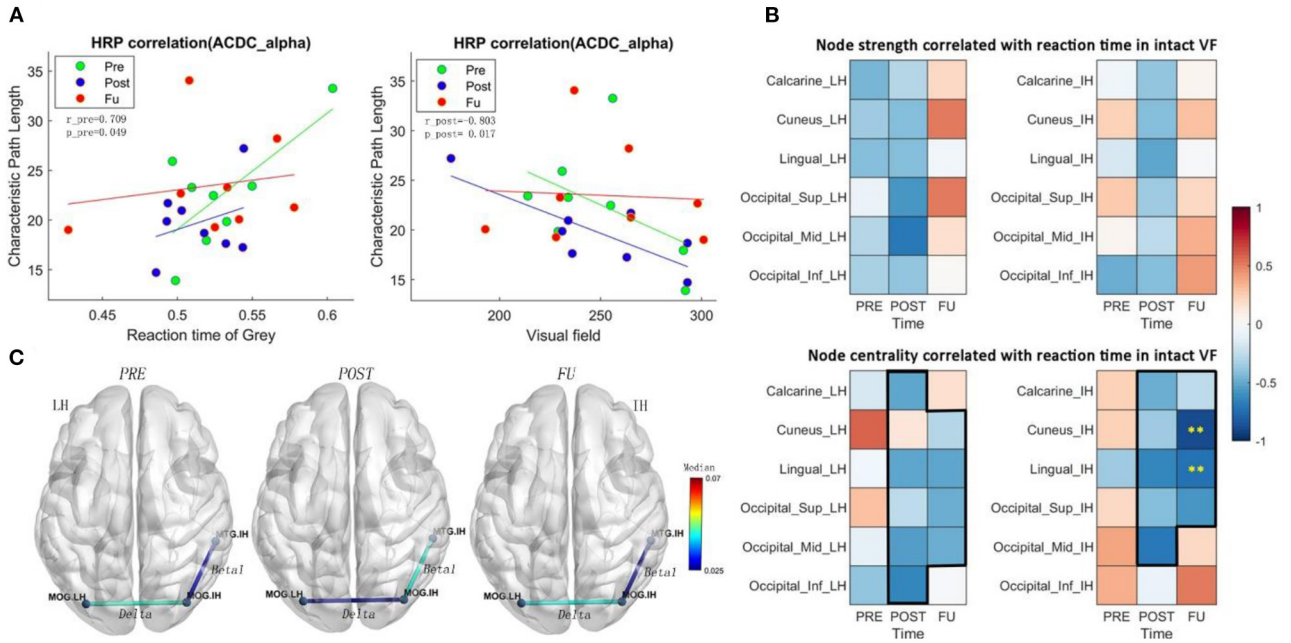

FIGURE 3 | (A) CPL in the alpha band of ACDC patients correlates positively with RT of residual visual area before treatment and correlates negatively with the intact visual field after treatment. It indicates that the larger the intact visual field in the ACDC group after treatment, the lower is the CPL in the ACDC group in the alpha band. A lower CPL is a sign of decreased average shortest path length in the resting state of brain functionality. When neural processing in the brain has a lower CPL; this can be interpreted as a biomarker that brain process is globally enhanced and more efficient. **(B)** Heat map showing correlation coefficients (ranging from −1 to +1) between brain node measures and reaction time in the intact VF of the ACDC group. The upper panel shows a trend of a treatment effect in the intact hemisphere (IH) and the lesioned hemisphere (LH) in both hemispheres; the lower panel shows a clear pattern after treatment: at follow-up, faster reaction time was associated with higher brain node centrality. Significant negative correlation was observed in cuneus and lingual in the IH. This could indicate that the visual function recovery after brain stimulation could be due to the multifactor integration of the lesioned and the intact hemisphere. **(C)** ACDC significantly reduced the long coherence between the lesion and intact occipital cortex in the delta band after POST ($p < 0.05$). Also, low beta was enhanced after POST between the intact occipital and intact temporal ($p < 0.05$). Each connectivity was measured between LH and IH occipital lobe; LH, lesion hemisphere; IH, intact hemisphere; MTG, Temporal_Mid; MOG, Occipital_Mid; LO, lesion Occipital_Mid lobe; IO, intact Occipital_Mid lobe; IT, intact Temporal_Mid lobe.

$p = 0.002$). No significance was observed for brain network measure centrality. However, centrality of intact middle occipital at FU was lower than Pre in responders ($p = 0.32$, MD $= -44$).

Global Network Measures

Global network features are those that describe the state of the whole brain, irrespective of region. We first calculated the global clustering coefficient and global characteristic path length, followed by two-way repeated ANOVA (two groups/three time points). The p-value was corrected by the Tukey test in *post-hoc* analysis. The only significant finding was that global CC in FU was significantly lower than the Post (MD $\pm$ SEM $= -0.0068 \pm 0.0027$, $p = 0.05$) in the high alpha band (**Figure 5A**). This suggests that responders need fewer connections to handle the neuronal synchronization in the resting state.

Global Coherence for Responder and Non-responder

To investigate the long coherence fluctuation irrespective of the stimulation protocols, a two-way repeated-measure ANOVA was performed (three groups: control, responder, and non-responder, and two time points: Pre and FU). The p-value was adjusted for multiple comparisons by Tukey–Kramer test for *post-hoc* analysis.

A main effect on coherence was observed between intact occipital and lesion frontal in the alpha band ($F_{(1,45)} = 4.032$, $p = 0.05$) (**Figure 5B**). *Post-hoc*, the FU coherence between the occipital_IH and frontal_LH was significantly lower than baseline in responders (median $\pm$ SEM $= 0.0069 \pm 0.003$, $p = 0.025$), and an interaction effect was observed when investigating the difference between the control and responders during FU ($F_{(2,45)} = 4.04$, $p = 0.024$) in the alpha band. Furthermore, at FU, the coherence between the occipital_IH and temporal_IH was significantly higher in non-responders when compared to controls (MD $\pm$ SEM $= 0.0140 \pm 0.0053$, $p = 0.030$).

Correlation Between FOV and Brain Network Measures

Pearson correlations were calculated to investigate the relationship between visual functionality measurements (FOV: **Figure 6** and HRP: **Figure 7**) and node strength. We observed significant correlations both in the lingual_LH (r_resFU $= -0.783$, $p = 0.007$) and middle occipital_IH (r_resFU $= -0.725$, $p = 0.018$), where responders with

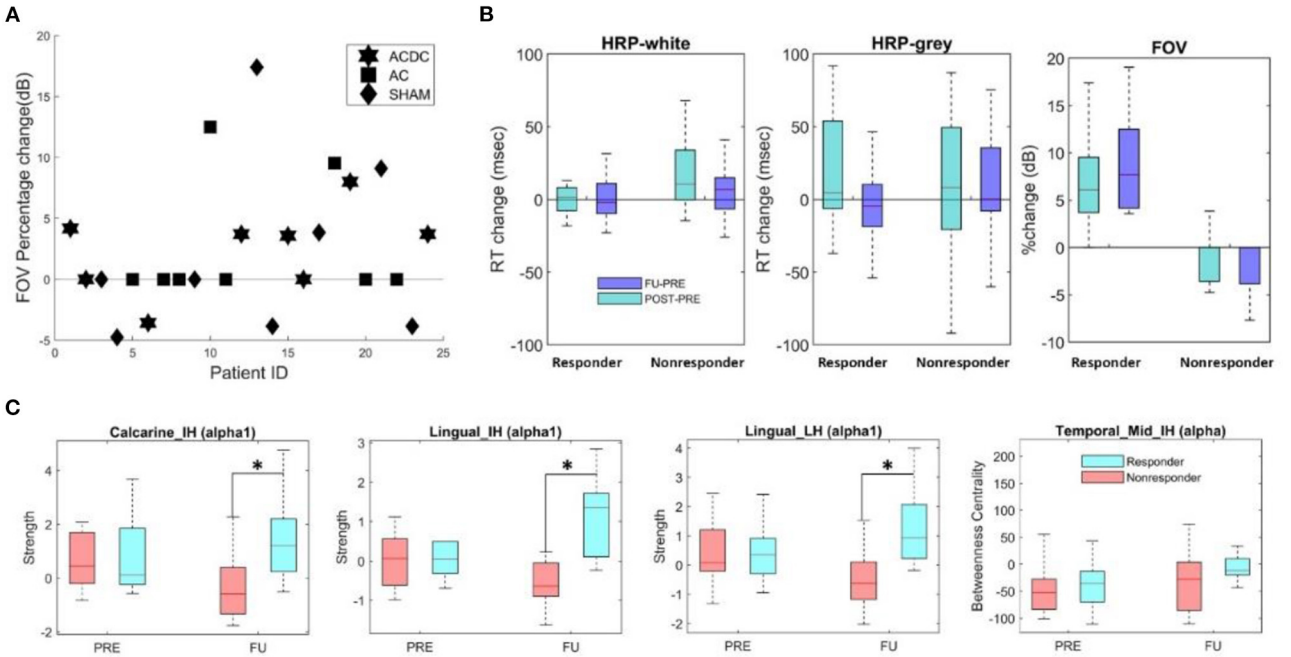

FIGURE 4 | (A) Percentage change of FOV per group for responders with values above zero ($n = 10$) and non-responders ($n = 14$). **(B)** Boxplot of absolute median change (HRP) and percentage of FOV (unit: dB) in responder and non-responders. Both groups had comparable reaction times (RT), but (per definition) the percentage change of FOV was significantly higher ($z = 4.17$, $p < 0.001$). **(C)** The local node strength in the low alpha band was significantly enhanced in responders in calcarine and lingual areas of both hemispheres (*$p < 0.05$). The FU centrality of Temporal_Mid_IH was higher than the PRE ($p > 0.05$).

higher FOV showed lower node strength in the delta band and higher node strength in non-responders in lingual_LH (r_resFU = 0.609, $p = 0.021$) and middle occipital_IH (r_resFU = 0.573, $p = 0.032$). This suggests that in both hemispheres, responders with higher FOV had lower delta band strength, whereas non-responders had higher delta band strength.

The same delta band pattern was also noted in both hemisphere of calcarine (lesion hemisphere: r_nonresFU = 0.608, p_nonresFU = 0.023, intact hemisphere: r_nonresFU = 0.539, p_nonresFU = 0.047) in non-responders. Delta band node strength was positively correlated with FOV in non-responders. This may be one possible reason why non-responders failed to improve their vision because of the delta band oscillation in visual cortex.

High alpha-band node strength correlated significantly with FOV in lingual_IH (r_nonresFU = −0.686, $p = 0.004$) and middle frontal_LH (r_nonresFU = −0.686, $p = 0.007$) in non-responders. This indicates that alpha-band node strength decreases with higher FOV measure in non-responders.

DISCUSSION

To study brain FCN reorganization following NIBS in hemianopic stroke, we used graph theory to analyze the local and global network features and how they correlate with visual field recovery. The study's aim was to find a stimulation protocol for clinical use in stroke rehabilitation.

Behavioral Performance

We studied different visual field parameters (FOV and HRP), which were already reported in detail elsewhere (35). For the present study, FOV and HRP data were used to establish correlations with FCN parameters (**Figures 1D**, **4A,B**; **Table 1**). As we showed, ACDC patients showed only a trend of an improvement over baseline of FOV and faster RTs. In contrast, AC and Sham patient at Post and FU showed a slower RT and no change over baseline of the FOV. But the combined tACS and tDCS enhanced visual performance compared to baseline, which was not observed in the other two groups. The output of observable behavior performance enhancement of visual functions was ACDC >AC > Sham. Because only the ACDC had improved visual performance, this raises the question as to possible brain FCN reorganization in this group.

Local and Global Network Alteration After NIBS

Neuroplasticity is a critical factor in many neurological or neuropsychiatric diseases (29). Hence, modifying cortical activities by NIBS might be a promising therapeutic approach for clinical application (68). For example, tDCS shifts the suprathreshold of the resting state membrane potentials toward depolarization or hyperpolarization (69). Another approach is tACS, which entrains the neural oscillation in a frequency- and

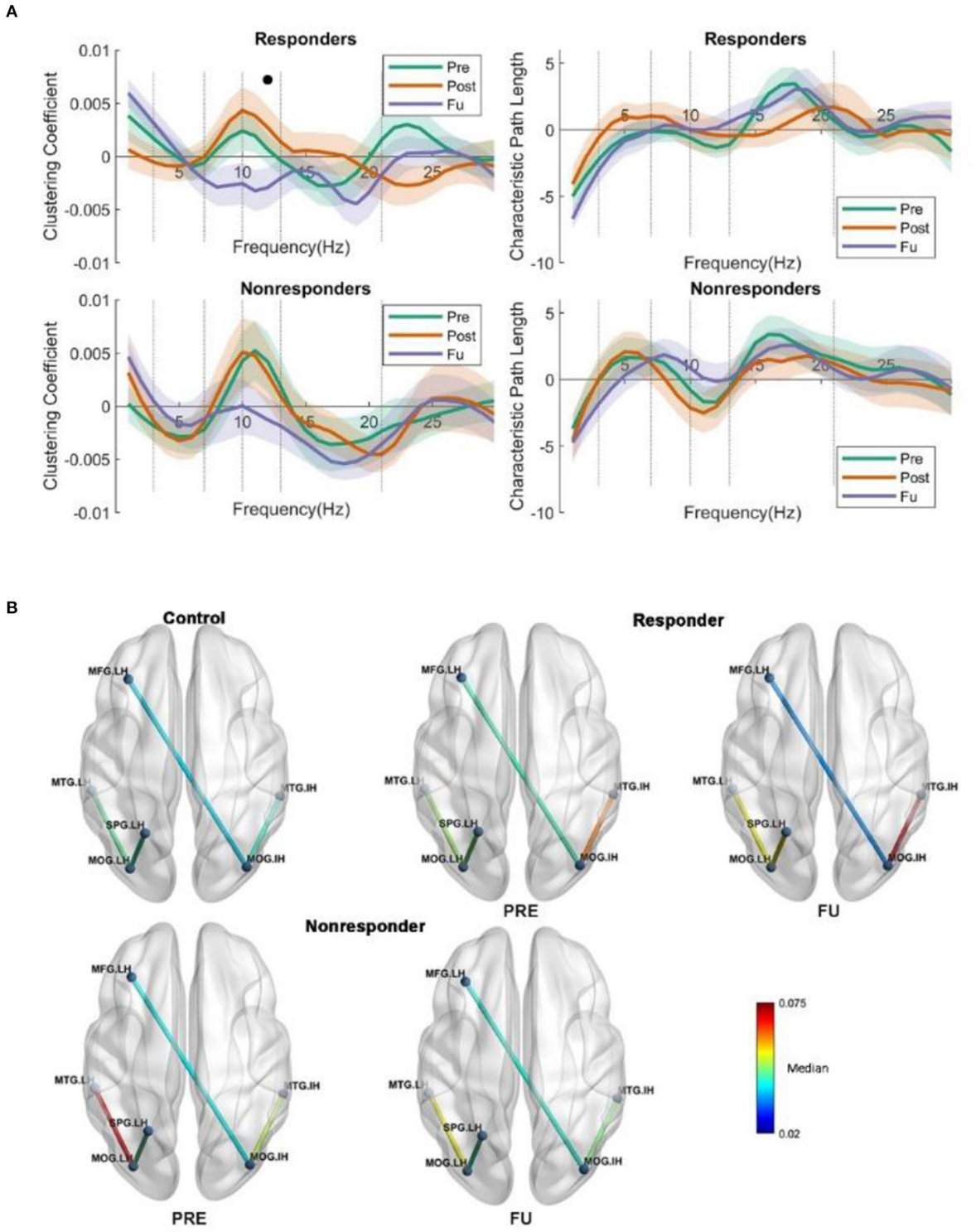

FIGURE 5 | (A) Global clustering coefficient and CPL show no interaction or main effect for characteristics path length (two groups/three time points). But a main effect was observed in the responders when comparing FU and POST, namely, a lower clustering coefficient. **(B)** The global coherence. From **(B)**, we could see the strength of the intact middle occipital increased, whereas the centrality decreased, which is very interesting; we may suggest that intact middle occipital gets rid of redundant connections from various regions but enhanced the connection with intact temporal lobe, as the temporal lobe could help the vision loss patient to handle the daily perception or movement identification. The long coherence between lesion frontal and intact occipital was observed significantly reduced at FU; the coherence was lower than that in PRE in the alpha band. The coherence between the lesion temporal and lesion occipital was significantly changed; both the responders and non-responders show higher coherence than the control subject.

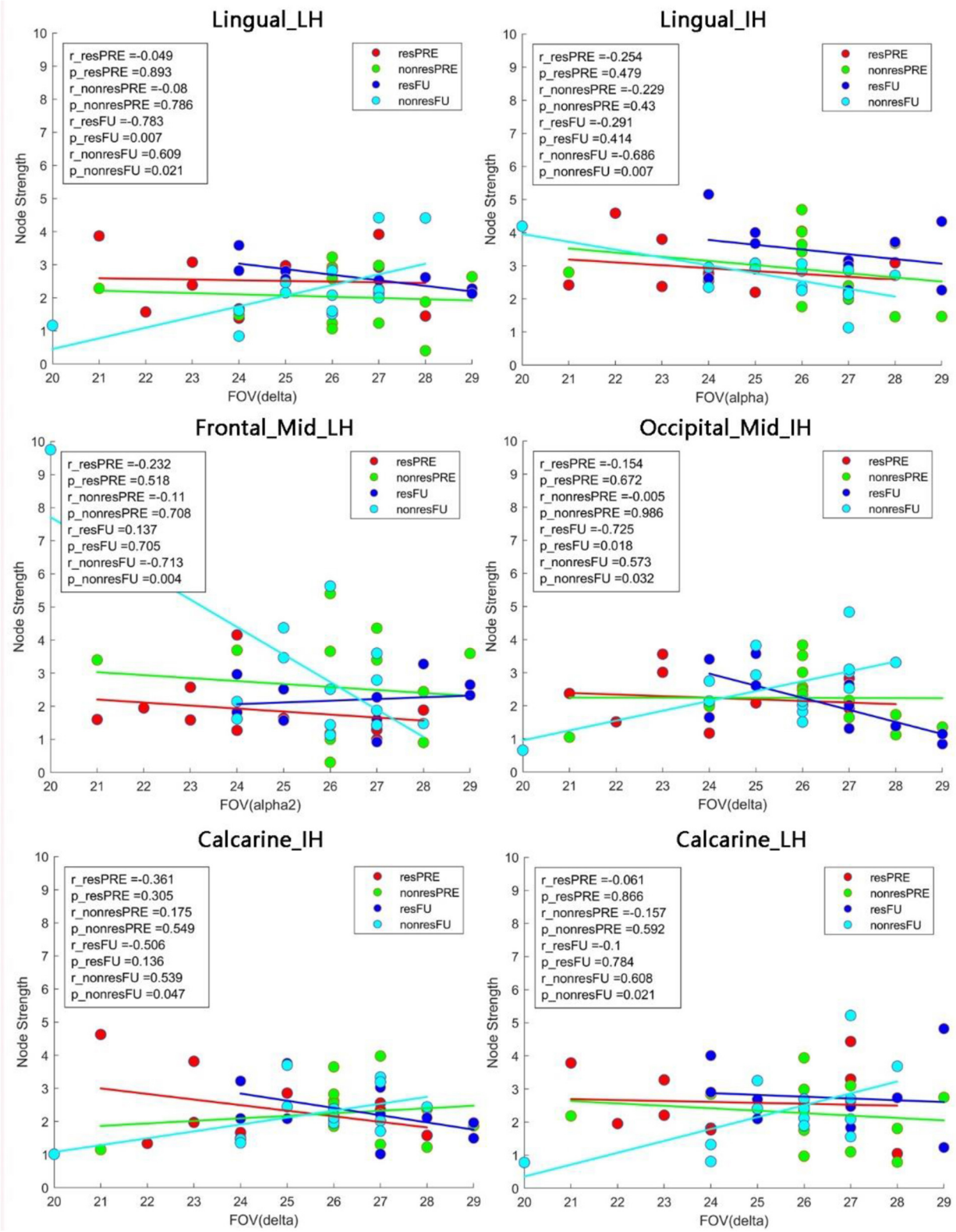

FIGURE 6 | Pearson correlation between the FOV and node strength. In non-responders, we observed a positive correlation between FOV and node strength in the lingual_LH and calcarine_LH in the delta band. In the alpha band, node strength of both the lingual_IH and middle frontal_LH was negatively correlated with FOV. resFU, responders at FU; nonresFU, non-responders at FU; resPRE, responders at baseline; nonresPRE, non-responders at baseline.

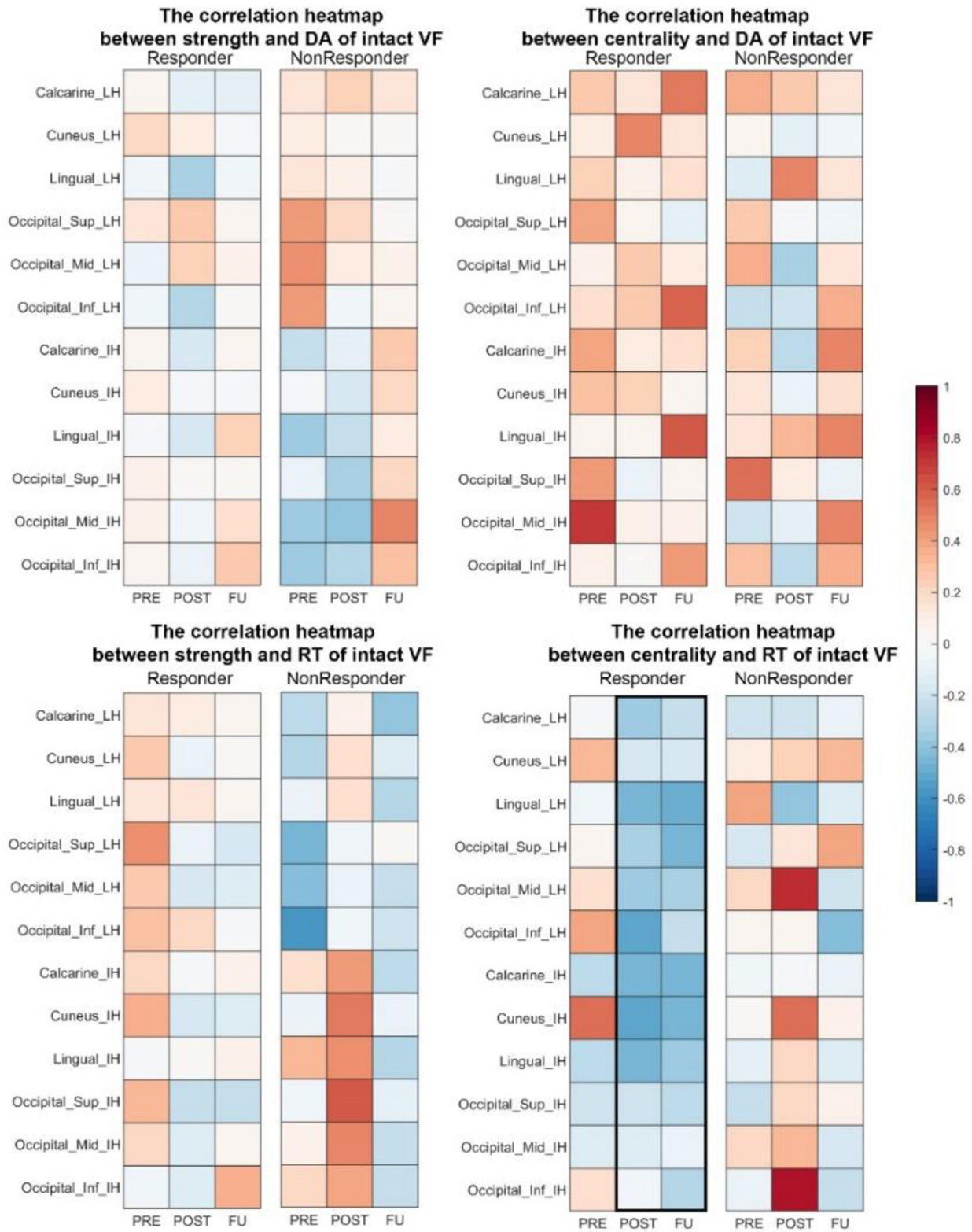

FIGURE 7 | Correlation heat map between brain network measures (strength and centrality) and visual performance in responders. At POST and FU, there was a trend of faster RT being associated with higher centrality in both hemispheres. DA, detection accuracy; VF, visual field; RT, reaction time.

phase-specific manner (23) and induces an endogenous network coupling or decoupling in a long-lasting manner (70, 71). Vision loss in the blind is induced not only by primary tissue damage but can also be interpreted by a breakdown of synchronization in brain networks (72). Here, the intact hemisphere hyperactivity may be a possible mechanism of spontaneous compensation (73, 74), which may—or may not—be beneficial for neuron rehabilitation. In fact, compensation could be a possible barrier for recovery of the disturbed balance between both hemispheres, because hyperactivity of the intact hemisphere has the potential to inhibit the lesioned hemisphere's residual function (39, 40). We chose to test tDCS protocols because they allow for lateralized anode and cathode positioning tDCS protocols to modulate cortical imbalance between excitation and inhibition (45). But we also studied tACS, which allows manipulation of phase coherence between distant brain regions. The long-lasting effects of tACS were not only studied in optic nerve patients (see Introduction) but also reported in cognitive tasks (19, 75–78). Based on the above, the active tACS electrode was positioned at Fpz to entrain intrinsic neuron oscillation with a frequency of 5 to 30 Hz. These montages were tested in the present randomized and sham-controlled clinic trial using a sequential approach of tDCS followed by tACS.

Interhemispheric Balance After NIBS

Cortical network reorganization after an injury is a widely recognized phenomenon (79). One study reported hemianopia patients with damage on the left primary visual cortex who showed greater activation on other lobes in the lesion hemisphere and intact hemisphere associated with the visual cortex (80). Another study showed that bilateral SMA activation was increased after intensive rehabilitation of postural balance (81). Yet, others suggested that plastic reorganization of cognitive resources serves to compensate for impairment in stroke patients during motor rehabilitation tasks (82). However, such studies of cortical balance and recovery using EEG were not carried out with hemianopic stroke patients. Most recently, another study reported that vision restoration training can improve visual field defects in chronic hemianopia and that this correlated with functional brain network reorganization as measured by MRI in precuneus, which may help quantify patient's ability to direct spatial attention (83). In the present study, we first applied the cathodal tDCS over the intact visual hemisphere with the goal to inhibit the increased excitability caused by brain network reorganization after the stroke, which was then immediately followed by tACS applied at Fpz to entrain oscillations for both hemisphere. In the ACDC group, the middle and superior occipital lobe of the lesion hemisphere had significantly higher strength in Post and FU compared to baseline and showed greater network strength in the intact middle occipital lobe. An enhancement of the lesioned hemisphere in the ACDC group was also observed in the superior occipital lobe. The strength of both AC and sham group fell back to slightly below the original level during follow-up. Both occipital lobes' enhanced strength could demonstrate that interhemispheric connections were more balanced in the ACDC group. Because this correlated with visual performance in the ACDC group, this observation is compatible with the hypothesis that postlesion FCN plasticity reduces the imbalance between the lesioned and the intact hemisphere. As we showed, the unique protocol design of ACDC is able to modulate brain plasticity between the lesion and intact hemisphere, where the continuous stimulation can produce sustained and long-lasting neuronal modulation of the brain's neural networks. However, in stroke patients, ACS alone is largely ineffective, except for a benefit of foveal sensitivity (35).

The strength of calcarine_IH increased in the ACDC group, whereas the other two groups did not show similar patterns. The same change was also observed in the responder group. The centrality of both calcarine_IH and lingual_IH positively correlated with the RT in Pre and correlated negatively with RT both in Post and RT. This shows that the ACDC modulation enhanced the efficiency of information transfer on these two brain regions, which is associated with recovery of visual function (faster RT).

Regarding the issue of global brain network modulation, a lower CC was observed only in the ACDC group compared to baseline, where ACDC reduced alpha-band whole-brain connections. Our interpretation is that reduced connections are a sign of greater efficiency of visual processing, where less connectivity (greater processing efficiency) could comprise a possible mechanism of visual recovery.

Correlation of Visually Guided Behavior and Global Network FCN Measures

CPL is the average shortest path length in the network; a lower CPL indicates that fewer intermediary nodes are needed to transfer information between two unlinked nodes. In this case, the efficacy within a network is considered to be high. We found a significant positive correlation between the gray dots' RT and alpha-band CPL in the ACDC group at baseline, which disappeared at follow-up. This suggests that vision processing after ACDC modulation needs fewer nodes, i.e., fewer steps to process neural information. In the ACDC group, a significant negative correlation was observed between the number of white dots in HRP and CPL after treatment. This also suggests that ACDC decreased the whole-brain alpha-band CPL, and this was associated with an enlarged visual field. In contrast, CPL shows a very low negative correlation at FU. In summary, we suggest that ACDC can enhance processing efficiency in the alpha band, which also contributes to vision recovery.

Global Coherence After Brain Stimulation

The changes of the brain network in global coherence at both Post and FU show that NIBS can trigger brain plasticity by altering functional interaction between multiple brain regions. Specifically, ACDC reduced the functional connectivity between the lesion and the intact occipital lobe in the delta band and enhanced the connectivity between the intact occipital and the intact temporal lobe in the low beta band. In contrast, in the sham and ACS groups, no significant network changes were observed. Therefore, the combination of tACS and tDCS is apparently

able to modulate neural plasticity by increasing the efficiency of communication between remote regions of the brain, possibly by improving interhemispheric balance.

The Challenge and Efficacy of Sham and AC Design

The design of a proper sham condition is one of the biggest challenges in NIBS studies because NIBS can elicit cutaneous sensations that gradually disappear due to habituation, and tACS induces phosphene perception (47). We used 5-Hz burst/min current bursts rather than "no stimulation" in the Sham tACS group. The current level was ramped up for the 30 s, then stopped, and at the end of the session ramped down for another 30 s in the sham tDCS group (45). In this way, we ensured a comparable effect and duration of cutaneous sensations for all the patients during stimulation with this unique design. In the sham group, however, the strength of temporal_mid_IH increased significantly after 10 days of stimulation and at follow-up returned back toward baseline levels. This suggests that the sham condition was not neutral but altered the strength, which might mean that the temporal lobe is sensitive to slow burst current in sham tACS, although no long-lasting effect was observed. Yet, node strength in the occipital cortex did not change after ACS.

Comparison of Responders and Non-responders

Compared to non-responders, responders had less gray and more white visual field sectors. This is in agreement with the hypothesis that "areas of residual vision" (gray sectors) can be activated, improving regions of partial vision (84). Most patients with residual structures and functions spared by the damage have such "gray" regions where function is neither completely lost nor normal (85). The faster RT of white and gray regions of the visual field demonstrates that visual processing was enhanced in responders compared to baseline. Responders had significantly higher FOV than non-responders, both after treatment and at FU. This raises the question how the local and global brain network compares between responders and non-responders, irrespective of their NIBS treatment.

Local and Global Network in Responders

The total group of responders (i.e., irrespective to which group each patient belonged) showed significantly enhanced strength in the low alpha band in the lingual and calcarine lobe of both hemispheres, which non-responders did not. The lingual gyrus located between the middle of the temporal lobe and occipital lobe is relevant for complex visual processing such as object shape and contour information (86, 87). The calcarine sulcus is mainly involved in the primary visual cortex (V1) with a role in early-stage visual processing, creating a bottom-up saliency map from visual inputs to guide the shifts of attention (88, 89). The strength enhancement in both hemispheres could be a sign of compensation following the occipital damage. Similarly, the strength of the middle occipital region of the intact hemisphere was enhanced. We conclude that the reorganization occurs in two hemispheres symmetrically as a consequence of the occipital lobe. The correlation between network strength and behavior performance indicates that the delta band and alpha band play a vital role in vision recovery. Possibly regions with less alpha and higher delta are less responsive to the NIBS-induced oscillations, at least with regard to behavior output.

While in the delta band of the lingual and calcarine node non-responders had higher connection weights with higher FOV values, responders had fewer connection weights with higher FOV. Thus, delta band connectivity might play a critical role in enhancing visual functions and be a possible recovery biomarker of brain network reorganization. The same was noted in the intact middle occipital lobe; in responders, better vision was associated with lower delta band connectivity strength of the intact middle occipital, whereas the non-responders had higher node strength. The pattern is consistent with the neural correlation between the intact and lesion occipital lobe in the ACDC group: here, a lower coherence in the delta band between two occipital lobes was associated with visual field parameter improvement. Similarly, the global CC of the responder group in FU was significantly decreased in high alpha band compared to baseline. Thus, this finding also suggests that responders (with better vision recovery) needed fewer whole-brain connections in the high alpha band.

Correlation Between the FOV and Network Measures

In non-responders, greater visual acuity correlated with lower strength and FOV in the alpha band, especially at the frontal and lingual region. We also observed that the correlation between intact occipital and lesioned frontal lobe was decreased in responders. Thus, a local and global pattern of decreased connections between the intact occipital cortex and the lesioned frontal cortex signal seems to be a physiological correlate of vision recovery, and it shows that the middle frontal lobe plays an important role as a visual information-processing bridge, which was weakened after ACDC treatment.

Coherence Between the Intact Occipital and Intact Temporal Lobe

In responders, the FU coherence between intact occipital and intact temporal lobe was significantly higher than at baseline. It is known that the temporal lobe is responsible for handling perception and movement identification. Therefore, an enhanced connection between two lobes following NIBS suggests that the intact temporal lobe adjusts the internal information transmission state more rapidly. It may temporarily disengage connections with other regions that are less important, providing more support for the visual cortex to process visual movement information. Centrality of the intact temporal lobe demonstrates how much information is transferred through this area. In responders, we noticed a trend of local node enhancement in centrality and strength during FU compared with baseline and control. In responders, the centrality of Occipital_mid_IH remained unchanged compared to baseline, whereas centrality of Temporal_mid_IH increased. Considering the global coherence enhancement between the intact occipital and intact temporal regions,

this suggests that the communication between the intact occipital and temporal lobe plays a critical role in visual function enhancement, and it is this enhancement that seems to be adaptive.

In summary, occipital damage following stroke creates partial vision loss with brain network alteration in the delta and alpha band, and ACDC, but not AC alone, improves visual functions. As we now showed, brain network plasticity patterns such as interhemispheric (im-) balance and long-lasting plasticity were consistent with behavior performance in the ACDC group. This demonstrates that modulating brain network plasticity is a promising tool to induce vision recovery. An analysis of responders vs. non-responders (irrespective of the treatment they received) also helped us understand NIBS effects, highlighting the role of a reduction of the coherence between the LH and IH occipital lobes in the delta band and a reduced high alpha-band coherence between the frontal and occipital lobe; these two FCN patterns might comprise biomarkers of vision recovery and shed light on the role of coherence between intact occipital and intact temporal regions. Future experiments are needed to confirm this proposal.

Limitations

Our study has several limitations. First, the sample size per group was relatively small, but recruitment problems to find patients who met all inclusion and exclusion criteria were a challenge. While finding significant effects despite a small sample is suggestive, our results are not conclusive until a larger-sample study is done. Another limitation is the low spatial resolution of the EEG signals and a common fMRI template from MNI when resourcing. A better resolution would be preferable with individual head model for both patients and controls. Some researchers reported that intraindividual variability in response to tDCS and tACS was found (90–93). There are different possible sources of outcome variability. First, the individual anatomy varies between patients, which generates differences in electric fields inside the brain (91). Even in a fixed stimulation montage and intensity, there is substantial variability of spatial distribution and strength considering individual anatomical differences (91). In our study, the data were warped into MNI space during source reconstruction. Some researchers argue that the standard template would make the anatomy less precise especially in the lesion area; however, because we used the same pipeline and could still demonstrate consistent and interpretable results from our brain network analysis, this limitation is acceptable for an exploratory study. Second, there may be other systemic factors (such as blood flow differences, hormonal or nutritional influences) that may influence neurophysiological activity during FU, and third, we recently observed that vision recovery following ACS treatment in patients with optic nerve damage depends on patients' personality traits and stress history (94).

CONCLUSIONS

Our exploratory clinical trial of hemianopic stroke patients showed that ACDC, but not ACS treatment, is able to induce greater hemispheric balance of brain FCNs in the alpha band, which correlates with vision recovery. In addition, ACDC decreases delta band coherence between the lesioned and intact occipital cortex and modifies the connections with other regions. A lowered global clustering coefficient observed in responders may be a physiological biomarker or mechanism of vision recovery, in that the brain's FCN can process visual information more efficiently. Here, visual processing is achieved with lower functional connectivity in the alpha band. In summary, brain FCN reorganization is relevant for the postlesion response and plasticity of the damaged visual system. This finding can inspire our search for more effective stimulation protocols to induce vision restoration in ways that are more effective and more long-lasting.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

JX: design of the analysis and interpretation, statistics, and drafting and revision of the manuscript for intellectual content. ZW and AN: critical revision of the manuscript for intellectual content. BS: design and conceptualized study, interpretation of the data, and drafting and revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Current Incidence and Risk Factors of Fecal Incontinence After Acute Stroke Affecting Functionally Independent People

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Background: Previously published retrospective series show a high prevalence of fecal incontinence (FI) in stroke patients. We aimed to analyze in a prospective series the current incidence of FI in acute stroke in functionally independent patients and its evolution over time and the patient characteristics associated with the appearance of FI in acute stroke.

Methods: We included consecutive patients with acute stroke admitted in our stroke unit who fulfilled the following inclusion criteria: a first episode of stroke, aged >18 years, with no previous functional dependency [modified Rankin Scale (mRS) ≤ 2] and without previous known FI. FI was assessed by a multidisciplinary trained team using dedicated questionnaires at 72 ± 24 h (acute phase) and at 90 ± 15 days (chronic phase). Demographic, medical history, clinical and stroke features, mortality, and mRS at 7 days were collected.

Results: Three hundred fifty-nine (48.3%) of 749 patients (mean age 65.9 ± 10, 64% male, 84.1% ischemic) fulfilled the inclusion criteria and were prospectively included during a 20-month period. FI was identified in 23 patients (6.4%) at 72 ± 24 h and in 7 (1.9%) at 90 days ± 15 days after stroke onset. FI was more frequent in hemorrhagic strokes (18 vs. 5%, p 0.007) and in more severe strokes [median National Institute of Health Stroke Scale (NIHSS) 18 (14–22) vs. 5 (3–13), $p < 0.0001$]. No differences were found regarding age, sex, vascular risk factors, or other comorbidities, or affected hemisphere. Patients with NIHSS ≥12 (AUC 0.81, 95% CI 0.71 to 0.89) had a 17-fold increase for the risk of FI (OR 16.9, IC 95% 4.7–60.1) adjusted for covariates.

Conclusions: At present, the incidence of FI in acute stroke patients without previous functional dependency is lower than expected, with an association of a more severe and hemorrhagic stroke. Due to its impact on the quality of life, it is necessary to deepen the knowledge of the underlying mechanisms to address therapeutic strategies.

Keywords: fecal incontinence, acute stroke, incidence, acute, epidemiology

INTRODUCTION

Fecal incontinence (FI) is defined as an involuntary loss of solid or liquid feces. It is a highly prevalent condition in the general population, although its incidence and prevalence are usually underestimated due to reluctance of patients to report its symptoms (1). Large community-based studies have shown a wide variability of rate of FI in the general population ranging from 1 to 24% (2, 3). The maintenance of fecal continence is the result of the integration of somatic pelvic motor coordination and visceral and sensory functions. Therefore, FI may present as a result of an anal sphincter dysfunction, an abnormal rectal compliance, a decreased rectal sensation, or a combination of any of those abnormalities (4, 5).

FI has been reported to be a common complication after stroke. Previous studies have estimated an incidence from 10 to 40% (6–9) according to the time of assessment after stroke (6). In one of the largest epidemiological studies, the prevalence of post-stroke FI ranged from 30% within 10 days to 15% at 3 years after stroke (6), whereas a prevalence of 5 to 6% was detected in two more recent studies beyond the acute phase (10, 11). Additionally, severe FI was reported in 5% of stroke survivors in a large population-wide survey, a four-fold increase compared with non-stroke patients (9).

FI in stroke patients has been associated with age, diabetes mellitus, stroke severity, and other comorbidities (6). Importantly, stroke patients with FI had higher risk of short- and long-term mortality (6) and an increased need for institutionalization and nursing support in the community (10, 11), leading to a healthcare estimated costs of 55% higher compared with stroke patients without FI (12). However, the available published data about FI after stroke are mostly based on studies conducted before the widespread use of intravenous thrombolysis and especially, mechanical thrombectomy in acute stroke treatment, and additionally, FI information has been retrospectively collected through the use of general questionnaires or non-specific clinical scales for FI diagnosis.

Remarkably, the general approach to stroke care has been deeply changing over the last decades. The implementation of dedicated stroke units managed by trained personnel, as well as the focus on rehabilitation strategies, with its facilities and the unequivocal benefit of reperfusion treatments have significantly reduced stroke patient dependency (13). In this new scenario, the aims of this study were to identify (1) the current incidence of FI in acute stroke in previous functionally independent patients, (2) the incidence of persistent FI in stroke patients beyond the acute phase, and, (3) the patient characteristics associated with the appearance of FI in acute stroke.

METHODS

We conducted a prospective observational study of consecutive stroke patients admitted to our stroke unit from May 2018 to December 2019.

Data Sample

Patients fulfilling the following criteria were included in the study: age $\geq$18 years, first-ever anterior circulation stroke, functionally independent patients defined as a modified Rankin Scale (mRS) score $\leq$2, and absence of previous FI due to other etiologies. Every included patient was prospectively screened for the presence of new-onset fecal incontinence at 72 $\pm$ 24 h (acute phase) after stroke onset and at 90 $\pm$ 15 days (chronic phase).

Out of 743 patients admitted to the stroke unit for a 20-month period, 359 (48.3%) patients (mean age 65.2 $\pm$ 10 years, 63.2% male, and 86.2% ischemic stroke) fulfilled the inclusion criteria and were included in the study. **Figure 1** shows the flow chart of the study and the reasons to exclude patients.

Fecal Incontinence Assessment

Data about fecal depositions are routinely collected by our trained stroke unit nurses during hospitalization, and when suspected, FI diagnosis was confirmed by a trained physician both in the acute and chronic phase. FI was defined as any involuntary leakage of feces according to the Rome IV criteria (14), and patients were classified for the purpose of the study in FI and No FI subgroups accordingly. At 3 months follow-up, a dedicated questionnaire [the Wexner score (15)] was administered by a trained surgeon. This questionnaire investigates the presence of uncontrolled loss of gas, liquid, and solid stools, if their presence requires the use of physical restraints such as dressings or diapers and the impact on the quality and sexual life. The score range from the minimum score = 0 which means "perfect continence" to the maximum score = 20 points which means "totally incontinent."

Studied Variables

Demographic, previous functional status, vascular risk factors, comorbidities, gastrointestinal tract diseases, history of abdominal surgeries, and stroke characteristics were recorded in a dedicated database. Abdominal surgeries and gastrointestinal diseases were defined as any intervention or relevant pathology involving the gastrointestinal tract previous to stroke.

Stroke severity was defined using the National Institute of Health Stroke Scale (NIHSS) (16). Ischemic stroke etiology was determined according to the Trial of ORG 10172 in acute stroke treatment (TOAST) (17). Functional status was defined by the modified Rankin Scale Score (mRS) at admission and discharge

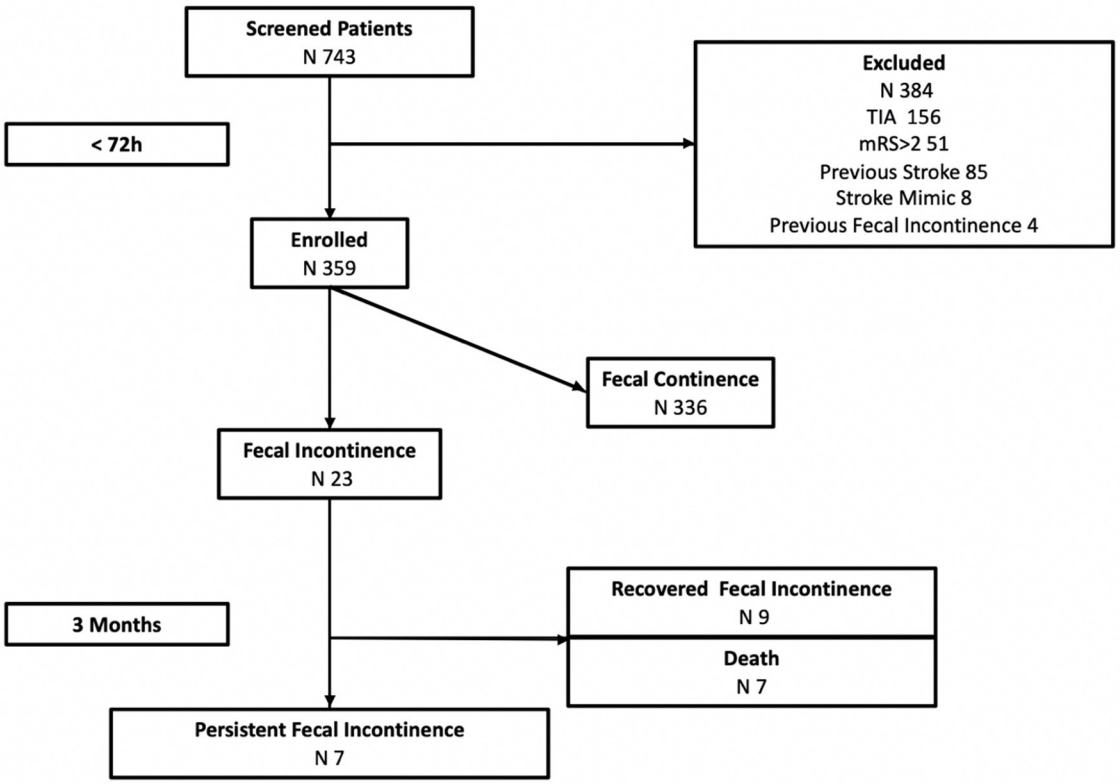

FIGURE 1 | FINISH study workflow. TIA, transient ischemic attack; mRS, modified Rankin Scale.

(18). Favorable functional outcome was defined as a mRS ≤ 2 at 3 months.

The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from patients or relatives.

Statistical Analysis

Descriptive analyses were obtained for all demographic and clinical variables. Baseline characteristics between groups (patients with FI and non-FI) were compared using X^2 test, Fisher's test, *t*-test, or Mann–Whitney's U-test, as appropriate. Logistic regression analysis was used to determine predictor factors independently associated with the presence of FI in the univariate analysis ($p < 0.05$) and variables previously related to in other published articles. Receiver-operator characteristics (ROC) curves were constructed by plotting basal NIHSS that better predict the presence of FI, according to the best specificity and sensitivity. Statistical significance was defined as two-sided *p*-value < 0.05. All the statistical analyses were made using SPSS statistical package vs. 22 (IBM Deutschland GmbH, Ehningen, Germany).

RESULTS

FI was identified in 23 (6.4%) out of 359 included patients in the acute phase. Of those, at 3 months, seven (30.4%) patients died (three during hospitalization, four after discharge), nine (39.1%) patients recovered FI, and seven (30.4%) patients had persistent FI. Thus, 2% of the first-ever anterior circulation strokes and 44% of stroke patients with FI in the acute phase had persistent FI after stroke.

Patients Characteristics Associated With Post-stroke Fecal Incontinence

Demographic and clinical data according to the presence of FI are shown in **Table 1**.

Patients with FI had higher stroke severity [NIHSS 18 (14–22) vs. 5 (3–13)] at admission compared with patients with fecal continence. FI was more frequent in hemorrhagic stroke (12 vs. 5%) compared with ischemic stroke. No significant differences were found in age, sex, vascular risk factors, history of abdominal surgery, or other comorbidities, affected hemisphere, vessel occlusion, intracranial hemorrhage location, or ischemic stroke etiology between patients with and without FI. At discharge, patients with FI had higher stroke severity, poor functional outcome, and higher mortality rate compared with those without FI (**Table 1**).

Independent Predictors of Post-stroke Fecal Incontinence Appearance

A logistic regression model adjusted for age, sex, and affected hemisphere showed that hemorrhagic stroke and NIHSS were

TABLE 1 | Baseline clinical characteristics and functional outcome of fecal incontinence and continence stroke patients.

	Total sample N = 359	Fecal incontinence N = 23	Fecal continence N = 336	*P*
Demographics and medical history				
Gender, male	229 (64)	12 (52.1)	217 (64.5)	*0.129*
Age (years)	65.9 ± 10	65.7 ± 10	67.8 ± 11	*0.115*
Smoking habit	90 (25.1)	5 (21.7)	85 (25.3)	*0.639*
Alcohol abuse	25 (6.9)	0 (0)	25 (7.4)	*0.239*
Hypertension	237 (66)	16 (69.5)	221 (65.8)	*0.899*
Diabetes	104 (29)	6 (26.1)	98 (29.2)	*0.919*
Hypercholesterolemia	194 (54)	12 (52.1)	182 (54.2)	*0.766*
Atrial Fibrillation	63 (17.5)	6 (26.1)	57 (16.7)	*0.413*
Heart disease	41 (11.4)	2 (8.6)	39 (11.6)	*0.753*
COPD	36 (10)	3 (13)	33 (9.8)	*0.729*
Chronic kidney failure	9 (2.5)	0 (0)	9 (2.7)	*1.000*
Obesity	42 (11.7)	1 (4.3)	41 (12.2)	*0.271*
Urinary incontinence	0 (0)	0 (0)	0 (0)	*1.000*
Abdominal surgery	28 (7.8)	3 (13)	25 (7.4)	*0.431*
Gastrointestinal disease	18 (5)	1 (4.3)	17 (4.2)	*0.881*
Clinical features				
Ischemic stroke	302 (84.1)	16 (69.5)	286 (85.1)	*0.008*
Hemorrhagic stroke	57 (15.9)	7 (20.5)	50 (14.9)	
Affected side				0.717
Left	200 (55.7)	16 (69.5)	184 (55.3)	
Right	149 (41.5)	7 (30.4)	140 (42)	
Bilateral	9 (2.5)	0 (0)	9 (2.7)	
Arterial occlusion	N = 302	N = 16	N = 286	0.500
No	86 (28.4)	3 (18.7)	83 (29)	
TICA	18 (5.9)	1 (6.2)	17 (5.9)	
ACM M1	158 (44)	6 (37.5)	152 (53.1)	
ACM M2	25 (8.2)	2 (12.5)	23 (8)	
TANDEM	8 (2.6)	2 (12.5)	6 (2)	
ACA	7 (2.3)	2 (12.5)	5 (1.7)	
Reperfusion treatment	N = 302	N = 16	N = 286	0.252
No	162 (53.6)	9 (56.2)	153 (53.1)	
IV tPA	52 (17.2)	0 (0)	52 (18.2)	
EVT	49 (16.2)	4 (25)	45 (15.8)	
IV tPA + EVT	41 (13.6)	3 (18.8)	38 (13.3)	
Intracranial hemorrhage location	N = 57	N = 7	N = 50	0.102
Lobar	22 (38.6)	3 (42.8)	19 (38)	
Basal ganglia	33 (57.9)	4 (57.2)	29 (58)	
Both	2 (3.5)	0 (0)	2 (4)	
TOAST classification	N = 302	N = 16	N = 286	0.152
Atherothrombotic	103 (34.1)	5 (31.5)	98 (34.2)	
Cardioembolic	100 (33.1)	8 (50)	92 (32.1)	
Lacunar	45 (14.9)	0 (0)	45 (15.7)	
Undetermined	39 (12.9)	3 (18.5)	36 (12.5)	
Other causes	15 (5)	0 (0)	15 (5.2)	
NIHSS at baseline	6 [3–6]	18 [14–22]	5 [3–13]	<0.001
NIHSS at 7 days	2 [0–5]	13 [5–21]	2 [0–5]	<0.001
mRS ≤2 at 7 days or discharge	182 (50.6)	2 (9)	180 (53.6)	<0.001
Mortality at 7 days or at discharge	11 (3.1)	3 (13)	8 (2.7)	0.029

Numbers are expressed as mean ± SD, median [quartiles] and number (percentages). COPD, chronic obstructive pulmonary disease; heart disease, coronary heart disease or heart failure; TICA, terminal internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; Tpa, tissue plasminogen activator; EVT, endovascular treatment; TOAST, Trial of ORG 10172 in acute stroke treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Score.

TABLE 2 | Multivariate analysis of factors associated with fecal incontinence (FI) during the acute stroke phase.

	OR	95% IC	p
Age	1.010	0.967–1.056	0.65
Female gender	2.308	0.876–6.084	0.091
Left side stroke	1.629	0.613–4.327	0.328
Hemorrhagic stroke	4.743	1.701–13.224	0.003
NIHSS admission >12	16.915	4.759–60.120	0.001

independently associated with the presence of FI in the acute phase of stroke (**Table 2**). A further model adjusted for vascular risk factors or other comorbidities as well did not modify the effect (data not shown). A cut-off point of NIHSS ≥12 in the ROC curve (AUC 0.81, 95% CI 0.71 to 0.89; $p < 0.001$) predicted the presence of FI with a sensitivity of 84% and specificity of 75%. Stroke patients with NIHSS≥ 12 had a 17-fold increase in the risk of FI compared with those with NIHSS <12 (OR 16.9 IC 95% 4.7–60.1) adjusted for covariates. Moreover, when we classified stroke patients according to stroke severity in mild stroke (NIHSS ≤ 6), moderate stroke (NIHSS 7–15), and severe stroke (NIHSS>15) (19), we found that the higher the stroke severity, the higher the rate of FI in the acute phase and in the chronic phase (**Figure 2**).

Table 3 shows the patient and stroke characteristics associated with persistent FI at 3 months. No differences were found in clinical, demographic features, stroke subtype, baseline NIHSS, and severity of FI measured by the Wexner's score between patients with persistent FI or recovered FI at 3 months. Thus, no independent predictors of persistent FI beyond acute stroke phase were identified in a logistic regression analysis (data not shown).

DISCUSSION

Stroke patients may suffer different complications both during the acute (such as neurological worsening or stroke recurrence, seizure, infections) and the chronic phase (cognitive impairment, depression, and emotional lability, among others) (20). Fecal incontinence in stroke patients has been poorly investigated during the last decade, probably due to a lack of interest of

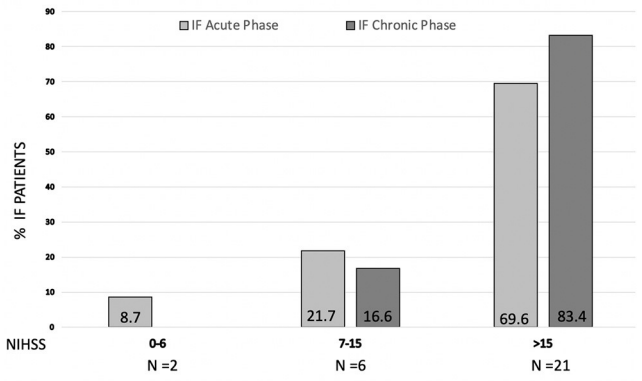

FIGURE 2 | Prevalence of fecal incontinence (FI) in acute phase (gray bar) and chronic phase (black bar) according to stroke severity (NIHSS) at admission. Inside each bar % of FI patients is shown.

TABLE 3 | Baseline clinical characteristics of patients with persistent fecal incontinence and recovered fecal incontinence at 90 days.

	Total sample *N* = 16	Persistent fecal Incontinence *N* = 7	Recovered fecal incontinence *N* = 9
Demographics and medical history			
Gender, male	6 (37.5)	2 (28.5)	4 (44.4)
Age (years)	66.4 ± 12.4	69.7 ± 10.7	62.7 ± 18.2
Smoker	3 (18.7)	1 (14.3)	2 (22.2)
Alcohol abuse	0 (0)	0 (0)	0 (0)
Hypertension	6 (37.5)	1 (14.3)	5 (55.5)
Diabetes	4 (25)	3 (42.9)	1 (11.1)
Hypercholesterolemia	6 (37.5)	3 (42.9)	3 (33.3)
Atrial fibrillation	1 (6.2)	0 (0)	1 (11.1)
Heart disease	2 (12.5)	2 (28.6)	0 (0)
COPD	1 (6.2)	1 (14.3)	0 (0)
Chronic kidney failure	0 (0)	0 (0)	0 (0)
Obesity	1 (6.2)	1 (13.3)	0 (0)
Urinary incontinence	0 (0)	0 (0)	0 (0)
Abdominal surgery	3 (18.7)	2 (28.6)	1 (11.1)
Gastrointestinal disease	1 (6.2)	1 (14.3)	0 (0)
Clinical features			
Ischemic stroke	10 (62.5)	4 (57.1)	6 (66.7)
Hemorrhagic stroke	6 (37.5)	3 (42.9)	3 (33.3)
Side			
Left	9 (56.2)	4 (57.1)	5 (55.6)
Right	7 (43.7)	3 (42.94)	4 (44.4)
Bilateral	0 (0)	0 (0)	0 (0)
Arterial occlusion	*N* = 10	*N* = 4	*N* = 6
No	1 (10)	0 (0)	1 (16.7)
TICA	0 (0)	0 (0)	0 (0)
ACM M1	5 (50)	3 (75)	2 (33.3)
ACM M2	1 (10)	1 (25)	0 (0)
TANDEM	1 (10)	0 (0)	1 (16.7)
ACA	2 (20)	0 (0)	2 (33.3)
Hemorrhage localization	*N* = 6	*N* = 3	*N* = 3
Lobar	3 (50)	3 (100)	0 (0)
Basal ganglia	3 (50)	0 (0)	3 (100)
Both	0 (0)	0 (0)	0 (0)
TOAST classification	*N* = 10	*N* = 4	*N* = 6
Atherothrombotic	3 (30)	2 (50)	1 (16.7)
Cardioembolic	5 (50)	1 (25)	4 (66.7)
Lacunar	0 (0)	0 (0)	0 (0)
Undetermined	2 (20)	1 (25)	1 (16.7)
Incomplete	0 (0)	0 (0)	0 (0)
NIHSS at baseline	18 [17–20]	18 [17–21]	19 [9–21]
Wexner Score	9 [8–12]	10 [8–12]	9 [8–13]

Numbers are expressed as mean ± SD, median [quartiles] and number (proportion). COPD, chronic obstructive pulmonary disease; heart disease, coronary heart disease or heart failure; TICA, terminal internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; tPA, tissue plasminogen activator; EVT, endovascular treatment; TOAST, Trial of ORG 10172 in acute stroke treatment; NIHSS, National Institute of Health Stroke Scale.

The p-values are not shown due to no statistical significance.

neurologists and its main prevalence in long-term hospitalized stroke patients. However, FI has a strong impact on a person quality of life and on its caregiver (21).

The present study shows an incidence of 6% of FI in first-ever functionally independent stroke patients during the acute phase that decreases to 2% at 3 months. This rate is significantly lower than expected and reported before. Brocklehurst et al. (22) observed FI in 23% of patients immediately after stroke, which diminished down to 16% after 2 weeks, and eventually to 8% at 1 year. The large registry of the Copenhagen Stroke study (23) reported FI in 40% of stroke patients at hospital admission, in 18% at hospital discharge, and in 9% at 6 months. Of note, the Harari et al. (6) study showed that the prevalence of FI was of 30% at 7 to 10 days, 11% at 3 months, 11% at 1 year and 15% at 3 years. Recently, Jacob et al. (24) showed that up to 6% of stroke survivors presented FI at some point during the 10-year study period in a large retrospective cohort. It is important to highlight that these studies identified FI through the use of Barthel Index scale or a customized questionnaire (9, 11), and no other specific or dedicated scales, or clinical or electrophysiological assessments were done to properly diagnose FI. We selected the Wexner score (15) because it is a widely used scale in fecal incontinent patients, usually employed by proctologists and gastroenterologists to evaluate fecal incontinence and its severity. It has been widely validated in FI assessment and it strongly correlates with FI severity. Wexner score has been related to subjective perception of FI and it could be self-assessed by patients. This fact and the retrospective evaluation of some of these previous studies could partly explain the difference in the incidence rates with respect to our series, in which the patients were prospectively assessed with scales designed to the detection of FI. In addition and importantly, the improvement in stroke care through its management in stroke units and the advancement in reperfusion treatments, rehabilitation strategies, and patient and caregiver education, have played an important role on the functional outcome of stroke patients in the last decade (25), and it could have strongly modified the incidence and the natural history of fecal incontinence in acute stroke.

Moreover, It is known that the lack of mobility, the functional dependence, and indeed, the use of multiple medications are risk

factors to develop fecal incontinence (6, 10, 25, 26). One of the pillars of stroke rehabilitation is the early mobilization and the implementation of instrument use to improve the self-care and autonomy of the patient, so, this approach could as well have reduced the incidence of FI during the last years. Nevertheless, 30% of patients with FI detected during the acute phase in our cohort died before 90-days follow-up evaluation, so we cannot rule out a potential higher incidence of persistent FI after stroke (up to 3.8% higher).

According to our results, the strongest independent predictor to have FI was stroke severity at admission, since patients with a severe stroke (NIHSS >12) have a 17-fold increase in the probability of developing FI in the acute phase compared with patients with NIHSS $\leq$ 12 (**Figure 2**). Harari et al. (6) already described the association between stroke severity and FI although using only clinical features (neglect, dysphagia, etc.) instead of a validated and widely used stroke scale for severity assessment such as NIHSS (16). In our cohort, patients suffering from a hemorrhagic stroke were five times more likely to present FI during the acute phase compared with patients with ischemic stroke, which was not previously found associated with FI. The limited acute treatment strategies able to modify the natural course and functional outcome of intracranial hemorrhage and, as already described, the more severe disability that usually implies hemorrhagic stroke compared with ischemic stroke (27) [median NIHSS 20 (15–23) vs. 18 (14–22) in hemorrhagic/ischemic stroke in our series], might explain the higher incidence of FI in these patients. Interestingly, no association has been found with vascular risk factors, deliveries, and previous abdominal surgeries that have been already related to FI (6). Although it could be due to the sample size, we infer that this could strengthen the role of the acute stroke as the primary cause of FI appearance.

To the best of our knowledge, this is the first study specifically designed to prospectively investigate the appearance of FI using a multidisciplinary approach. We implemented a comprehensive protocol that allowed us to study our patients by means of the stroke neurologist and the proctologist. We used the Wexner scale instead of the Barthel index to quantify fecal incontinence in the chronic phase that provides a deeper description of the FI compared with the dichotomic item within the functional clinical assessment of the Barthel Index. Our results show a moderate severity of FI in our patients (Wexner score 9–10).

Remarkably, half of the incontinent patients in the acute phase of stroke were still affected 3 months after stroke, although no differences were found in clinical or demographic features between those patients with persistent or recovered FI. Of note, the severity of the FI diagnosed in the acute phase did not correlate with its persistence at 3 months follow-up.

Interestingly, the cerebral mechanisms underlying the appearance of FI in stroke patients are not completely understood (28–31). The maintenance of fecal continence is the result of a coordination of pelvic motor, visceral and sensory functions; therefore, the loss of fecal continence may be the result of an anal sphincter dysfunction, an abnormal rectal compliance, a decrease rectal sensation, or a combination of any of these abnormalities (5, 32, 33). We found that FI was linked to a more severe stroke, with a probable large hemispheric lesion, and contrarily, no association was found to stroke lateralization. Until now, there is no knowledge about the precise cortical area involved in the fecal continence (the "continence" area), so, further anatomical and radiological functional studies are needed.

The main strengths of this study are the high-quality data due to the systematic and prospective data collection, the multidisciplinary approach, the use of FI specific clinical scales and stroke severity assessment. Thus, it has followed a large sample of patients in an observational study in a short period of time without differences in the acute stroke care, recanalization techniques, and rehabilitation facilities for a long time between patients. However, several limitations have to be stated. First, our study was carried out in a single comprehensive tertiary stroke center, so these results might not be generalizable to other settings. Second, we focused on the incidence of FI in the acute phase until 3 months after stroke. Consequently, we did not assess the potential resolution or the new appearance of FI beyond this period. Third, we excluded patients with previous stroke and/or other gastrointestinal tract disease to select patients in whom the acute stroke was the single cause of FI, a fact that could contribute to rule out patients in whom FI was multifactorial. Fourth, we did not specifically collect language impairment or cognitive disturbance, which might have altered the continence independently of the stroke; however, we included only functionally independent patients (mRS < 2), able to live alone and to carry on daily life activities by themselves. So, we think that the cognitive impairment, if present, would have been mild or very mild. Last, we also excluded patients with vertebrobasilar stroke territory to minimize clinical heterogeneity in the sample of patients, so a higher incidence of FI could have been identified.

Sacral nerve stimulation is an established treatment for FI due to several etiologies (34). Its neuromodulatory effect on cortical areas would be promising for incontinent patients due to stroke in addition with standard care based on rehabilitation.

Therefore, prospective randomized clinical studies analyzing the real effect of neuromodulation for FI in stroke patients are warranted.

CONCLUSION

At present, the incidence of persistent fecal incontinence reaches 2% of the previous functionally independent patients with a first anterior circulation stroke, lower than expected and strongly related to stroke severity. However, due to its impact on the quality of life, it is necessary to deepen the knowledge of the underlying mechanisms to address therapeutic strategies.

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 Ethic Committee of our center - CEIC (comité ético de Investigación Hospital Germans Trias i Pujol). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GL, DP, MM, JC, JS, JB, LR-E, MA, and AM-P designed the study. JC, JB, AP, MH-P, MA, and AM-P selected the patients and included the subject. SC, MH-P, HO, and SD revised the patients included. GL, MM, and DP wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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The Role of Continuous Theta Burst TMS in the Neurorehabilitation of Subacute Stroke Patients: A Placebo-Controlled Study

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Objectives: Transcranial magnetic stimulation, in particular continuous theta burst (cTBS), has been proposed for stroke rehabilitation, based on the concept that inhibition of the healthy hemisphere helps promote the recovery of the lesioned one. We aimed to study its effects on cortical excitability, oscillatory patterns, and motor function, the main aim being to identify potentially beneficial neurophysiological effects.

Materials and Methods: We applied randomized real or placebo stimulation over the unaffected primary motor cortex of 10 subacute (7 ± 3 days) post-stroke patients. Neurophysiological measurements were performed using electroencephalography and electromyography. Motor function was assessed with the Wolf Motor Function Test. We performed a repeated measure study with the recordings taken pre-, post-cTBS, and at 3 months' follow-up.

Results: We investigated changes in motor rhythms during arm elevation and thumb opposition tasks and found significant changes in *beta* power of the affected thumb's opposition, specifically after real cTBS. Our results are consistent with an excitatory response (increase in event-related desynchronization) in the sensorimotor cortical areas of the affected hemisphere, after stimulation. Neither peak-to-peak amplitude of motor-evoked potentials nor motor performance were significantly altered.

Conclusions: Consistently with the theoretical prediction, this contralateral inhibitory stimulation paradigm changes neurophysiology, leading to a significant excitatory impact on the cortical oscillatory patterns of the contralateral hemisphere. These proof-of-concept results provide evidence for the potential role of continuous TBS in the neurorehabilitation of post-stroke patients. We suggest that these changes in ERS/ERD patterns should be further explored in future phase IIb/phase III clinical trials, in larger samples of poststroke patients.

Keywords: continuous theta burst stimulation, transcranial magnetic stimulation, neurophysiology, brain oscillations, stroke, neurorehabilitation

INTRODUCTION

Stroke is the third most frequent cause of death (1) and one of the most prevalent causes of disability (2–4). Motor deficits occur quite often in stroke and affect up to 75% of patients for several months (3, 5–7). In spite of the available interventions, search for alternative therapeutic solutions is an active research area (8, 9).

Transcranial magnetic stimulation (TMS) is under investigation for this purpose, as a potential alternative for the study, diagnosis, and treatment of various diseases given its non-invasive nature with rare adverse effects (10, 11). When applied in its repetitive form, it can produce effects that last beyond the stimulation period (11, 12). Given these effects it might act as a neuromodulatory tool, providing a potential device to restore the balance of activity between the hemispheres, through the modulation of plasticity. In fact, following stroke, it has been postulated that the lesioned hemisphere decreases its activity while the excitability of the unaffected hemisphere becomes pathologically increased (2, 13, 14). Hence, repetitive TMS can be applied to augment the excitability of the stroke-affected hemisphere or to reduce activity in the unaffected hemisphere, depending on stimulation parameters (1, 2, 4, 13).

Although this technique is becoming popular, several issues remain to be elucidated. These include response variability and the still unknown mechanisms behind its application (12, 15). One of the inhibitory protocols that are currently being studied is continuous theta burst stimulation (cTBS), a recent form of patterned TMS that consists of 3 pulses at 50 Hz repeated every 200 ms during 40 sec, inducing inhibitory effects that last up to 60 min (16, 17).

In our previous work in healthy individuals (18), we observed that cTBS induced an unexpected inhibition in the contralateral hemisphere during arm elevation, contradicting the ipsilateral inhibition vs. contralateral disinhibition theory. We hypothesized that this unexpected effect was a result of propagation of effects from the stimulation site, which might have implications for neurorehabilitation. However, it is still possible that such effects only occur in the presence of two healthy hemispheres, and that the theory still holds when one hemisphere is lesioned.

Here we aimed to study the impact of cTBS when applied to the unaffected hemisphere of stroke patients. Cortical activity was evaluated at rest to study the baseline physiological state and during motor tasks, in which concerns brain oscillatory patterns. When sensory information or motor output are absent, there is an inhibition of cortical activity that is observed as an increase in oscillatory activity (event-related synchronization, ERS). In opposition, motor readiness induces an activation observed as a decrease in brain rhythms, designated by event-related desynchronization (ERD) in the *mu* and *beta* bands (19–23). To accomplish our goals, we recorded brain activity using electroencephalography (EEG) to analyze *alpha*, *mu,* and *beta* rhythms, before (T0) and after (T1) one session of real (experimental group: group E) or sham (control group: group C) cTBS and at 3-months' follow-up (T2, although at this time point we did not expect a change). Moreover, we evaluated motor-evoked potentials, using electromyography (EMG), and motor function, with the Wolf Motor Function Test (WMFT), at the same time points.

MATERIALS AND METHODS

We conducted this work in accordance with the Declaration of Helsinki. It has the approval of the Ethics Committee of the Faculty of Medicine of the University of Coimbra. All volunteers gave their written informed consent after explanation of the study procedures and objectives.

Study Design

This was a proof-of-concept study, wherein only a single-session of cTBS was applied. Patients were randomized in a 1:1 ratio into an active intervention or a placebo group. Subjects allocated to the experimental group (group E) received real continuous theta burst stimulation, while patients who were included in the control group (group C) underwent sham stimulation. Patients, but not investigators, were blinded to group allocation.

Sample

Patients included in this study were recruited from the Neurology Department of the Coimbra University Hospital and met the following criteria: (1) age between 18 and 85 years, (2) first-ever middle cerebral artery ischemic stroke, (3) cortico-subcortical lesion, (4) time since stroke onset within 7 ± 3 days (subacute phase), (5) upper-limb motor deficit, (6) modified Rankin Scale previous to the stroke event ≤ 1, and (7) capability to understand the tasks. We excluded subjects that (1) were clinically unstable; had (2) cognitive impairment, (3) diagnosed dementia, (4) history of epilepsy, (5) posterior or global aphasia, (6) neglect; (7) were pregnant, or presented (8) drugs or alcohol abuse, or (9) contraindications to transcranial magnetic stimulation.

Ten right-handed stroke patients that fulfilled the eligibility criteria composed the sample. Clinical and demographic data from the participants are detailed in **Table 1**.

All the patients who were admitted in this study underwent a prior stroke evaluation protocol at the University Hospital, which included the compilation of demographic information and clinical history, the assessment of stroke severity with the National Institutes of Health Stroke Scale, performed by a neurologist, and neuroimaging investigation reviewed by a neuroradiologist.

Magnetic Resonance Imaging (MRI)

We started by conducting formal neuroradiological evaluation with structural magnetic resonance imaging to confirm lesion location and characteristics. Data scans were collected on a 3.0 Tesla scanner (Magnetom TIM Trio, Siemens, Erlangen, Germany), equipped with a phased array 12-channel birdcage head coil (Siemens), at the Portuguese Brain Imaging Network Facilities, in Coimbra. We acquired a 3D anatomical T1-weighted MPRAGE (magnetization-prepared rapid acquisition gradient echo) pulse sequence for each patient [repetition time (TR) = 2,530 ms, echo time (TE) = 3.42 ms, inversion time (TI) = 1,100 ms, flip angle (FA) 7°, 176 single-shot slices, voxel size $1 \times 1 \times 1$ mm^3, field of view (FOV) 256×256 mm^2].

TABLE 1 | Clinical and demographic data of volunteers[a].

	Total of participants $N = 10$	Group E $N = 5$	Group C $N = 5$
Age (years; mean ± SD)	67.10 ± 13.470	70.20 ± 8.701	64.00 ± 17.564
Gender (female/male)	4 / 6	1/4	3/2
Handedness (points[b]; mean ± SD)	36.00 ± 0.000	36.00 ± 0.000	36.00 ± 0.000
Time since stroke (days; mean ± SD)	8.50 ± 1.581	8.20 ± 1.643	8.80 ± 1.643
Lesion side (right/left hemisphere)	4 / 6	3/2	1/4
NIHSS (mean ± SD)	6.40 ± 3.718	5.60 ± 2.302	7.20 ± 4.919
Baseline WMFT log time (mean ± SD)	2.14 ± 0.651	2.25 ± 0.729	2.04 ± 0.627
Baseline WMFT FAS (points; mean ± SD)	48.80 ± 31.255	45.80 ± 36.341	51.80 ± 29.235

[a]*FAS, functional ability scale; NIHSS, National Institutes of Health Stroke Scale; WMFT, wolf motor function test; Group E, experimental group; Group C, control group.*
[b]*All patients scored the maximum (36 points) in an adapted Edinburgh Handedness Inventory questionnaire, which corresponded to being strongly right-handed.*

Wolf Motor Function Test (WMFT)

The motor function of the affected upper-limb was evaluated before (T0), after stimulation (T1), and at 3-months' follow-up (T2), with the WMFT (24). The WMFT consists of an instrument for the assessment of the upper extremity function, in stroke patients. This test combines a series of motor tasks [detailed in (24)], from simple to more complex movements, comprising not only joint-specific but also total limb movements. Speed and quality of the movement are both quantified to evaluate the performance of the upper limb (24). In this work, each patient performed 15 tasks with the affected upper extremity and the performance times were recorded in seconds, with a maximum of 120 s for each task; when the patient could not perform the movement, the time was recorded as 120 s. In addition, we assessed the quality-of-the-movement with the functional ability scale (FAS), where the subject was rated a "0" when the movement was not performed and a "5" when the movement appeared to be normal, with a maximum total of 75 points.

Electroencephalography (EEG)

The EEG methodology was similar to the one adopted in our previous work in healthy volunteers (18). Briefly, we set up a block-design task, with three conditions performed in the following order: eyes opening/closure, arm movements, and thumb movements. The first condition was composed by 9 blocks × 10 s of eyes opening and 9 blocks × 10 s of eyes closure. For the arm movements, we had 18 blocks of 15 s of activity and another 18 blocks of 15 s without motor activity. The same design was used for the thumb opposition task. The outcomes of the EEG were as follows: *alpha* power for the eyes opening/closure condition; *mu* and *beta* ERD for the movement conditions (arm elevation and thumb opposition tasks). We first recorded cerebral activity at rest, asking the subject to open and close the eyes nine times, keeping the eyes opened/closed for 10 s each block, to evaluate the *alpha* power [8–13 Hz, (25)] as a control outcome measure, in an area far from the stimulation site. Then, we recorded brain activity with motor tasks, namely 90°-arm elevation and thumb opposition. We studied the 10–12 and 15–25 Hz frequency ranges to quantify *mu* and *beta* rhythms, respectively (19, 25–28). Movements were repeated six times with each upper limb and another six with both limbs simultaneously, for 15 s each block and with a no motor activity period between blocks with the same duration. "GO" and "STOP" commands were used to instruct patients to begin and stop the movement, respectively, and online triggers were inserted during the recording. This procedure was implemented at T0, T1, and T2. One of the participants from the control group could not fully perform the EEG protocol, being excluded from the EEG analysis.

The acquisition was performed with a 64-channel EEG cap (QuickCap, Neuroscan, U.S.), using a SynAmps2 RT amplifier and the Scan 4.5 software (Compumedics, Charlotte, NC). We kept impedances below 10 kΩ, added a low-pass filter at 200 Hz and a high-pass filter at DC, and selected a 1,000-Hz sampling rate. After data collection, we performed the following data preprocessing and analysis steps [Scan 4.5 and EEGLAB v.14.1.1b, (29)]. We filtered the signal from 1 to 45 Hz and down-sampled data to 250 Hz. We checked for muscle artifacts and eliminated them. We referenced the data to the average of the channels. After running Independent Component Analysis (ICA), we removed components including blinks and eye movements. For power quantification, custom MATLAB (version R2017b, The MathWorks, U.S.) scripts were implemented [adapted from our previous studies by Castelhano et al. (30) and by Silva et al. (31)], as described in our previous work in healthy participants (18). For quantification purposes, the baseline was defined between −2,000 ms and 0 for the eyes' closure and opening, and between −2,000 and −1,500 ms, before movement, for the motor tasks. *Alpha* power was quantified for the eyes conditions between −2,000 and 10,000 ms. Quantification of motor rhythms (*mu* and *beta* power) was performed between −2,000 ms and 0 ms (pre-movement and preparation) and from 0 to 4,000 ms (time-locked to the start of the early phase of movement execution).

We used posterior electrodes to assess visual *alpha* for the eyes opening/closure condition and central electrodes to study *mu* and *beta* with motor tasks (arm elevation and thumb opposition). The selection of the channels is detailed in **Figure 1**.

Electromyography (EMG)

For the recording of electromyographic signal, we first prepared the skin in the areas wherein electrodes would be placed. Then,

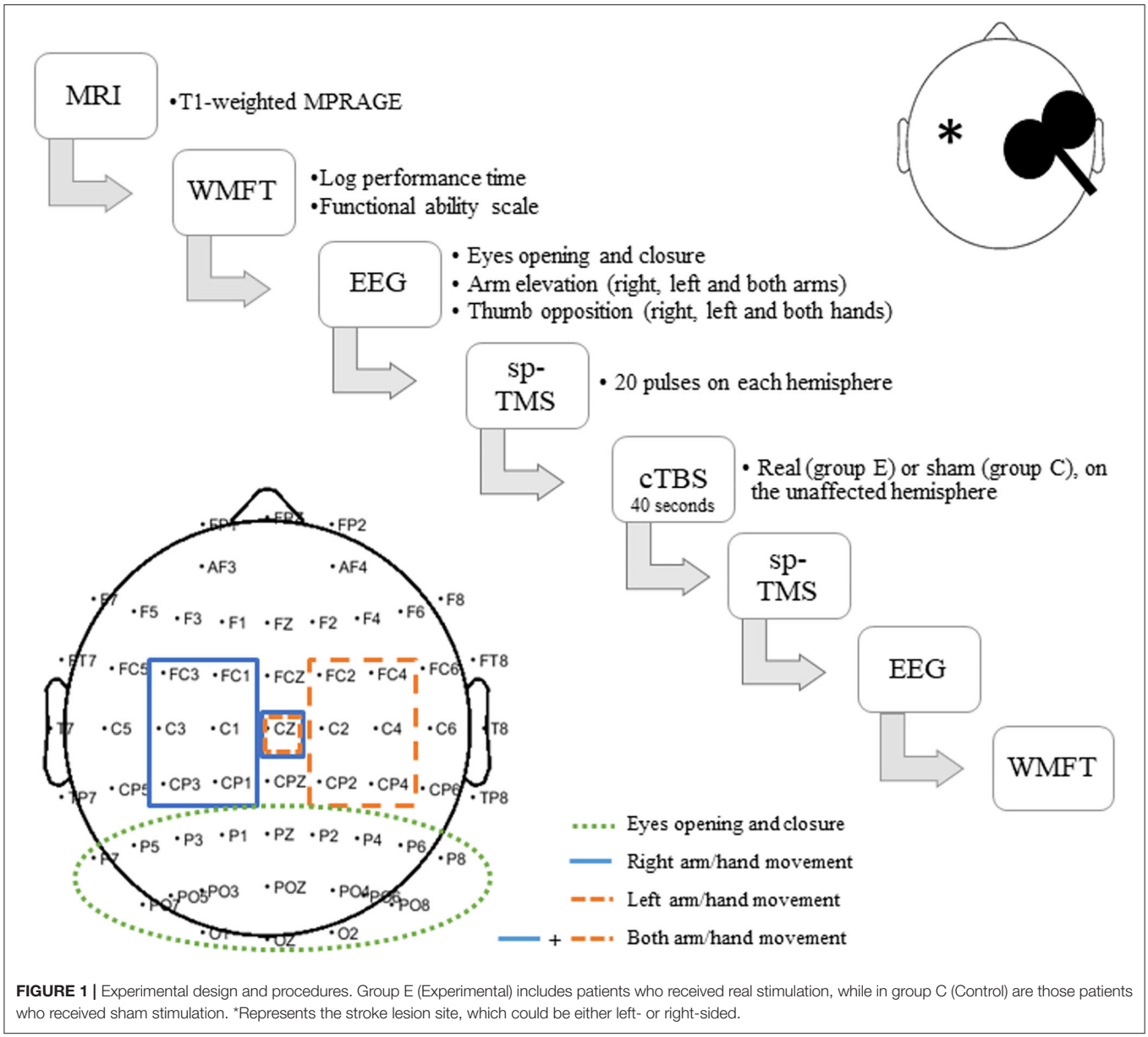

FIGURE 1 | Experimental design and procedures. Group E (Experimental) includes patients who received real stimulation, while in group C (Control) are those patients who received sham stimulation. *Represents the stroke lesion site, which could be either left- or right-sided.

we placed Ag/AgCl electrodes with conductive paste, in a belly-tendon montage and used BIOPAC MP-150 system and EMG 100C amplifier (Biopac Systems, CA) to record motor-evoked potentials (MEPs) on the abductor pollicis brevis (APB) muscle, using the AcqKnowledge 4.2 software (Biopac Systems, CA) with a 2.500-kHz sampling rate and a 1,000 gain. The peak-to-peak amplitude of motor-evoked potentials was measured *offline* in the same software. Motor-evoked potentials of the unaffected M1 were positive in all participants and we were able to find MEPs of the affected M1 in all patients but three (one from the sham group and two from the real stimulation group).

Transcranial Magnetic Stimulation (TMS)

Both single-pulse and continuous theta burst were administered with a 70-mm figure-of-eight coil plugged into a MagPro X100 magnetic stimulator (MagVenture, Denmark). All the participants were comfortably seated and wore earplugs during the experiment.

For each hemisphere, we determined the intensity which generated MEPs with a peak-to-peak amplitude ranging from 0.5 to 1 mV and gave 20 single pulses at 100% of the rest intensity determined for the respective hemisphere. Then, we measured MEPs' amplitude, using the same intensity before (T0), 5 min after the cTBS application (T1) and at 3-months' follow-up (T2), to analyze changes in excitability. The cTBS was applied over the motor hotspot of the primary motor cortex of the unaffected hemisphere, at 45° to the sagittal plane, as described in the literature (16, 17), with a total of 600 pulses in 40 s. We defined active motor threshold as being the minimum intensity that triggered at least one

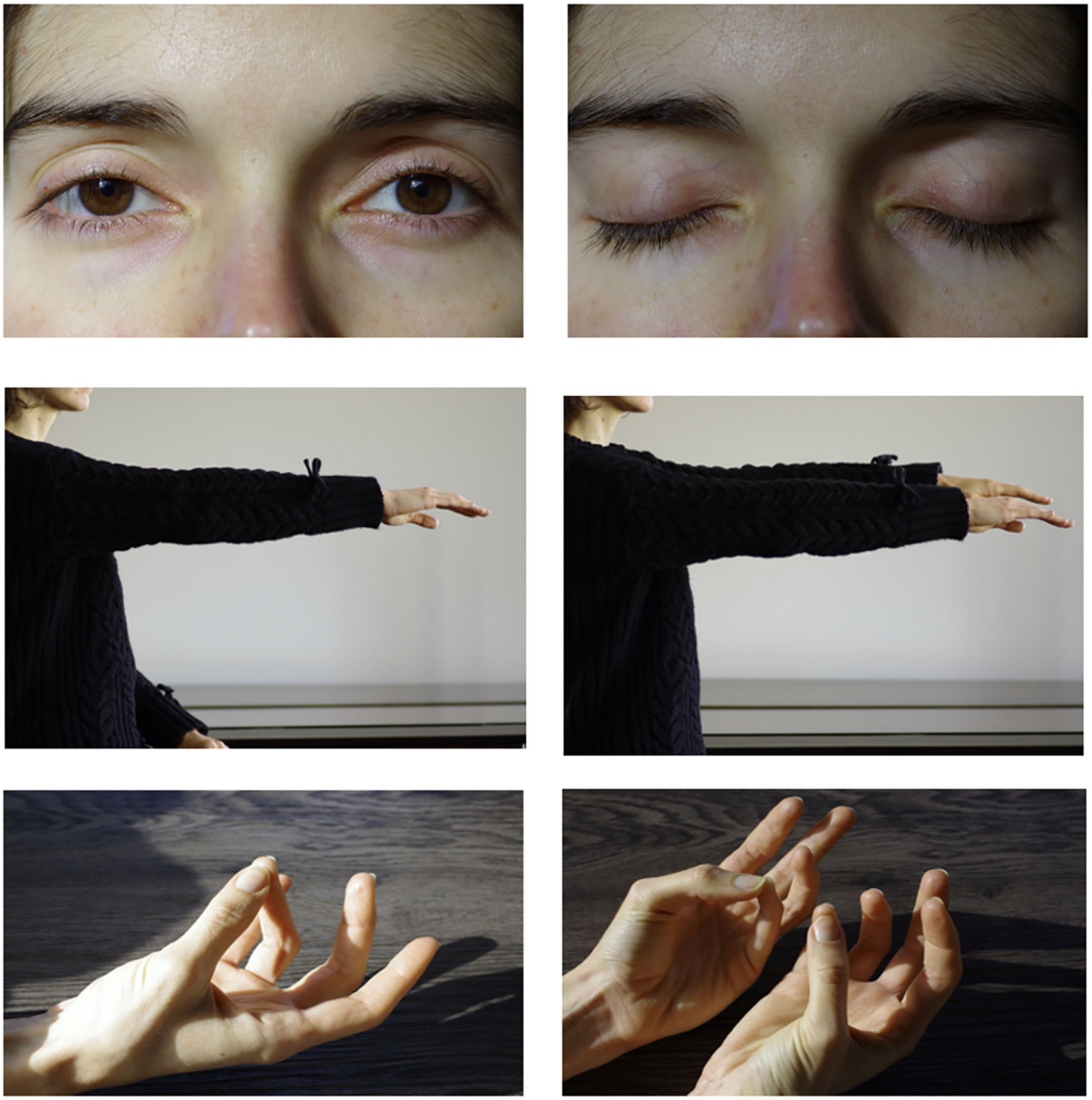

FIGURE 2 | EEG tasks: eyes opening + closure **(top)**, arm elevation **(middle)**, thumb opposition **(bottom)**.

minimal muscle twitch on the hand out of three trials, during an isometric contraction, and selected this measure as the intensity for the cTBS protocol (18). We established this number of trials for the active motor threshold definition in order to minimize the discomfort and fatigue associated with the voluntary contraction, since our patients were within the first days after stroke and this task was highly demanding for them. We performed sham stimulation by reducing the intensity to zero level stimulation and using a sham noise generator. All patients from both groups were naïve to TMS and reported perceived real stimulation.

Experimental design is illustrated in **Figures 1**, **2**. All measurements performed after the cTBS, namely EMG, EEG, and WMFT, were acquired within 1 h, which is believed to be the theoretical duration of the neurophysiological effects of cTBS (17).

Statistical Analysis

Statistical analysis was carried out on SPSS Statistics software v.24 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). For all data, we adopted a 95% confidence interval. Differences between experimental and control groups related to clinical and demographic data were assessed by Mann–Whitney *U*-test, for age, handedness, time-since-stroke onset, National Institutes of Health Stroke Scale at admission, and WMFT baseline measurements, and by the Fisher's exact test, for gender and lesion side. Friedman and Wilcoxon tests were computed to evaluate changes in WMFT, MEPs' amplitude, and mean power of brain rhythms, throughout the three time points (T0, T1, and T2).

RESULTS

Experimental and control groups were matched. They did not differ significantly regarding age ($U = 10.500$, $p = 0.730$), gender ($p = 0.524$), handedness assessed by Edinburgh Handedness Inventory (32) ($U = 12.500$, $p = 1.000$), lesion side ($p = 0.524$), time-since-stroke ($U = 10.000$, $p = 1.000$), score in the National Institutes of Health Stroke Scale ($U = 11.500$, $p = 0.881$), or WMFT at baseline (log performance time: $U = 10.000$, $p = 0.690$; FAS: $U = 12.000$, $p = 0.952$).

Magnetic Resonance Imaging

Magnetic resonance structural images were examined by a neuroradiologist, who confirmed the presence of an ischemic unilateral lesion and its location at the vascular territory of the middle cerebral artery.

Wolf Motor Function Test

WMFT log performance time, which included the duration for all the 15 tasks performed with the affected upper extremity, showed a non-significant reduction trend (Group E: $\chi^2 = 4.800$, $p = 0.124$; Group C: $\chi^2 = 0.500$, $p = 0.931$). We observed marginally significant score difference between pre- and post-intervention in Group E ($Z = -2.023$, $p = 0.063$).

Changes in FAS for the same tasks were not significant [experimental group (E): $\chi^2 = 3.125$, $p = 0.259$; control group: $\chi^2 = 2.286$, $p = 0.370$].

Results from the WMFT are illustrated in **Figure 3**.

Motor-Evoked Potentials

Differences were not statistically significant at any time point, concerning MEPs' amplitude of the affected (experimental group: $\chi^2 = 4.667$, $p = 0.194$; control group: $\chi^2 = 4.000$, $p = 0.167$) or the unaffected hemisphere (experimental group: $\chi^2 = 0.400$, $p = 0.954$; control group: $\chi^2 = 0.667$, $p = 0.944$), as observed in **Figure 4**.

Electroencephalography

Regarding the thumb opposition task, we found a statistically significant change of *beta* rhythm across the three assessment points, in the pre-movement and preparation for movement performed with the affected limb only in the real-stimulation group (Group E: $\chi^2 = 6.400$, $p = 0.039$, **Figure 5**; Group C: $\chi^2 = 0.667$, $p = 0.944$). Wilcoxon test detected, for this group, a trend toward a decrease in *beta* rhythm between T0 and T1, when preparing for the task with the affected limb (Group E: $Z = -2.023$, $p = 0.063$; Group C: $Z = -1.461$, $p = 0.250$). For movements of the unaffected thumb or of both thumbs simultaneously we did not detect significant changes ($p \geq 0.05$).

Concerning bilateral arm elevation, the Wilcoxon test identified a trend toward a significant increase in *beta* power from pre- to post-cTBS in the pre-movement and preparation (Group E: $Z = -2.023$, $p = 0.063$; Group C: $Z = -1.461$, $p = 0.250$), and at the early phase of movement execution (Group E: $Z = -2.023$, $p = 0.063$; Group C: $Z = 0.000$, $p = 1.000$), only in the experimental group. When assessing movements performed with each arm individually (affected or unaffected), differences were not observed following real or sham stimulation ($p \geq 0.05$).

Neither visual *alpha* (studied for the eyes condition) nor *mu* rhythm (quantified for the motor tasks) were significantly affected by the stimulation of M1 ($p \geq 0.050$ in both groups).

DISCUSSION

This interventional exploratory study is based on the hypothesis that applying an inhibitory TMS protocol to the unaffected hemisphere in stroke will release the lesioned hemisphere from such inhibition. The predicted increase in excitability might potentially help promote recovery (1, 2, 13).

Analyzing our findings, we observed that significant neurophysiological effects were obtained indeed only for the experimental group, post-cTBS, with no measure showing statistical effects for participants who received placebo stimulation. Even marginally significant effects were observed only for the former group.

Regarding motor rhythms, the thumb opposition task revealed significant differences across time measurements for the *beta* band, only for the experimental group, in the pre-movement and preparation for movements performed with the affected hand. A trend toward a significant decrease in *beta* power at T1, in Group E, was suggestive of an excitatory response to the protocol (increase in ERD) (22, 23) from the affected hemisphere, as expected. We also predicted to find changes in the *mu* rhythm, but we did not. Regarding the arm elevation task, we did not detect statistically significant differences following the application of cTBS. We suggest that it is possible that the effect was more pronounced in the thumb task partially because we stimulated the hand representation M1 as a motor hotspot. We also hypothesize that more complex thumb movements potentiate stronger activation of the motor areas (33) in the affected hemisphere, comparing with the unaffected hemisphere or with a healthy brain, leading to better detectability of TMS effects.

Interestingly, motor rhythms did not change significantly during arm elevation or thumb opposition of the unaffected limb alone, after stimulation, which indicates that the protocol can have a larger impact in the hemisphere contralateral to the stimulation thus potentially improving the lesioned hemisphere functional status. This finding was supported

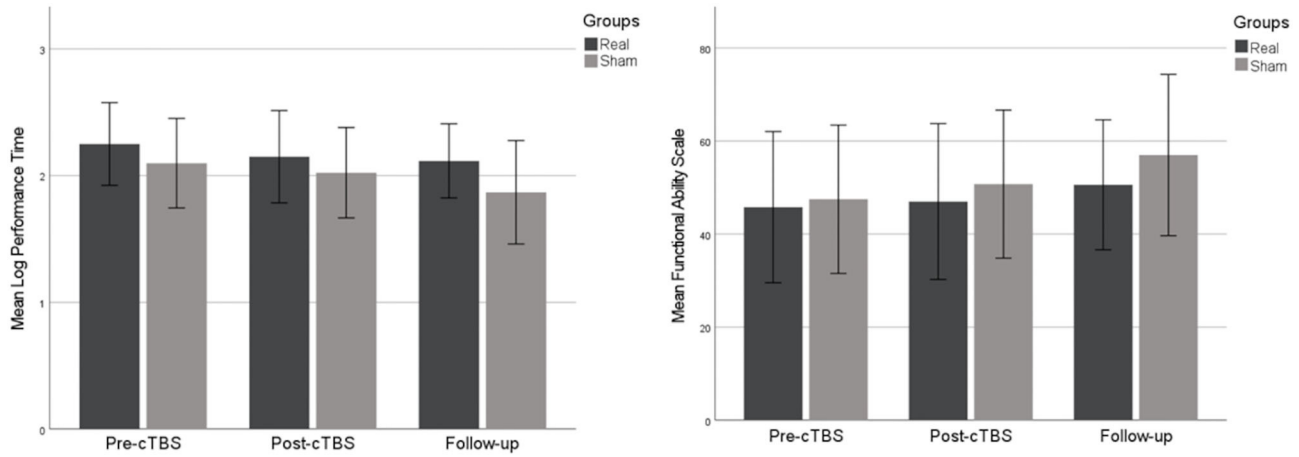

FIGURE 3 | Scores in the Wolf Motor Function Test log performance time **(left chart)** and functional ability scale **(right chart)**, throughout the three time points. Error bars depict ±1 SE.

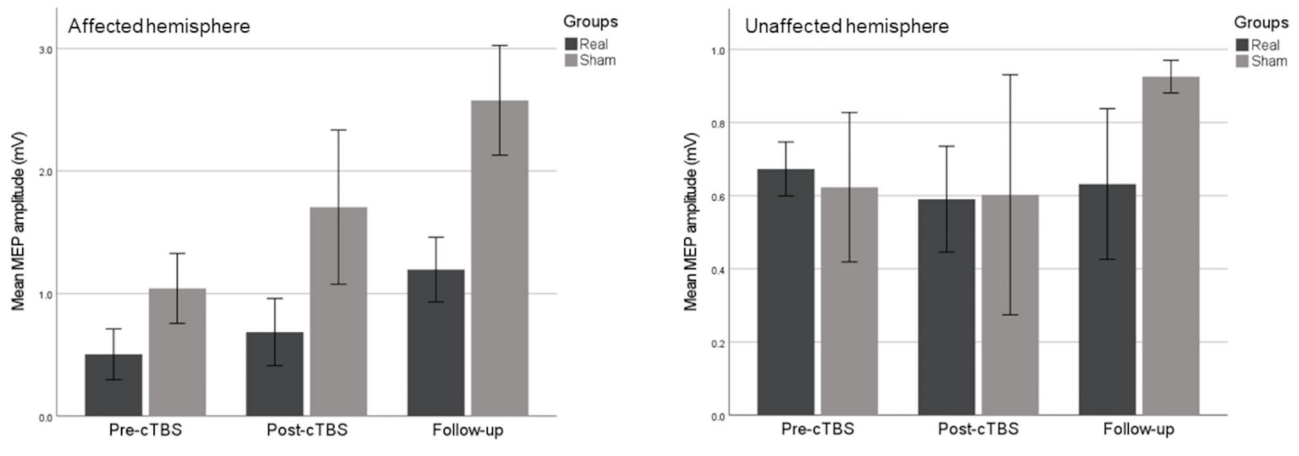

FIGURE 4 | Non-significant changes in motor-evoked potentials of the affected **(left chart)** and unaffected **(right chart)** hemispheres. Error bars show ±1 SE.

by our results in healthy individuals, where we found a significant impact of the cTBS protocol only on the contralateral hemisphere (18).

There is nevertheless an important distinction with the effects observed in healthy participants and subacute stroke patients, concerning the main aim of this study, which was to identify potentially beneficial neurophysiological effects. While in healthy subjects we had observed a significant and paradoxical inhibition of the contralateral hemisphere, for the arm elevation task, in stroke patients we found instead significant excitation expected from the above-mentioned conceptual framework, with thumb opposition. This suggests that changes in cortical excitability in response to distinct neuromodulation protocols may be task-dependent and, more importantly, might be different in health and in disease. We believe that this difference in the effects of cTBS when applied to stroke patients, in comparison with healthy controls, is due to the altered interhemispheric balance following the stroke event, which completely changes underlying physiology [as observed in a previous functional MRI study from our group (34)]. The idea that TMS effects might be influenced by the brain status, particularly the presence of a brain lesion, is highly relevant for neurorehabilitation approaches and warrants future studies to be conducted.

Visual *alpha*, quantified for the posterior electrodes, was not significantly changed by cTBS over M1, as expected.

Electromyographic motor output showed no significant differences in the peak-to-peak amplitude of motor-evoked potentials after stimulation. We consider that this absence of effect might be justified by distinct reasons, as reported and detailed in our previous study in healthy participants (18). Even though the intensity for the application of the cTBS protocol is customarily defined as a function of the active motor threshold, the voluntary contraction could possibly impact the neuromodulation, rendering no effects for the motor-evoked potentials (35, 36). Importantly, the large variability inherent to the measurement of MEPs may have precluded significant

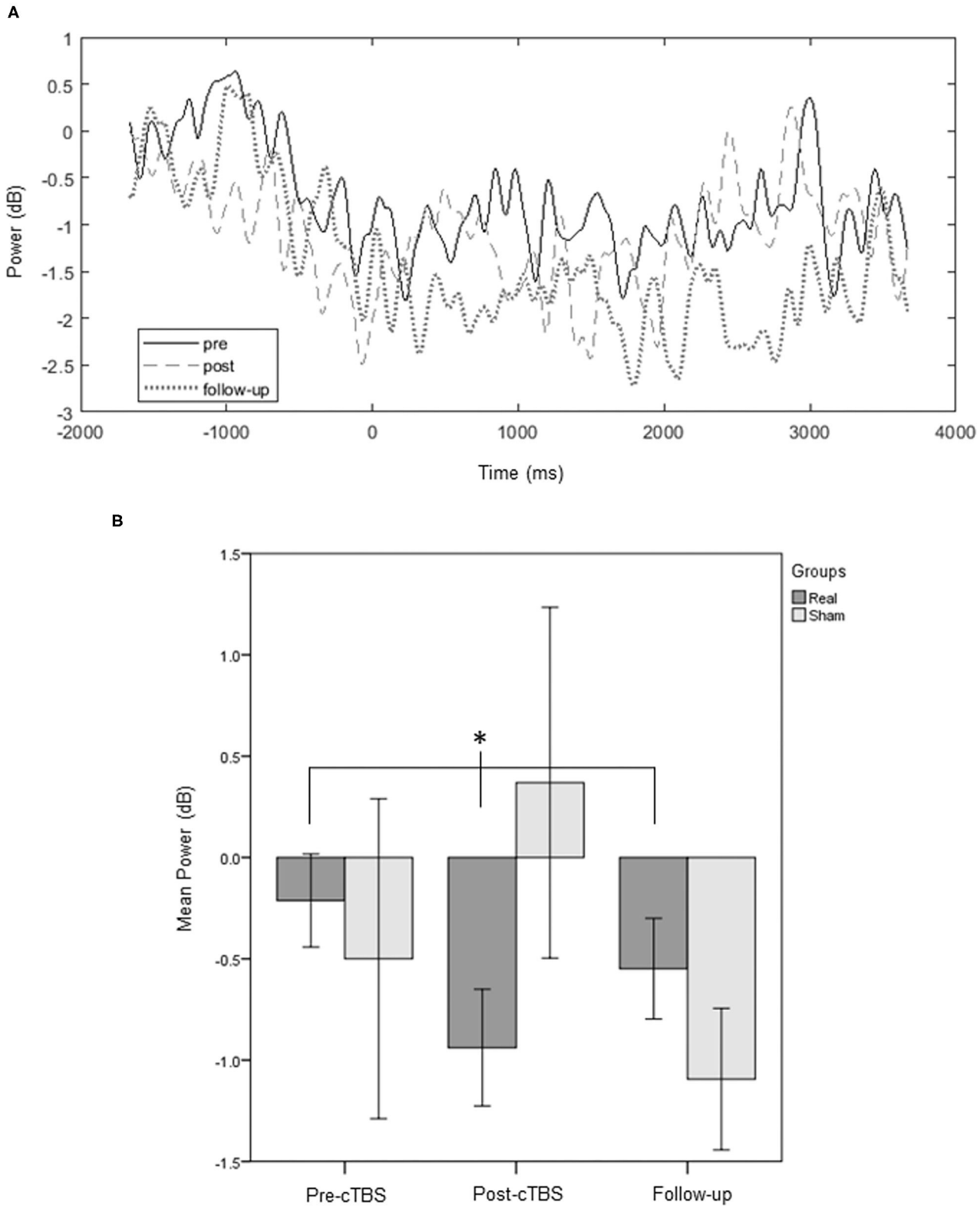

FIGURE 5 | Time-response plots of the mean *beta* power. A group average response of the ipsilesional motor area for an average of the channels of interest (FC3 or 4; FC1 or 2; C3 or 4; C1 or 2; Cz; CP3 or 4; CP1 or 2) is represented, for the experimental group, throughout the three assessment points. Pre-movement and preparation of the affected thumb opposition reveal changes induced by the protocol on *beta* power of the affected hemisphere **(A)**. Significant differences (*$p < 0.05$) are also illustrated in the bars chart **(B)**. Error bars represent ±1 SE.

changes to be observed. In fact, in opposition to MEPs, EEG oscillations are not predicted to be influenced by remote events such as spinal cord processes, and are thought to produce more consistent responses (37, 38), which might help explain why we have detected statistically significant effects of cTBS with EEG but not with EMG.

We only found trends concerning behavioral data, evaluated in this study by the WMFT of the affected upper extremity, which may be due to the fact that this study mainly aimed at a short-term physiological proof-of-concept in patients with a recent episode of stroke, at a subacute stage. We propose that more stimulation sessions would be needed to obtain significant improvements in the motor function, detectable by the WMFT.

The main limitation of this study is the small sample size, which requires the interpretation of the results to be cautious. The involvement of patients in the first days following the stroke event and the complexity of our study design that was highly demanding in this subacute stage precluded us from including a greater number of patients. Still, our findings provide preliminary evidence on a possible neurophysiological mechanism of action of TMS and, particularly, continuous theta burst stimulation, which might have a great impact in the neurorehabilitation of stroke patients, if supported by future studies conducted in a larger sample of patients.

The neurophysiology of subacute post-stroke patients was changed, consistently with the hypothesis that inhibitory cTBS over the unaffected hemisphere leads to increased excitation of the lesioned hemisphere. Continuous TBS may be useful in stroke neurorehabilitation by altering the ERS/ERD pattern and potentially improving the motor functions, when applied for several sessions. The results from this preliminary work encourage future clinical trials to study the neurophysiological responses to transcranial magnetic stimulation, in particular cTBS, in a specific disease context.

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 Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AD, RG, GCS, JS-F, FD, and MC-B researched literature and conceived the study. MC-B was involved in gaining ethical approval. MC-B and FD gained funding. AD, RG, GCS, and JS-F were involved in participants' recruitment. AD, RG, and ICD acquired the data. AD, RG, JC, and MC-B made a substantial contribution to data analysis and interpretation. AD wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content and approved the version to be published.

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Dependency in Activities of Daily Living During the First Year After Stroke

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Background: Dependency in personal activities of daily living (ADL) is a common short-term and long-term consequence of stroke and requires targeted rehabilitation. As the duration of hospital stay has become shorter in recent decades, early identification of patients who require rehabilitation has become vital. To our knowledge, no study has investigated whether ADL dependency in the very early stages after admission to the stroke unit can explain ADL dependency 3 and 12 months later. This knowledge would facilitate planning for very early discharge and patient-centered rehabilitation.

Objective: This study evaluated whether ADL dependency within 2 days after stroke could explain ADL dependency at 3 and 12 months after stroke.

Methods: This longitudinal cohort study included patients with stroke who were treated at a stroke unit in the Sahlgrenska University Hospital (Gothenburg, Sweden) between May 2011 and March 2016. The primary independent variable was ADL dependency at 36–48 h after admission to the stroke unit, which was assessed using a Barthel Index (BI) score of $\leq$90. The dependent variables were self-reported personal ADL dependency at 3 and 12 months after stroke. Binary logistic regression analyses were performed.

Results: Of 366 eligible patients (58% male; median age 71 years), a majority (76%) had mild stroke and 60% were ADL dependent 36–48 h after stroke. Univariable and multivariable logistic regression analyses showed that patients who were dependent within the first 2 days after stroke had higher odds for being dependent 3 months as well as 12 months after stroke.

Conclusion: The results indicated that dependency in personal ADL during the first 2 days can explain dependency at 3- and 12-month post-stroke. Therefore, early ADL assessments post-stroke can be used for understanding rehabilitation needs after stroke.

Keywords: activities of daily living, longitudinal studies, outcome assessment, stroke rehabilitation adherence, prognosis, p-ADL, cross validation (CV), logistic regression

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INTRODUCTION

Cerebrovascular diseases are amongst the most prevalent causes of disability (1). Although the age-adjusted rates of stroke are decreasing, the total number of strokes are increasing due to global population growth and aging populations (2, 3). Furthermore, the early stroke fatality rate is decreasing (4), leading to an increasing number of stroke survivors with stroke-related disability and years lived with disability (5). Early rehabilitation is the key in reducing the burden of stroke-related disability.

Activities of daily living refer to various tasks and activities that people perform on daily basis (6). They can be grouped into instrumental activities of daily living (e.g., shopping, paying the bills) and personal activities of daily living (referred to as ADL in this article e.g., eating, getting dressed). ADL dependency is a common consequence post-stroke and persists in 35% of stroke survivors during the first year after stroke (7). Increased disability after stroke has been linked to various factors, including older age (8), co-morbidity (8), impaired cognition (9), and stroke severity at onset (10). However, patients with mild stroke can also experience ADL dependency in everyday life (11) and have unmet rehabilitation needs (12). Hence, prognosis cannot be accurately estimated based on stroke severity alone.

Most of the recovery in ADL typically occurs within the first 6 weeks after stroke and is related to initial stroke severity (13, 14). In the later stages of stroke, there is generally no decline or improvement in ADL (15, 16). Studies have shown that patients with ADL dependency during the first week after stroke are also dependent at 6 months and 3 years after stroke (8, 17). However, the explanatory value of ADL assessment very early after stroke has not been thoroughly investigated. This is important as the length of stay in Swedish hospitals has decreased in recent decades (18). The current median length of hospital stay is 7 days (19). Patients with mild-to-moderate stroke can be discharged shortly after admission, resulting in a limited period for the assessment of rehabilitation needs and prognosis.

While very early ADL assessments are routinely performed in stroke units, it is unclear how the results of these assessments are related to long-term outcomes. The finding of a positive association between very early ADL assessments and ADL ability in the later stages of stroke would facilitate planning for patient-centered rehabilitation and early hospital discharge. Therefore, the present study evaluated whether ADL assessments within 2 days after admission to the stroke unit could explain dependency in personal ADL 3 and 12 months after stroke.

MATERIALS AND METHODS

Study Design

This longitudinal cohort study evaluated data from a research database of patients who were treated at one stroke unit in the Sahlgrenska University Hospital (SU) between May 2011 and March 2016 (20, 21). The SU is the largest hospital in western Sweden. It is a regional center for neurosurgery and thrombectomy. The research database was linked to the Swedish national stroke quality register, Riksstroke (22). Data pertaining to acute care parameters and self-reported outcomes at 3 and 12 months after stroke were collected. A statistician affiliated with the Riksstroke registry performed data linkage by using each patient's unique personal identification number. The data used for the present study did not contain personal identification numbers or other identifiable information.

The inclusion criteria comprised: confirmed stroke diagnosis according to the World Health Organization criteria; age $\geq$ 18 years; availability of ADL assessment results obtained within 36–48 h after admission to the stroke unit; and availability of the completed Riksstroke acute form. Data from patients who passed away during their hospital stay were not analyzed.

Ethics

The study complied with the Declaration of Helsinki and was approved by the Gothenburg Regional Ethical Review Board (http://www.epn.se/sv/goeteborg/om-naemnden/, reference number: 042–11, amendment: T966-17). The Swedish Data Protection Authority does not require informed consent for research use of registry data. In addition, the Personal Data Act (Swedish law #1998:204, issued April 29, 1998) allows medical chart data to be collected for clinical research and quality control purposes without written informed consent.

Data Availability Statement

According to the Swedish regulations (https://etikprovning.se/for-forskare/ansvar/), complete data cannot be made publicly available for ethical and legal reasons. However, researchers can submit requests for data to the principal investigator (contact: ks.sunnerhagen@neuro.gu.se).

Data Collection

Patients were screened for ADL dependency and cognitive impairment by occupational therapists working at the stroke unit at SU, within 36–48 h after admission. Data pertaining to the patients' initial neurological status (as assessed by physicians) and ischemic stroke classification were extracted from patients' medical charts. The Riksstroke acute form, which was completed by research nurses working at the stroke unit, was used to collect data regarding medical treatments (thrombolysis and thrombectomy), comorbidities, living conditions, and ADL dependency before stroke. Self-reported outcomes at 3 and 12 months were collected from the Riksstroke self-administered questionnaires that were sent to the patients.

Study Variables

The dependent variables comprised ability to perform personal ADL at 3 and 12 months after stroke. This was evaluated using self-administered patient questionnaires. Dependency in personal ADL was considered present based on a response indicating dependency in one or more of the following activities: mobility, using the toilet, and getting dressed or undressed.

The primary independent variable was ADL dependency, which was assessed using the Barthel Index (BI) (23) at 36–48 h after stroke. The BI score ranges from 0 to 100, with a higher score

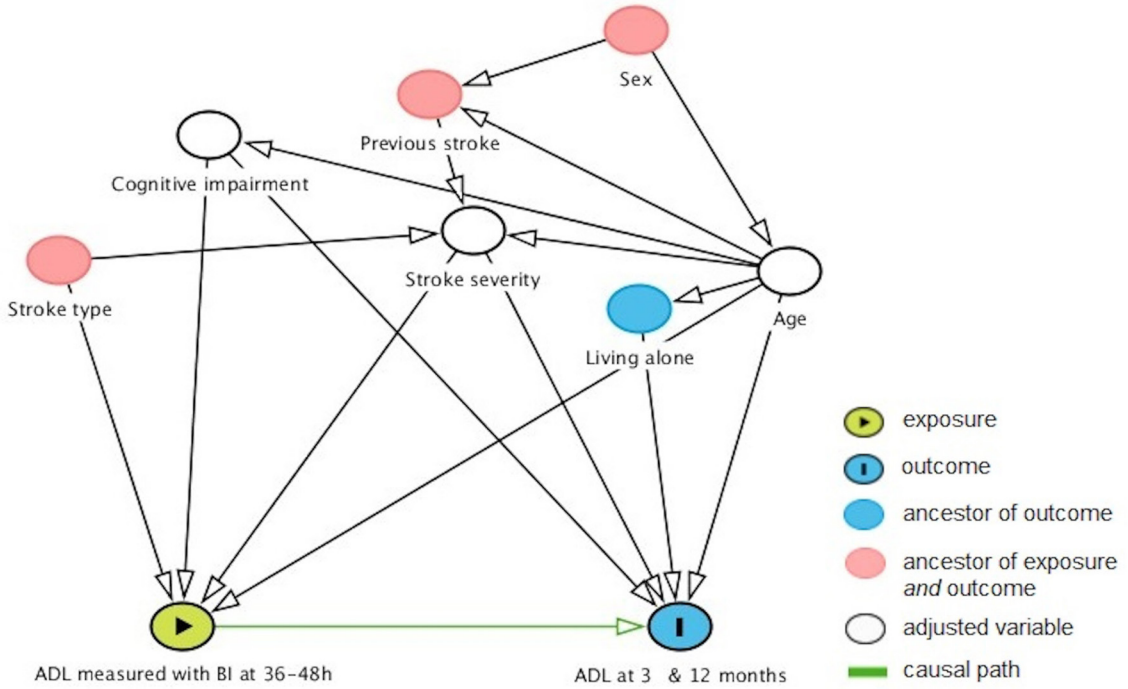

FIGURE 1 | Directed acyclic graph showing factors that might confound the relationship between early and later ADL outcomes. Age, stroke severity, and cognitive impairment were identified as the minimal sufficient adjustment set. ADL, activities of daily living; BI, Barthel Index.

indicating a higher level of ADL independence. ADL dependency is defined by scores of ≤90 (24).

Neurological symptoms were evaluated at admission to SU. The National Institutes of Health Stroke Scale (NIHSS) was used. NIHSS is a stroke scale with scores ranging from 0 to 42, where 0 indicates no neurological deficits (25). Mild stroke is identified based on scores of ≤3 (26). The Montreal Cognitive Assessment (MoCA) was performed within 36–48 h after admission to the stroke unit. The MoCA is a cognitive screening instrument with scores ranging from 0 to 30; a score of 30 indicates the absence of cognitive impairment (27), while a score of ≤25 indicates the presence of cognitive impairment (27). The following data were also collected: age at stroke onset, smoking status, diabetes, hypertensive treatment, accommodations and ADL dependency before the stroke, discharge destination following discharge from the stroke unit, length of hospital stay, and ischemic stroke classification according to the Oxfordshire (Bamford) Community Stroke Project classification system (28).

Statistics

The Mann–Whitney *U*-test for ordinal variables and Pearson's chi-squared test for nominal variables were used for drop-out analyses (baseline vs. 3 months follow-up and baseline vs. 12 months follow-up) and for comparing dependent and independent patients 36–48 h after admission to the stroke unit. McNemar's test was used to compare the following four dichotomized variables: ADL dependency before the stroke and 36–48 h, 3 months, and 12 months after the stroke.

Binary logistic regression analyses were performed to explain ADL dependency 3 and 12 months (coded as one) after stroke. The independent variables were selected based on previous studies (9, 29) and a discussion between the authors, who have a broad range of experience with stroke rehabilitation and research. The primary explanatory variable was baseline ADL dependency. A directed acyclic graph was used to select secondary explanatory variables (age, stroke severity, and cognitive impairment) for the analysis (**Figure 1**).

The assumptions of the binary logistic regression were assessed by exploring multicollinearity between independent variables with Spearman's rank correlation test. Correlation coefficients between variables $< \pm 0.7$ (30) were accepted for inclusion in the regression model.

Univariable and multivariable binary regression models were built for explaining dependency at 3 and 12 months after stroke. In the univariable models, only the primary exploratory variable, ADL, assessed with BI 36–48 h after stroke, was entered. In the multivariable models, both primary and secondary explanatory variables were entered (age, NIHSS, and MoCA, full scores). The results on the variable level are reported with odds ratio (OR), 95% confidence intervals (95% CI), and *p* values.

For the full model, the analyses were performed as follows:

- The binary logistic regression model was fitted.

- The Receiver Operating Characteristic (ROC) analysis was performed with dependent variables as a state variable and predicted probabilities as a test variable. The best threshold for optimal sensitivity and specificity was identified by evaluating the coordinates of the ROC curves.
- The regression model was fit again. We used the classification threshold identified from the previous step. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden's index (Yi, [sensitivity (%) + specificity (%) – 100]) of the model were reported.
- The AUC of the model was evaluated, AUC > 0.7 indicated a very good fit (30).

Cross-validation. The 10-fold cross-validation was performed. The dataset was divided into 10 folds. Each fold contained 90% of the data and 10% of the data was set as a holdout set. The cross-validation process was as follows:

- The model was fitted for a given 90% subset of data and identified the best threshold for balancing of Yi (sensitivity + specificity – 1).
- The threshold was further tested on the holdout set (10%). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Yi of the model were reported.
- The AUC of the model fitted on the holdout set was evaluated, AUC > 0.7 indicated a very good fit of the model (30).
- All abovementioned steps were performed for each fold separately and aggregated results were reported. Mean and standard deviation (S.D.) were used for reporting

TABLE 1 | Baseline characteristics of the 366 patients.

	Total ($n = 366$)	Barthel index		*p*-value
		≤90 ($n = 159$)	≥95 ($n = 207$)	
Female sex, *n* (%)	153 (42)	75 (47)	78 (38)	0.07[a]
Age in years, mean (standard deviation)	69 (15)	75 (13)	64 (15)	**<0.001**[b]
Living situation/condition pre-stroke, *n* (%)				
Lives at home without help	334 (91)	134 (85)	200 (97)	**<0.001**[a]
Independent in activities of daily living	354 (97)	151 (95)	203 (98)	0.10
Living alone	155 (42)	84 (53)	71 (34)	**<0.001**[a]
Risk factors, *n* (%)				
Diabetes	47 (13)	22 (14)	25 (12)	0.62[a]
Smoking	55 (16)	16 (11)	39 (20)	**0.02**[a]
Previous stroke	64 (18)	32 (21)	32 (16)	0.23[a]
Hypertensive treatment	184 (51)	91 (58)	93 (46)	**0.02**[a]
Stroke type, *n* (%)				0.68[a]
Hemorrhagic	32 (9)	15 (9)	17 (8)	
Ischemic classification[c], *n* (%)				
Total anterior circulation	3 (1)	2 (1)	1(0.5)	
Partial anterior circulation	54 (15)	29 (18)	25 (12)	
Posterior circulation syndrome	122 (33)	60 (38)	62 (30)	
Lacunar syndrome	155 (42.3)	53 (33)	102 (49)	
Treatments, yes, *n* (%)				
Revascularization (Thrombolysis or/and thrombectomy)	81 (23)	39 (25)	42 (21)	0.33[a]
Thrombolysis	72 (20)	37 (23)	35 (17)	
Thrombectomy	22 (6)	13 (8)	9 (4)	
Stroke-related outcomes, median (range[Q1–Q3])				
National Institutes of Health Stroke Scale[d]	2(0–19[0–3])	2(0–19[1–5])	1(0–14[0–2])	**<0.001**[b]
Barthel Index[e]	95(10–100[80–100])			
Montreal cognitive assessment[e]	24(3–30[20–27])	22(4–30[18–25])	25(3–30[23–27])	**<0.001**[b]
Length of hospital stay in days	7(0–43[4–11])	10(1–43[5–17])	5(0–20[4–8])	**<0.001**[b]
Discharge destination, *n* (%)				**<0.001**[a]
Own home	317 (87)	122 (77)	195 (94)	
Nursing home	15 (4)	11 (7)	4 (2)	
Another acute clinic	9 (2)	4 (3)	5 (2)	
Geriatric/rehabilitation clinic	25 (7)	22 (14)	3 (1)	

[a]Pearson's chi-squared test; [b]Mann–Whitney U test; [c]According to the Oxfordshire Community Stroke Project classification system; [d]Assessed at ≤24 h after admission; [e]Assessed within 36–48 h after admission. Bold text indicates significant results. Data were missing for the following variables, diabetes (seven patients, 2%), smoking (20 patients, 5%), previous stroke (eight patients, 2%), hypertensive treatment (seven patients, 2%), revascularization (seven patients, 2%), and National Institutes of Health Stroke Scale score (10 patients, 3%).

the results, as cross-validation results cannot be assumed as independent.

Analyses were performed using IBM SPSS (software version 26.0, IBM Corp., Armonk, NY. The software license was provided by the University of Gothenburg) and R software (R Core Team, version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria. R can be downloaded free of charge at https://cran.r-project.org/bin/windows/base/). The level of statistical significance was set at $\alpha = 5\%$.

RESULTS

Study Sample

Baseline data were available for 366 patients (**Figure 2**), 3-month outcome data were available for 325 patients, and 12-month outcome data were available for 285 patients. There were no significant differences between the groups with and without outcome data in terms of sex, age, stroke severity, and BI scores.

The 366 patients with baseline data (42% female) had a median age of 71 years (range 19–97 years) and typically had a mild stroke (76%, NIHSS score of ≤3) (**Table 1**). Patients with early ADL dependency (BI score of ≤90 within 36–48 h after stroke unit admission) were more likely to be older ($p < 0.001$), have experienced more severe strokes ($p < 0.001$), and have longer hospital stays ($p < 0.001$) (**Table 1**).

Dependency in ADL was evaluated for 253 patients with complete ADL data at four time points (**Figure 3**). Dependency was observed before stroke in 2% of patients and in 42, 13, and 11% of patients at 36–48 h, 3 months, and 12 months after stroke, respectively. The proportion of patients with ADL dependency was significantly increased at 36–48 h after admission (vs. before stroke, $p < 0.001$) and significantly lower at 3 months than at 36–48 h ($p < 0.001$) (**Figure 3**).

Explaining ADL Dependency After 3 Months

Multicollinearity was not observed between the independent variables. The univariable model showed that ADL, as assessed with BI within 36–48 h after admission, was associated with significantly increased odds of dependency after 3 months (OR: 0.96, 95% CI: 0.94–0.97. AUC of the model 0.76), (**Table 2**). The multivariable model confirmed that ADL within 36–48 h after admission was associated with increased odds of dependency after 3 months (OR: 0.96, 95 % CI: 0.94–0.98. AUC of the model 0.80) (**Table 2**). Psychometric properties of the models as well as cross-validated models are presented in **Table 2**.

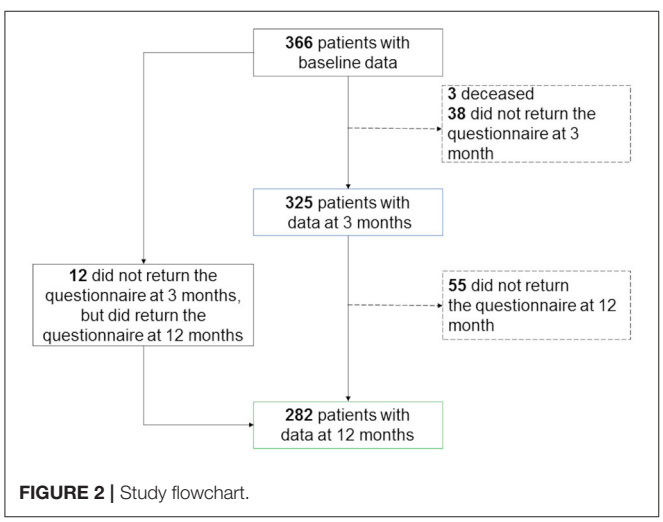

FIGURE 2 | Study flowchart.

Explaining ADL Dependency After 12 Months

Multicollinearity was not observed between the independent variables. The univariable model showed that ADL as assessed with BI within 36–48 h after admission was associated with significantly increased odds of dependency after 12 months (OR: 0.95, 95 % CI: 0.94–0.97. AUC of the model 0.77), (**Table 3**). The multivariable model confirmed that ADL within 36–48 h after admission was associated with increased odds of dependency after 12 months (OR: 0.96, 95 % CI: 0.94–0.98. AUC of the model 0.80), (**Table 3**). Psychometric properties of the models as well as cross-validated models are presented in **Table 3**.

DISCUSSION

The results of this study indicated that dependency in ADL within 36–48 h after admission to the stroke unit could explain dependency in personal ADL at 3 and 12 months after stroke. These results are in line with previous findings that patients with ADL dependency after stroke were more likely to have long-term dependency (8, 31); nevertheless, these prior studies did not conduct very early ADL assessments after admission. A few studies have examined early ADL

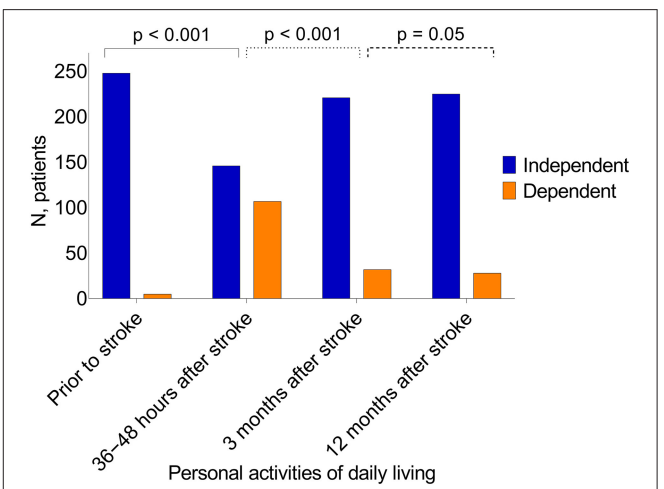

FIGURE 3 | Activities of daily living performance at four different time points. Statistics, McNemar's test, *P*-values indicate statistical difference between following time points, ADL dependency before the stroke and 36–48 h after stroke, 36–48 h and 3 months after stroke, 3 and 12 months after the stroke.

TABLE 2 | Explaining dependency in activities of daily living 3 months after stroke.

	B coefficient	OR (95% CI)	*P*-value	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Y_i	AUC
Univariable model				74.1(60.4–85.0)	64.1(57.9–69.9)	30.1(25.5–35.1)	92.2(88.2–94.9)	38.2	0.76(0.69–0.83)
ADL (BI, range 10–100p), per 5 gained points	−0.04	0.96(0.94–0.97)	<0.001						
Multivariable model				78.9(66.3–88.9)	72.4(66.5–77.8)	36.9(31.4–42.8)	94.4(90.8–96.6)	51.3	0.80(0.73–0.87)
ADL (BI, range 10–100p), per 5 gained points	−0.04	0.96(0.94–0.98)	<0.001						
Cognitive function (MoCA, range 3–30p), per 1 gained point	−0.10	0.91(0.85–0.97)	0.005						
Stroke severity (NIHSS, range 0–19 p), per 1 gained point	−0.03	0.97(0.87–1.07)	0.55						
Age (range 19–97), per 1 gained year	0.03	1.03(1.00–1.07)	0.03						

10 – fold cross-validation (90% training set and 10% testing set), mean ± S.D.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Y_i	AUC
Univariable model	0.57 ± 0.10	0.81 ± 0.24	0.27 ± 0.07	0.94 ± 0.06	0.38	0.76 ± 0.08
Multivariable Model	0.73 ± 0.07	0.70 ± 0.19	0.34 ± 0.07	0.92 ± 0.05	0.43	0.79 ± 0.11

Y_i, Youden's index (sensitivity (%) + specificity (%) – 100[or 1 for cross validated results]); ADL, personal activities of daily living; BI, Barthel index, the score in BI is increased with 5 points; MoCA, the Montreal Cognitive Assessment; NIHSS, the national institutes of health stroke scale; BI and MoCA were administered 36–48 h after admission to the stroke unit. NIHSS, hospital admission point; BI and MoCA, a higher score indicates better outcome; NIHSS, a higher score indicates worse outcome; The results of tuned univariable and multivariable logistic regression models and 10-fold cross validation performed per respective model.

TABLE 3 | Explaining dependency in personal activities of daily living 12 months after stroke.

	B coefficient	OR (95% CI)	*P*-value	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Y_i	AUC
Univariable model				78.6(63.2–89.7)	63.3(56.8–69.4)	27.5(23.2–32.3)	94.3(90.3–96.8)	41.9	0.77(0.70–0.85)
ADL (BI, range 10–100p), per 5 gained points	−0.04	0.95(0.94–0.97)	<0.001						
Multivariable model				75.0(58.8–87.1)	71.9(65.6–77.6)	31.6(26.0–37.6)	94.3(90.6–96.6)	46.9	0.80(0.72–0.87)
ADL (BI, range 10–100p), per 5 gained points	−0.04	0.96(0.94–0.98)	<0.001						
Cognitive function (MoCA, range 3–30p), per 1 gained point	−0.06	0.94(0.87–1.01)	0.10						
Stroke severity (NIHSS, range 0–19 p), per 1 gained point	0.03	1.03(0.92–1.15)	0.62						
Age (range 19–97), per 1 gained year	0.04	1.04(1.01–1.08)	0.02						

10 – fold cross-validation (90% training set and 10% testing set), mean ± S.D.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Y_i	AUC
Univariable model	0.57 ± 0.15	0.70 ± 0.40	0.22 ± 0.17	0.95 ± 0.06	0.27	0.76 ± 0.11
Multivariable Model	0.70 ± 0.09	0.69 ± 0.32	0.29 ± 0.19	0.94 ± 0.06	0.39	0.80 ± 0.12

The results of tuned univariable and multivariable logistic regression models and 10-fold cross validation performed per respective model. Y_i, Youden's index (sensitivity (%) + specificity (%) – 100[or 1 for cross validated results]); ADL, personal activities of daily living; BI, Barthel index, the score in BI is increased with 5 points; MoCA, the Montreal Cognitive Assessment; NIHSS, the national institutes of health stroke scale; BI and MoCA were administered 36–48 h after admission to the stroke unit. NIHSS, hospital admission point; BI and MoCA, a higher score indicates better outcome; NIHSS, a higher score indicates worse outcome.

assessments for explaining long-term dependency; while their findings support our results, these studies evaluated patients with more severe strokes and greater ADL dependency at baseline (17, 32).

Performance and performance repertoire of activis of daily living is formed during the lifetime. When it comes to personal ADL, the performance becomes automatized during the lifetime, as activities are performed on daily basis from the very early age. This means that the cognitive and physical demanand are different. Due to automatization, the cognitive demand on personal ADL might be samwhat low, while physical demand still remains high.

We found that cognitive impairment was a significant explaining factor of ADL dependency 3 months after stroke, which is consistent with prior reports (9, 33). Cognitive impairment is a common sequalae after stroke and can persist even after seemingly successful neurological recovery. It can affect ADL performance, especially in the early stages after stroke. However, cognitive functions may exhibit long-term improvements (34), and patients may develop compensatory strategies for managing ADL. Moreover, in our study ADL comprised personal activities of daily living, such as mobility, using the toilet, and getting dressed and undressed. These tasks generally have low complexities as performance has been mastered during the lifetime (35). Hence, cognitive demand can be low. Taken altogether, these factors may explain the lack of a significant relationship between cognitive impairment and ADL dependency at 12 months after stroke.

The present study also revealed that older age significantly explained ADL dependency at 3 and 12 months after stroke; this is supported by the results of previous studies (8, 10). This relationship may be linked to typical age-related decreases in physical ability, which are thought to be associated with both aging and a higher number of comorbidities (36).

We found that stroke severity assessed with NIHSS did not explain ADL dependency at 3 or 12 months; this conflicts with previously reported results (10, 37). However, these studies had substantially higher median stroke severity values, while patients in our study had predominantly mild strokes (19). Thus, accurate explanation of ADL dependency in the later stages after stroke may not be possible if it is solely based on the NIHSS in a population in which most strokes are mild (19). Moreover, very early NIHSS might be an insignificant explanatory variable for stroke-related outcomes, as many people experience good neurological recovery after reperfusion treatment (38). In addition, the results of the present study indicated that while the proportion of patients with ADL dependency at 3 months was significantly lower than that at baseline, there was no significant difference between 3 and 12 months. This seems to support the belief that recovery primarily occurs early after stroke (13, 14).

The present study has several strengths and limitations. First, we did not have access to complete data regarding all variables, as we evaluated data from a national registry (22) and a research database (20). Second, the dependent variables (ADL dependency at 3 and 12 months after stroke) were based on self-reported data, and non-responders were excluded from the regression analyses. Although this exclusion may have resulted in selection bias, drop-out analyses revealed no significant differences in terms of baseline characteristics (e.g., age, sex, stroke severity, and BI score). Moreover, excluded patients did not differ from included patients in terms of age (according to the Swedish dementia registry, the median and mean age at first dementia diagnosis is 80 years). In addition, the severity of cognitive impairment, as well as stroke severity was not that high in the study sample. Therefore, there is a low probability that dropout could be explained due to dementia. The BI was used to assess ADL at baseline. While this tool is considered valid and reliable for evaluating stroke patients, it may have a ceiling effect in an acute care setting (39). In this study, four binary logistic regression models were built. Sensitivity, Specificity, PPV, and NPV were evaluated under cross-validation, where the threshold value was selected to optimize Y_i. The number of variables in our logistic regression models were restricted by the fact that our sample had low proportions of ADL dependency at 3 and 12 months, similarly to the general population of Swedish stroke patients. A larger sample size might have permitted more variables to be used in the models; however, variable selection would be dependent on the algorithm of the binary regression analyses. As variable selection was based on a directed acyclic graph, which was based on clinical reasoning and prior studies, the results of the present study would be of high clinical relevance.

CONCLUSION

The results of this study indicated that ADL dependency within the first 2 days after stroke may explain dependency in personal ADL 3 and 12 months later in a group of Swedish patients. These results, in addition to stroke severity and ADL at discharge, may help to increase understanding regarding rehabilitation needs and follow-up for patients with minor strokes, as their hospital stays have typically become shorter in recent decades. The external validation of the study results is recommended.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because according to the Swedish regulations (https://etikprovning.se/for-forskare/ansvar/), complete data cannot be made publicly available for ethical and legal reasons. However, researchers can submit requests for data to the principal investigator (contact: ks.sunnerhagen@neuro.gu.se). Requests to access the datasets should be directed to Katharina S. Sunnerhagen, ks.sunnerhagen@neuro.gu.se.

ETHICS STATEMENT

The study was approved by the Gothenburg Regional Ethical Review Board (http://www.epn.se/sv/goeteborg/om-naemnden/, reference number: 042–11, amendment: T966-17). The Swedish

Data Protection Authority does not require informed consent for research use of registry data. In addition, the Personal Data Act (Swedish law #1998:204, issued April 29, 1998) allows medical chart data to be collected for clinical research and quality control purposes without written informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HE: analysis and interpretation of the data and drafting of the manuscript. TA: acquisition of data, conceptualization of the study, analysis, interpretation of the data, and revising the manuscript for intellectual content. LR: acquisition of data, conceptualization of the study, and revising the manuscript for intellectual content. KS: design or conceptualization of the study, interpretation of the data, and revising the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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OPINION
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Recovery After Stroke: New Insight to Promote Brain Plasticity

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Keywords: brain plasticity, recovery, stroke, trophic factors, stem cell, extracellular vesicles

INTRODUCTION

The recovery of the patient is the goal of the neuroscientists after a stroke. To achieve this recovery, there is a crucial need for increasing the understanding of the pathophysiological mechanisms that spontaneously engage early after stroke, which involve excitotoxicity, free radical damage, increased glutamate concentrations, and inflammation, leading to cell death. To assume that only neurons are vulnerable to these pathophysiological responses is simplistic. Stroke affects all components of the neurovascular unit, which consists of endothelial cells, pericytes, neurons, glial cells, white matter fiber tracts, myelin, and extracellular matrix proteins. It is, therefore, important to focus on brain protection as a whole rather than neuroprotection in isolation (1).

In the last 50 years, we have gained significant insights into the molecular mechanisms of recovery after stroke, in addition to the damage mechanisms. Due to its plasticity, the brain has the ability to reorganize its function and structure, which involves processes of self-protection and self-repair. Brain plasticity is a very complex process that involves adaptive structural and functional changes in the brain, including neurogenesis, synaptogenesis, angiogenesis, oligodendrogenesis, and astrogliosis modulation, and promotes collateral circulation, processes that begin immediately after stroke (2–4). Such is the self-repair ability brain that the stroke-induced neurogenesis is not only limited to the subventricular zone and hippocampal dentate gyrus. It has also been revealed that several additional areas of the brain promote mammalian adult neurogenesis, which include the hypothalamus, striatum, substantia nigra, cortex, and amygdala (5). The neural stem cells of the neurogenic areas generate new neural cells that migrate to the lesion site and become mature neurons, orchestrating neurological repair through nerve repair, neuron polarization, axonal sprouting and pruning, neurite outgrowth, and myelin repair, promoting post-stroke recovery (4). However, in the unfavorable microenvironment that occurs in the lesion, most new cells do not survive (4). Given that this self-repair capacity is limited, there has been a growing interest in the potential for brain plasticity-inducing interventions to enhance post-stroke recovery through rehabilitation, trophic factors, cell therapy, and extracellular vesicles. These therapeutic approaches currently hold great promise by targeting the mechanisms involved in brain plasticity (2, 6–8) (**Figure 1**). The beneficial effects of rehabilitation therapies in stroke recovery are well-known (9), although there are still certain aspects to be clarified, such as the optimal time to start rehabilitation, as well as its intensity and duration. Other approaches that involve brain stimulation, such as transcranial magnetic and electrical stimulation, can enhance recovery and post-stroke plasticity (10), and innovations with exoskeletons and brain-machine interfaces (11) have opened up new research lines. However, we would like to focus on other novel and promising strategies, such as the administration of trophic factors, stem cells, and extracellular vesicles.

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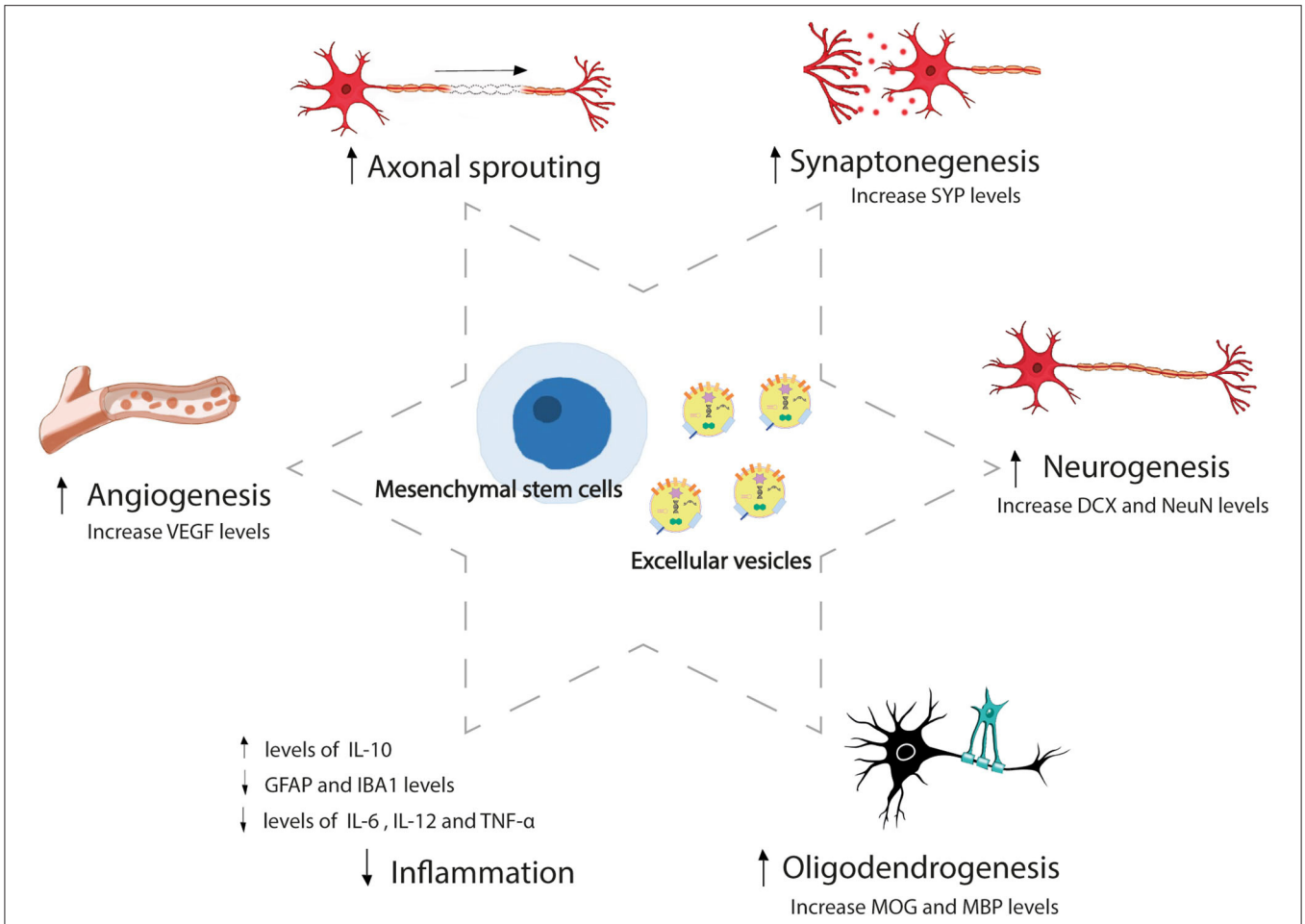

FIGURE 1 | Mesenchymal stem cell and extracellular vesicles-induced brain repair process after stroke. Mesenchymal stem cells and extracellular vesicles administration-induced brain plasticity that involves adaptive structural and functional changes, including angiogenesis, axonal sprouting, synaptogenesis, neurogenesis, oligodendrogenesis, and inflammation modulation after stroke. SYP, synaptophysin; DCX, doublecortin; NeuN, neuronal nuclear protein; MOG, myelin-oligodendrocyte glycoprotein; MBP, myelin basic protein; IL, interleukin; GFAP, glial fibrillary acidic protein; IBA, ionized calcium-binding adapter molecule; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

TROPHIC FACTORS AS THERAPEUTIC STRATEGY TO PROMOTE BRAIN PLASTICITY

In recent years, trophic factors have generated a great deal of interest in the clinical context, given that their administration is not restricted to a narrow therapeutic window. Several trophic factors, including erythropoietin, brain-derived neurotrophic factor, granulocyte-colony-stimulating factor, vascular endothelial growth factor, fibroblast growth factor, epidermal growth factor, and heparin-binding epidermal growth factor, have anti-inflammatory and anti-excitotoxic protective properties and have demonstrated efficacy in promoting neurogenesis and angiogenesis, stimulating progenitor cell proliferation, preventing blood-brain barrier (BBB) disruption and ultimately promoting functional recovery in experimental stroke models (12–15). However, a number of these approaches were lost in translation from a bench to a bedside (14, 15), while others have not yet been tested in clinical trials.

CELL THERAPY: THE FACTORY OF TROPHIC FACTORS AND KEY MOLECULES TO IMPROVE RECOVERY

But why settle for administering a single factor when we can administer the whole arsenal? This is where stem cell therapy plays an important role. Stem cells can secrete various trophic factors and key molecules, promote brain plasticity, and reduce overall inflammation. In particular, mesenchymal stem cells (MSCs) from bone marrow or adipose tissue have demonstrated efficacy in experimental animal stroke models (16–23). These positive findings are translated to clinical trials, where MSCs and other cells (such as bone marrow mononuclear cells) have demonstrated safety in patients with stroke (24–30) and even

efficacy in promoting improvement in white matter injuries at 1 year (31). Perhaps, one of the most stimulating findings in stem cell translational research is the discovery of an abundant quantity of MSCs within adipose tissue. Adipose tissue-derived MSCs (AD-MSCs) are of special interest, not only due to their abundance but also their relative ease of obtention through procedures such as liposuction and abdominoplasty, which obviate the ethical concerns with embryonic MSCs. Due to immunoprivileged characteristics of this cell type, allogeneic administration is possible, in our opinion (32). Treatment can, therefore, be administered at an early stage, which is crucial for a disease where delays result in irrevocable loss of brain function. The administration of AD-MSCs in the acute phase could inhibit the aforementioned pathophysiological mechanisms that are activated early after stroke, thereby participating not only in the repair processes of the neurovascular unit but also in its protection. In terms of clinical feasibility, the intravenous route for delivering AD-MSCs is attractive, given its low invasiveness, low risk, and greater comfort for the patient. Using this route, AD-MSCs are unable to reach the brain due to their lack of ability in crossing the BBB; however, they exert their beneficial therapeutic actions by delivering their secretome from the peripheral organs where they are confined (19). MSCs exert their action by the release of key molecules or extracellular vesicles (EVs) by paracrine effects (33), rather than through differentiation to replace damaged neurons (16, 18).

EXTRACELLULAR VESICLES: THE NOVEL STRATEGY TO ENHANCE BRAIN RECOVERY

Extracellular vesicles are released from all cell types, harbor important molecules such as proteins, DNA, lipids, mRNAs, and microRNAs, and participate in cell-to-cell communication. EVs can act as an active principle promoting several mechanisms of recovery after stroke, including brain plasticity. It has been shown that the intravenous administration of MSC-derived EVs promotes functional recovery and brain plasticity in an ischemic stroke rat model (34–37). Moreover, our group found that an intravenous administration of EVs-improved outcomes by promoting the processes involved in white matter repair in subcortical stroke in rats (35). Other authors have also shown that EVs induce higher axonal density and neurite remodeling (34), new formation of endothelial cells (36), sprouting of new capillaries, and higher endothelial integrity (37). MSC-derived EVs are, therefore, a promising approach for repairing the components of the neurovascular unit to promote overall post-stroke recovery (38, 39).

MSC-derived EVs are able to go one step farther than MSCs as a therapeutic strategy, given that MSC-EVs can cross the BBB, resolve cell-related problems, such as immune compatibility, tumor formation, and vascular occlusion, and can be stored in hospital settings without the need for toxic cryopreservative agents, offering an approach for acute ischemic stroke. Due to their small size, MSC-EVs can be saved from phagocytosis by macrophages. In addition, selective manipulation of their cargo by bioengineering can lead to individualized medicine (40, 41). There is, currently, only one ongoing clinical trial aimed at assaying the efficacy of the allogeneic administration of MSC-derived EVs enriched by miR-124 for improving the recovery of patients with acute ischemic stroke, registered in clinicaltrials.gov (Identifier: NCT03384433). A previous study using an animal model of stroke demonstrated that the administration of EVs loaded with miR-124 promoted cortical neural progenitors and neurogenesis (42). These functions of the microRNA content of EVs make them important not only as treatment but also as biomarkers. We showed that circulating EVs from patients with stroke contain miRNA and proteins related to risk factors and etiology, post-ischemic immune response, endogenous protection, and angiogenesis (43). We also observed differences in the levels of the microRNA content of EVs according to the topography of the stroke (subcortical and cortical-subcortical ischemic stroke) and related to improved recovery after stroke (44). Given the progress of research on EVs, further information on brain-derived EVs under stroke conditions is necessary (45). The content of EVs can be used as biomarkers that improve our understanding of the mechanisms by which EVs act in stroke to help develop new therapeutic strategies and find new molecular targets for this neurological disease.

DISCUSSION

The experimental studies in animal model and clinical trials have indicated that intravenously administered MSC therapy seems to be a promising therapeutic strategy after stroke (16–23, 26–28, 30). However, there are still some unresolved issues that have to be investigated such as the most appropriate administration timing, the doses required for successful recovery (46), and the dose regimen (single-dose or repeat-doses) that reach the higher threshold of brain repair after stroke. Likewise, the limitations of cell therapy will be determined by the results of clinical trials.

Moreover, MSC-derived EVs have some important advantages that can be exploited when translating a therapeutic strategy for stroke. EVs provide a great feature as a drug delivery system, given their ability to cross the BBB (40). Thanks to the development of delivery system technologies, MSC-derived EVs can be engineered and designed to carry specific therapeutic molecules (47) according to brain tissue repair needs, avoiding molecules that could induce adverse effects, moving toward personalized medicine.

Beyond the proven beneficial outcomes with the MSC-derived EV treatment in experimental animal models of stroke (34–39), many aspects are yet to be resolved about the production of EVs for their use in clinical practice, such us large-scale production, conditions in different physiologically environments, and standardized experimental protocol for extracting EVs to provide batch uniformity according to GMP regulations (40, 48, 49).

In conclusion, we are facing a disease that has a high incidence and prevalence and results in major disability. However, we are also finding new and promising therapeutic options, such as trophic factors, cell therapy, and EVs that can positively

contribute to stroke recovery by improving brain plasticity. For EVs, their ability to cross the BBB and their editable cargo provide live information on molecules that participate in damage and post-stroke repair, which could lead to personalized and precision medicine.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Functional Recovery and Serum Angiogenin Changes According to Intensity of Rehabilitation Therapy After Stroke

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Background: Rehabilitation is still the only treatment available to improve functional status after the acute phase of stroke. Most clinical guidelines highlight the need to design rehabilitation treatments considering starting time, intensity, and frequency, according to the tolerance of the patient. However, there are no homogeneous protocols and the biological effects are under investigation.

Objective: To investigate the impact of rehabilitation intensity (hours) after stroke on functional improvement and serum angiogenin (ANG) in a 6-month follow-up study.

Methods: A prospective, observational, longitudinal, and multicenter study with three cohorts: strokes in intensive rehabilitation therapy (IRT, minimum 15 h/week) vs. conventional therapy (NO-IRT, <15 h/week), and controls subjects (without known neurological, malignant, or inflammatory diseases). A total of seven centers participated, with functional evaluations and blood sampling during follow-up. The final cohort includes 62 strokes and 43 controls with demographic, clinical, blood samples, and exhaustive functional monitoring.

Results: The median (IQR) number of weekly hours of therapy was different: IRT 15 (15–16) vs. NO-IRT 7.5 (5–9), $p < 0.01$, with progressive and significant improvements in both groups. However, IRT patients showed earlier improvements (within 1 month) on several scales (CAHAI, FMA, and FAC; $p < 0.001$) and the earliest community ambulation

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achievements (0.89 m/s at 3 months). There was a significant difference in ANG temporal profile between the IRT and NO-IRT groups ($p < 0.01$). Additionally, ANG was elevated at 1 month only in the IRT group ($p < 0.05$) whereas it decreased in the NO-IRT group ($p < 0.05$).

Conclusions: Our results suggest an association of rehabilitation intensity with early functional improvements, and connect the rehabilitation process with blood biomarkers.

Keywords: angiogenin, intensive therapy, rehabilitation, biomarker, recovery

INTRODUCTION

Stroke is a leading cause of disability, with more than 16.9 million people having a first stroke every year, 5.9 million stroke-related deaths, and a calculated loss of 102 million Disability-Adjusted Life-Years (1, 2). In the last decades, there has been a marked decrease in stroke mortality as a result of improved primary care interventions, better neuroimaging diagnosis, and improved stroke management (with specialized stroke units, thrombolytic, and endovascular treatments) (3). Beyond this, the evidence-based approach to achieve functional improvement in daily-life activities and reduce disabilities in stroke survivors has been implementing personalized rehabilitation programs with multidisciplinary teams working under the physiatrist's supervision (4). Recently, an interesting debate has taken place on the need to implement early rehabilitation interventions (first 24 h) which might worsen the outcome at high doses but might be beneficial with high frequency (5, 6), highlighting the need for a fine-tuning of the interventions. Additionally, other studies have demonstrated that high-intensity therapies with a larger amount of hours are determinant for a good prognosis (7, 8), although the standard time and dose to achieve improvements is planned individually (9, 10). This is the case for intensive rehabilitation therapy (IRT), defined as rehabilitation therapy of more than 15 h per week by a physical therapist, an occupational therapist, and/or a speech therapist, with close monitoring of patient progress to adjust the program (11). Other clinical evidence has shown that with high-quality, high-dose, high-intensity upper limb neurorehabilitation during a 3-week (90 h) program clinical improvements in upper limb deficits and activity can be achieved in chronic stroke patients starting more than 6 months after the event (12). And in a retrospective analysis comparing this cohort with a conventional low-intensity treatment cohort it is described that, despite responsiveness of both treatments, the high-intensity approach showed a consistent higher impact at all stages post-stroke (13).

Neural plasticity and vascular remodeling are assumed as the basis of post-stroke recovery as reported in preclinical models (14, 15). In this context, understanding the role of specific biomarkers in pathophysiological brain changes might serve as a bridge between the fundamental science and patients' clinical management, including monitoring rehabilitation goals and the duration of the intervention (16, 17). In this regard, we focused on angiogenin (ANG), a member of the ribonuclease superfamily that acts as a potent angiogenic protein triggering cell proliferation, migration, or survival (18, 19), which has been recently identified as a repair-associated factor in post-stroke rehabilitation by our group (15).

In this multicenter study we aimed at studying the influence of the rehabilitation therapy intensity received after stroke on the functional improvements, and for the first time studying the response of a blood biomarker in response to the dose of therapy received during post-stroke recovery.

MATERIALS AND METHODS

Study Cohorts

This study comprises a cohort of 62 post-stroke patients recruited in two periods within the prospective, observational, longitudinal, and multicenter SMARRTS study (Studying Markers of Angiogenesis and Repair during Rehabilitation Therapy after Stroke): ischemic stroke patients under IRT (between February 2014 and May 2015) (15) and both ischemic and hemorrhagic stroke patients under IRT or conventional rehabilitation therapy (between February 2017 and June 2018) from seven Spanish hospitals. Inclusion criteria were: first-ever ischemic or hemorrhagic stroke, age $\leq$ 75 years, modified Rankin scale (mRS) $\leq$ 2 before stroke and mRS post-stroke from three to five, stable medical condition, and the signature of informed consent. The exclusion criteria were: previous stroke or transient ischemic attacks, malignant infarct, global aphasia, hemorrhage from arteriovenous malformations or cerebral aneurysms, previous cognitive decline, or recent infectious, inflammatory or malignant disease.

The study was approved by all the clinical research ethics committee sites [HUVH PR(IR)317/2013-PR(IR)346/2016, PI16/00981/CEI:PI-17-056, Comité de Ética de Investigación de A Coruña-Ferrol 2017-125, Corporació Sanitària Parc Taulí de Sabadell 2017521, Hospital Universitario Politécnico La Fe 2016/0727, Euskadi PI2016168]. Healthy subjects (43) without known neurological, malignant, infectious, or inflammatory diseases were enrolled as the control cohort. All subjects signed informed consent following the Declaration of Helsinki.

STROBE guidelines for reporting observational studies were followed in this study (20).

Rehabilitation Interventions

All included patients followed a comprehensive rehabilitation program, including physiotherapy, occupational therapy, speech

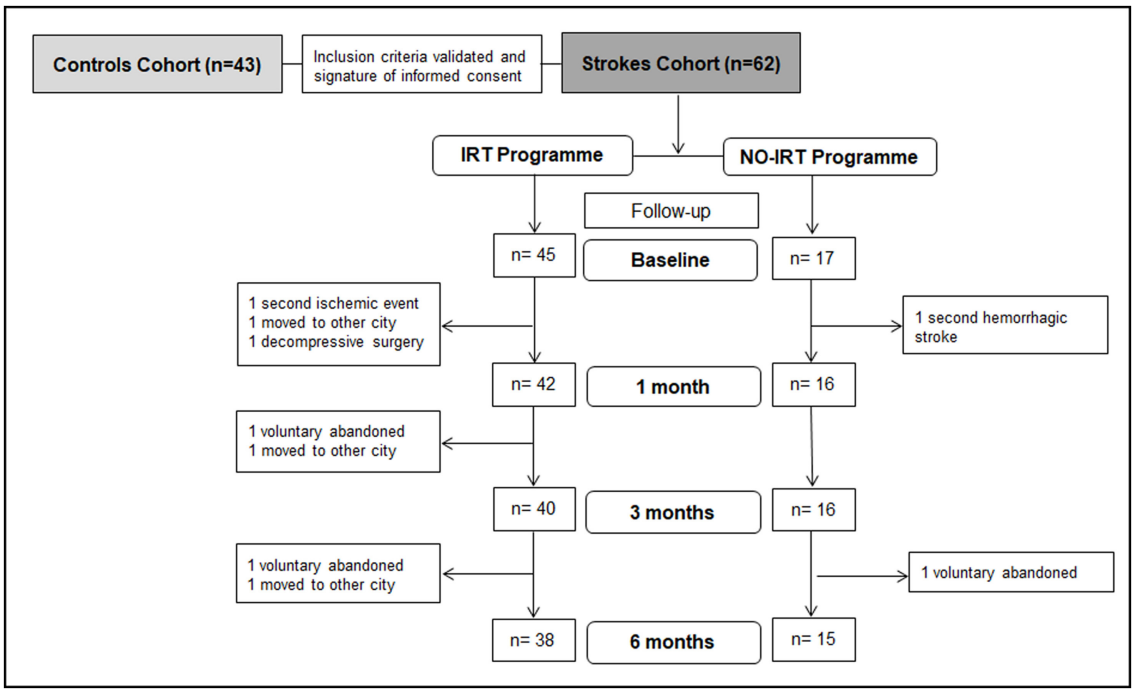

FIGURE 1 | Study design. Scheme showing the studied cohorts and follow-up visits when a battery of tests to assess motor and functional status was conducted together with blood samples extraction. Controls were recruited in a unique inclusion visit when blood samples were obtained.

therapy, and/or neuropsychology, however, some centers offered intensive rehabilitation therapies whereas others followed more conventional programs. For the IRT program only subacute post-stroke patients with moderate/severe disabilities in two or more areas (gait, transfers, activities of daily living, swallowing and/or communication), with mRS previous to stroke ≤ 2 who can participate in a minimum of 3 h of comprehensive therapy per day (5 days/week) were included, according to institutional guidelines (21). When the clinical stroke condition was stable patients started mobilizations followed by a comprehensive rehabilitation program defined as IRT ($\geq$15 h per week) or NO-IRT (conventional therapy with $<$15 h per week). For all centers, a physiatrist designed an initial rehabilitation program according to patients' impairments, and all patients were treated in inpatient rehabilitation units or day-hospital facilities. Rehabilitation continued until completion of a minimum of the proposed objectives or when functional stability was achieved. For further objectives, patients continued an outpatient rehabilitation program.

Study Protocol and Functional Follow-Up

A total of 62 patients were initially included in the study. However, 3 of them voluntarily abandoned the study, and 6 were withdrawn from the study due to the following: decompressive cranial surgery (1), secondary aneurismal hemorrhagic stroke (1), a second ischemic event (1), or moving to other cities (3). This reduced the number of subjects in the follow-up analysis, as represented in the flow diagram in **Figure 1**. A baseline inclusion visit was conducted before the rehabilitation program started by an experienced physiatrist who collected demographic, clinical, and stroke-related data together with a battery of tests to assess motor and functional status (details in the **Supplementary Methods**). During the baseline interview, previous physical activity was considered as any cardiovascular exercise routine such as running, swimming, cycling, and obesity was calculated BMI $>$ 29.

Follow-up visits were conducted by the same physiatrist at 1, 3, and 6 months after the start of rehabilitation including a battery of tests to assess neuro-functional status: the mRS (scores 0–6), the Granger modified Barthel Index (BI, scores 0–100) (22), the Fugl-Meyer Assessment score for the upper extremity (FMA, scores 0–66) (23), the Functional Ambulation Categories (FAC, scores 0–5), the Chedoke Arm and Hand Activity Inventory (CAHAI, scores 13–91) (24), the 10-m walk test (velocity is registered), the Medical Research Council scale (MRC, scores 0–5) of the upper and lower extremities at the proximal/distal level, and the Modified Asworth Scale (MAS, scores 0–4, including 1+) (25).

We also analyzed changes in the scores during follow-up visits vs. baseline scores to assess improvements in the neurological function: Rankin improvement was defined as a decrease of $\geq$1 point. For the FMA, the improvement was defined as an increase of $\geq$10 points, described previously as the minimal clinical important difference (26). For the Chedoke Arm and Hand Activity Inventory, an improvement was defined as an increase of $\geq$7 points (27). For the 10-m walk test, the walking velocity was calculated, and improvement was considered if walking velocity increased by $>$0.3 m/s. The FAC

TABLE 1 | Baseline characteristics of the control and stroke cohorts.

	Stroke cohort $n = 62$	Control cohort $n = 43$	*p*-value
Age (years)	57.59 ± 9.7	60.8 ± 10.8	0.11
Sex, males	79.7 (51)	20.3 (13)	**<0.01**
Risk factors and comorbidities			
Alcohol	27.4 (17)	23.8 (10)	0.65
Tobacco	37.1 (23)	16.7 (7)	**0.02**
Atrial fibrillation	9.7 (6)	0 (0)	0.07
Hypertension	61.3 (38)	46.5 (20)	0.16
Dyslipidemia	40.3 (25)	46.5 (20)	0.52
Diabetes mellitus	19.7 (12)	18.6 (8)	0.89
Obesity	29.5 (18)	34.9 (15)	0.56
Previous exercise	39.0 (23)	76.7 (33)	**<0.001**
Cardiopathy	6.5 (4)	0 (0.0)	0.14
Osteoarticular	12.9 (8)	32 (14)	**0.01**
Psychiatric	16.1 (10)	9.3 (4)	0.31
Previous medication			
Anti-platelets	21 (13)	14.3 (6)	0.38
Anti-coagulants	4.8 (3)	0 (0.0)	0.27
Statins	38.7 (24)	28.6 (12)	0.28
Anti-hypertensives	53.2 (33)	40.5 (17)	0.2
Anti-diabetic	17.7 (11)	14.3 (6)	0.64
Angiogenin			
Baseline levels (ng/mL)	520.8 ± 139.2	432.8 ± 155.7	**<0.01**

Variables are expressed as a percentage (number of cases, n) or mean ± SD. Differences were assessed with a t-test, chi-square test, or Fisher exact test.
Statistically significant differences are highlighted in bold.

TABLE 2 | Baseline characteristics of the IRT vs. NO-IRT cohorts.

	IRT $n = 45$	NO-IRT $n = 17$	*p*-value
Age	56.4 ± 9.1	60.6 ± 10.8	0.13
Sex, males	82.2 (37)	82.4 (14)	0.72
Risk factors and comorbidities			
Alcohol	28.9 (13)	23.5 (4)	0.72
Tobacco	40.0 (18)	29.5 (5)	0.53
Atrial fibrilation	8.9 (4)	11.8 (2)	0.64
Hypertension	66.7(30)	47.1 (8)	0.23
Dyslipidemia	46.7 (21)	23.5 (4)	0.09
Diabetes mellitus	25.0 (11)	5.9 (1)	0.15
Obesity	29.5 (13)	29.4 (5)	1
Previous exercise	38.1 (16)	41.2 (7)	0.8
Cardiopathy	11.8 (2)	4.4 (2)	0.3
Osteoarticular	8.9 (4)	23.5 (4)	0.18
Psychiatric	20 (9)	5.9 (1)	0.26
Previous medication			
Anti-platelets	22.2 (10)	17.6 (3)	1
Anticoagulants	4.4 (2)	5.9 (1)	1
Statins	46.7 (21)	17.6 (3)	**0.03**
Anti- hypertensives	55.6 (25)	47.1 (8)	0.58
Anti-diabetic	22.2(10)	5.9 (1)	0.26

Variables are expressed as a percentage (number of cases) or mean ± SD. Differences were assessed with a t-test, chi-square test, or Fisher exact test.
Statistically significant differences are highlighted in bold.

was categorized into three categories: cannot walk (score 0), dependent walk (scores 1–3), and independent walk (scores 4 and 5), and improvement was defined as a shift to a higher category (28). For the MRC scale, our analysis differentiated classification between normal (score 5) or impaired (scores 0–4) muscle strength.

At all visits blood sampling in serum-separating tubes was obtained, centrifuged at 1,500 rpm for 15 min, and serum stored at −80°C until use.

Angiogenin Measurement

Serum levels of ANG were measured by ELISA (#DAN00; R&D Systems, USA) and analyzed together with previous-obtained results from cohort one using the same test (15). Briefly, 200 µl of diluted serum samples (1:200) were loaded per duplicate, and only values with a coefficient of variation < 20% were accepted for the statistical analysis. To verify low inter-plate variability (7 ELISA plates were analyzed in total) we included a commercial internal control from Sigma-Aldrich (Human serum type AB, male, from clotted, cat#H6914), and a coefficient of variation < 20% was accepted.

Statistical Analysis

The SPSS 20.0 package was used for statistical analyses. The database entries were reviewed by an independent researcher. Descriptive statistics: categorical variables were reported as frequencies (percentages) and continuous variables as mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Missing data were considered at random and no imputations were used. The normality assumption of quantitative variables was checked with the use of quantile-quantile (Q-Q) plots. Statistical significance was assessed by Pearson's chi-square or Fisher's exact test for categorical variables, Student's *t*-test for continuous variables, and the Mann-Whitney U test for functional scores and numerical variables without normal distribution. Temporal profile changes in normally distributed variables were analyzed with repeated measures ANOVA (Bonferroni *post-hoc* test) or the Friedman followed by Wilcoxon tests for non-normal distributions. Box plots were used to represent the temporal profile of non-normal distributed variables (functional scores) and bar-graphs showing mean with 95% confidence interval to represent normally distributed variables (temporal profile of ANG). Pearson (normal distribution) or Spearman (non-normal distribution) tests were used. Repeated measures in general linear models were conducted to assess changes in the ANG temporal profile between the two rehabilitation groups, controlling for other baseline characteristics (CAHAI). The temporal profile changes in the functional scales were analyzed with Mixed Models Analysis generated by the SAS System (Version W32_7 PRO) adjusting for the baseline scores. A p-value < 0.05 was considered statistically significant.

TABLE 3 | Clinical characteristics of IRT and NO IRT group on admission.

	IRT $n = 45$	NO-IRT $n = 17$	*p*-value
Rankin	4.5 (4–5)	5 (4–5)	0.46
NIHSS	12 (7.5–17)	11 (6–14)	0.32
NIHSS (motor)	7 (4–9)	6.5 (5–11)	0.65
Stroke laterality, left	48.9 (22)	41.2 (7)	0.58
Stroke type, ischemic	73.3 (33)	70.6 (11)	0.82
Vascular territory			0.7
Carotid	78.8 (25)	83.3 (10)	
Vertebrobasilar	24.2 (8)	16.7 (2)	
Ischemic etiology			0.45
Cardioembolic	27.3 (9)	8.3 (1)	
Atherothrombotic	21.2 (7)	25 (3)	
Lacunar	18.2 (6)	41.7 (5)	
Others	12.1 (4)	8.3 (1)	
Undetermined	21.2(7)	16.7 (2)	
OCSP classification			0.35
TACI	46.9 (15)	27.3 (3)	
PACI	15.6 (5)	9.1 (1)	
LACI	25 (8)	54.5 (6)	
POCI	12.5 (4)	9.1 (1)	
Acute treatment			
Thrombolytic therapy	15.4 (4)	11.8 (2)	0.48
Endovascular treatment	6.7 (3)	17.6 (3)	0.33
Hemorrhagic transformation	4 (1)	0 (0)	1
Stroke type, hemorrhagic	26.7 (12)	29.4 (5)	0.53
Location			0.51
Deep	91.7 (11)	80 (4)	
Lobar	8.3 (1)	20 (1)	
Hemorrhagic etiology			0.33
Hypertensive	83.3 (10)	100 (5)	
Undetermined	16.7(2)	0 (0)	

Variables are expressed as a percentage (number of cases) or median (IQR). OCSP, Oxfordshire Community Stroke Project; TACI, total anterior cerebral infarct; LACI, lacunar cerebral infarct; PACI, partial anterior cerebral infarct; POCI, posterior cerebral infarct. Differences were assessed with a t-test, Mann-Whitney-U, chi-square test, or Fisher exact test.

TABLE 4 | Post-stroke rehabilitation characteristics at baseline visit.

	IRT $n = 45$	NO-IRT $n = 17$	*p*-value
Hospitalization regimen			
Inpatient rehabilitation	95.6 (43)	100 (17)	1
Day-hospital rehabilitation	4.4 (2)	0 (0)	1
Time stroke- RHB program in days	14 (9–19)	11 (8–14)	0.09
Time stroke-sample in days	14 (8.25–19)	10 (6–13.5)	0.08
RHB hour/week at baseline	15 (15–16)	7.5 (5–9)	**<0.01**
Functional scores			
Rankin	4 (3–5)	5 (3.2–5)	0.2
Barthel	35 (20–68)	23 (20–36.5)	0.12
NIHSS	9 (5–14)	9 (4–11)	0.38
CAHAI	13 (13–16)	18.5 (13–82)	**0.02**
FMA	8.5 (4–40.7)	9 (0–59)	0.94
FAC	0 (0–2)	0 (0–2.7)	0.78
MRC proximal upper limbs	2 (0–4)	2.5 (0–3)	0.99
MRC distal upper limbs	1 (0–4)	0.5 (0–3.5)	0.95
MRC proximal lower limbs	2 (1–4)	3 (2–4)	0.98
MRC distal lower limbs	1 (0–4)	1 (0–3)	0.34
MAS proximal upper limbs	0 (0–1)	0 (0–0)	0.3
MAS distal upper limbs	0 (0–0.5)	0.5 (0–3.5)	0.73
MAS proximal lower limbs	0 (0–1)	0 (0–1)	0.82
MAS distal lower limbs	0 (0–0.5)	0 (0–1)	0.36
Angiogenin			
Baseline levels (ng/mL)	502.7 ± 133.8	570.9 ± 145.8	0.09

Variables are expressed as a percentage (number of cases), mean ± SD, or median (IQR). mRS, modified Rankin scale; BI, Granger modified Barthel Index; FMA, Fugl-Meyer Assessment; FAC, the Functional Ambulation Categories; CAHAI, Chedoke Arm and Hand Activity Inventory; MAS, Modified Ashworth Scale. Differences were assessed with a t-test, Mann-Whitney-U, chi-square test, or Fisher exact test.
Statistically significant differences are highlighted in bold.

RESULTS

Characteristics of the Study Cohorts at Baseline

The baseline characteristics of the stroke cohort and controls are described in **Table 1**. Of note, our stroke cohort presented more men (79.7 vs. 20.3%, $p < 0.01$), more tobacco users (37.1 vs. 16.7%, $p = 0.02$), and less previous exercise (39 vs. 76.7%, $p < 0.001$) than the control. Importantly, our two rehabilitation groups presented similar baseline characteristics except for the previous statins medication which was more frequent in the IRT group (46.7 vs. 17.6%, $p = 0.03$) as shown in **Table 2**.

Clinical Characteristics and Functional Outcome

The two rehabilitation groups presented similar clinical characteristics at emergency admission: stroke characteristics, acute treatment, hospitalization regimen, or baseline functional scores (see **Tables 3**, **4**). Significant differences were only found in the number of rehabilitation hours per week: IRT 15 (15–16) vs. NO-IRT 7.5 (5–9), $p < 0.01$, and in the baseline CAHAI score which was lower in the IRT group: 13 (13–16) vs. 18.5 (13–82), $p = 0.02$.

Both groups presented significant improvements over the 6 month follow-up period in functional and motor tests, but the CAHAI score and MAS scale only improved in the IRT group (**Table 5**). Regarding the impact of the rehabilitation intensity on motor and functional scores, **Figure 2** shows improvements occurring earlier in the IRT group for the CAHAI, FMA, and FAC tests ($p < 0.001$ at 1 month), but not in the NO-IRT group, which achieved significance later at 3months ($p < 0.05$). Other tests presented similar profiles regardless of therapy intensity

TABLE 5 | Measures of functional and motor outcome.

IRT Group	Baseline	1st month	3rd month	6th month
BI (0–100)**	35 (20–68)	77 (49–94)	93 (84–100)	100 (93–100)
mRS**	4 (3–5)	3 (2–4)	3 (1–3)	2 (1–2)
FMA (0–66)*	8.5 (4–40.7)	44 (9–56.5)	47.5 (12.5–61.3)	50.5 (17.8–64.5)
FAC (0–5)**	0 (0–2)	2 (1–5)	4 (3–5)	5 (4–5)
CAHAI (13–91)**	13 (13–15.7)	43 (13–76)	73 (13–87)	74 (13–90)
10-m walk test (m/s)**	NA	0.50 (0–1)	0.89 (0.25–1.22)	0.90 (0.54–1.30)
MRC scale superior-proximal (0–5)**	2 (0–1)	4 (2–4)	4 (2.5–5)	4 (2–5)
MRC scale superior-distal (0–5)**	1 (0–4)	2.5 (0–4)	4 (0.5–5)	4 (1–5)
MRC scale inferior-proximal (0–5)**	1 (0–4)	5 (4–5)	5 (4–5)	5 (4–5)
MRC scale inferior-distal (0–5)**	1 (0–4)	4 (1–5)	4 (2–5)	4 (2–5)
MAS scale superior-proximal (0–4)**	0 (0–1)	1 (0–1)	1 (0–2)	1 (1–2)
MAS scale superior-distal (0–4)**	0 (0–0.5)	1 (0–1.5)	1 (0–2)	1 (1–2)
MAS scale inferior-proximal (0–4)**	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
MAS scale inferior-distal (0–4)**	0 (0–0.5)	0 (0–1)	1 (0–2)	1 (0–2.25)
NO-IRT Group				
BI (0−100)*	23 (20–36.2)	49.5 (40–93)	88.5 (59–99)	90 (75–100)
mRS**	5 (3.2–5)	4 (1.2–4)	2.5 (1–3)	1 (1–3)
FMA (0–66)*	9 (0.5–55.2)	31 (7.2–64.7)	40.5 (9–63.5)	50 (18–66)
FAC (0–5)*	0 (0–2.7)	2 (1–4.75)	4.5 (3–5)	5 (4–5)
CAHAI (13–91)	18.5 (13–82.2)	23 (13–90)	59.5 (13–90)	76 (13–91)
10-m walk test (m/s)**	NA	0 (0–0.70)	0.56 (0.28–0.99)	0.95 (0.62–1.10)
MRC scale superior-proximal (0–5)*	2.5 (0–3)	3 (0–4)	3 (1.5–5)	4 (2–4)
MRC scale superior-distal (0–5)*	0.5 (0–3)	2.5 (0–4)	3.5 (1.5–4)	3.5 (1.5–5)
MRC scale inferior-proximal (0–5)*	1 (0–3)	4 (3–4)	4 (3.5–5)	4 (3.5–5)
MRC scale inferior-distal (0–5)*	1 (0–3)	2.5 (0–4)	4 (1–5)	4 (2–5)
MAS scale superior-proximal (0–4)	0 (0–0)	0.5 (0–1)	0 (0–1)	0 (0–1)
MAS scale superior-distal (0–4)	0 (0–0)	0.5 (0–1)	0.5 (0–1.75)	0 (0–2)
MAS scale inferior-proximal (0–4)	0 (0–0.75)	0 (0–1)	0.5 (0–1)	0 (0–1)
MAS scale inferior-distal (0–4)	0 (0–1)	0.5 (0–1)	1 (0–1.75)	0 (0–2)

*Data are shown as median (IQR). mRS, modified Rankin scale; BI, Granger modified Barthel Index; FMA, Fugl-Meyer Assessment; FAC, the Functional Ambulation Categories; CAHAI, Chedoke Arm and Hand Activity Inventory; MAS, Modified Ashworth Scale; NA, not applicable. Every scale shows the Median and IRQ Differences were assessed with a Friedman test: *$p < 0.05$, **$p < 0.01$.*

Statistically significant differences are highlighted in bold.

(**Supplementary Figure 1**). Importantly, at 3 months the IRT group achieved a full community ambulation level (0.89 m/s), but not the NO-IRT group (0.56 m/s) (**Table 5**). However we did not find differences overtime between rehabilitation groups in a mixed model: FAC ($p = 0.86$), Walking ($p = 0.42$), mRS ($p = 0.82$), BI ($p = 0.41$), FMA ($p = 0.10$), and CAHAI ($p = 0.10$). In this regard, the effect of time was independent of the type of therapy ($p < 0.01$) for all tests and did not change when adjusting for baseline mRS or Barthel.

Angiogenin Temporal Profile Changes With Therapy Intensity

Baseline ANG was significantly higher in strokes than in controls (520 ± 139 vs. 432 ± 155 ng/mL; $p < 0.01$, see **Table 1**), with no baseline differences observed between the rehabilitation groups (see **Table 4**). No correlation was observed between baseline ANG and time-to-start RHB or baseline sampling. Notably, the number of rehabilitation hours were reduced according to the individual patient's achievements as represented in **Figure 3A**, with a substantial switch from IRT to NO-IRT over time. For this reason, the ANG level was analyzed only up to the 3rd month. In all strokes the ANG temporal profile showed significant differences ($p < 0.001$, see **Supplementary Figure 2**), being elevated at 1 month vs. controls ($p = 0.036$). Regarding the type of therapy, we found a significant interaction with ANG levels over time ($p = 0.030$, see **Figure 3B**). The ANG temporal profile in the NO-IRT and IRT groups showed differences ($p < 0.01$, see **Figure 3C**) in opposite directions since ANG increased after 1 month of IRT ($p < 0.05$ vs. baseline) but it decreased in the NO-IRT group ($p < 0.01$ vs. 3rd month).

Finally, we examined the relationship between outcome scores improvements from admission to 6 months follow–up with ANG, but we could not confirm a predictive value of ANG at any of the tested time points (data not shown).

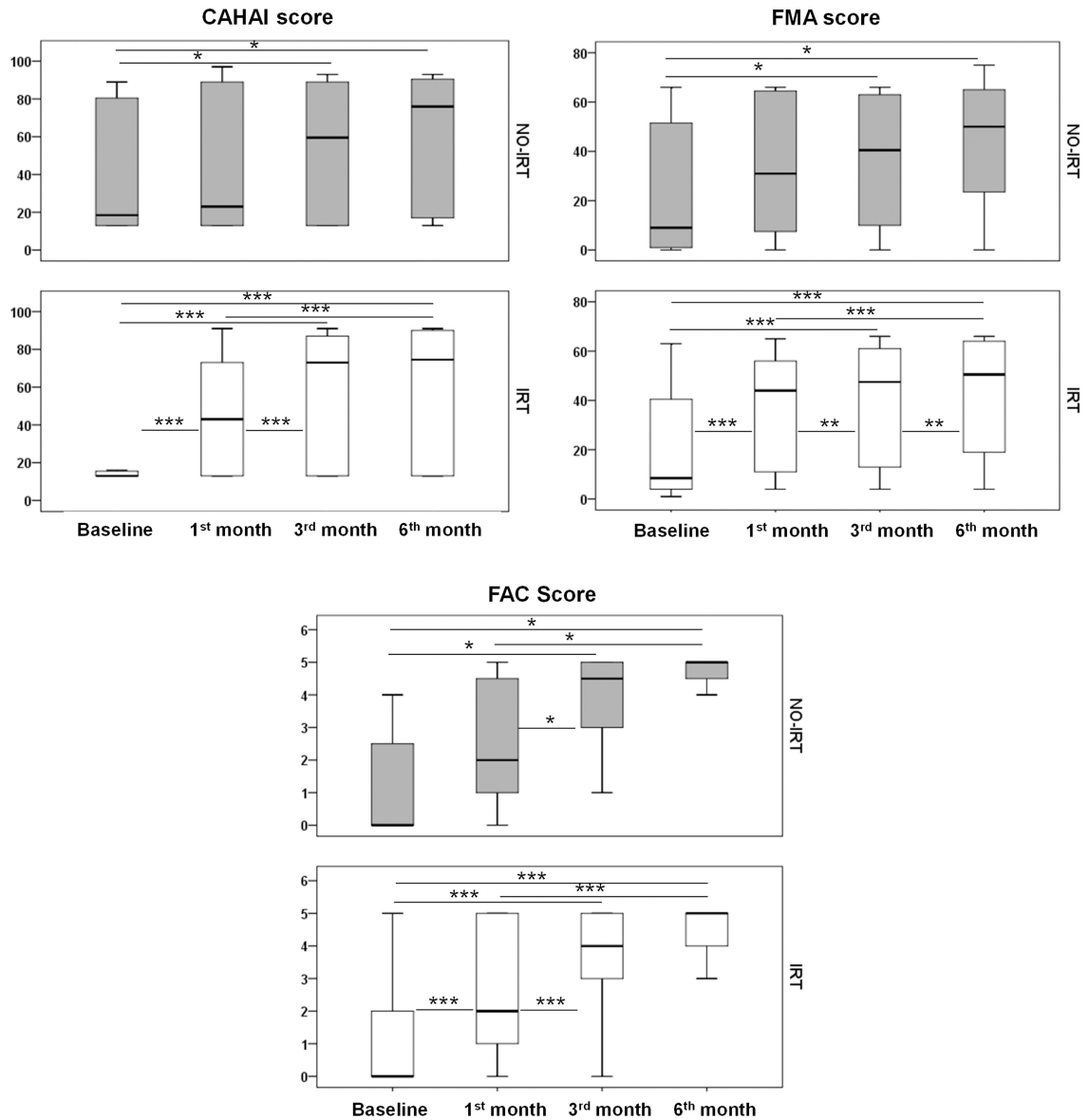

FIGURE 2 | Functional outcome. Temporal profile of the tested scales in IRT and NO-IRT cohorts. Note that in the 1st month significant improvements were only achieved in the IRT group. Differences were assessed with the Wilcoxon tests and the Man-Withney U for the transversal analysis. *$p < 0.05$; **$p < 0.01$, and ***$p < 0.001$. Median and IQR are represented in box plots.

DISCUSSION

The present study investigates the effects of rehabilitation therapy intensity on both functional outcome and blood levels of ANG, a potential biomarker of recovery. Our results suggest that stroke patients under more intense rehabilitation programs presented better outcomes earlier with a parallel increase of blood ANG. However, we could not confirm a predictive value of ANG.

Rehabilitation treatment is the gold-standard therapy for stroke survivors to recover functional status, and improve quality of life and independence (4) with programs personalized by multi-disciplinary teams, where the dose of the received therapy is a key factor in the recovery process (8, 13). In this study, we have followed two cohorts with similar clinical characteristics which primarily differed in the amount of scheduled therapy time at baseline. Our results suggest that patients under IRT receiving the highest therapy dose improved earlier at 1 month of therapy in the CAHAI and FMA scores, which according to the International Classification of Function (ICF-WHO) framework are designed to assess bilateral activity performance for daily life activities and brain structural recovery, respectively (29). Additionally, patients under IRT also achieved full community ambulation earlier during rehabilitation (30) and showed better BI scores earlier than NO-IRT patients, suggesting improved

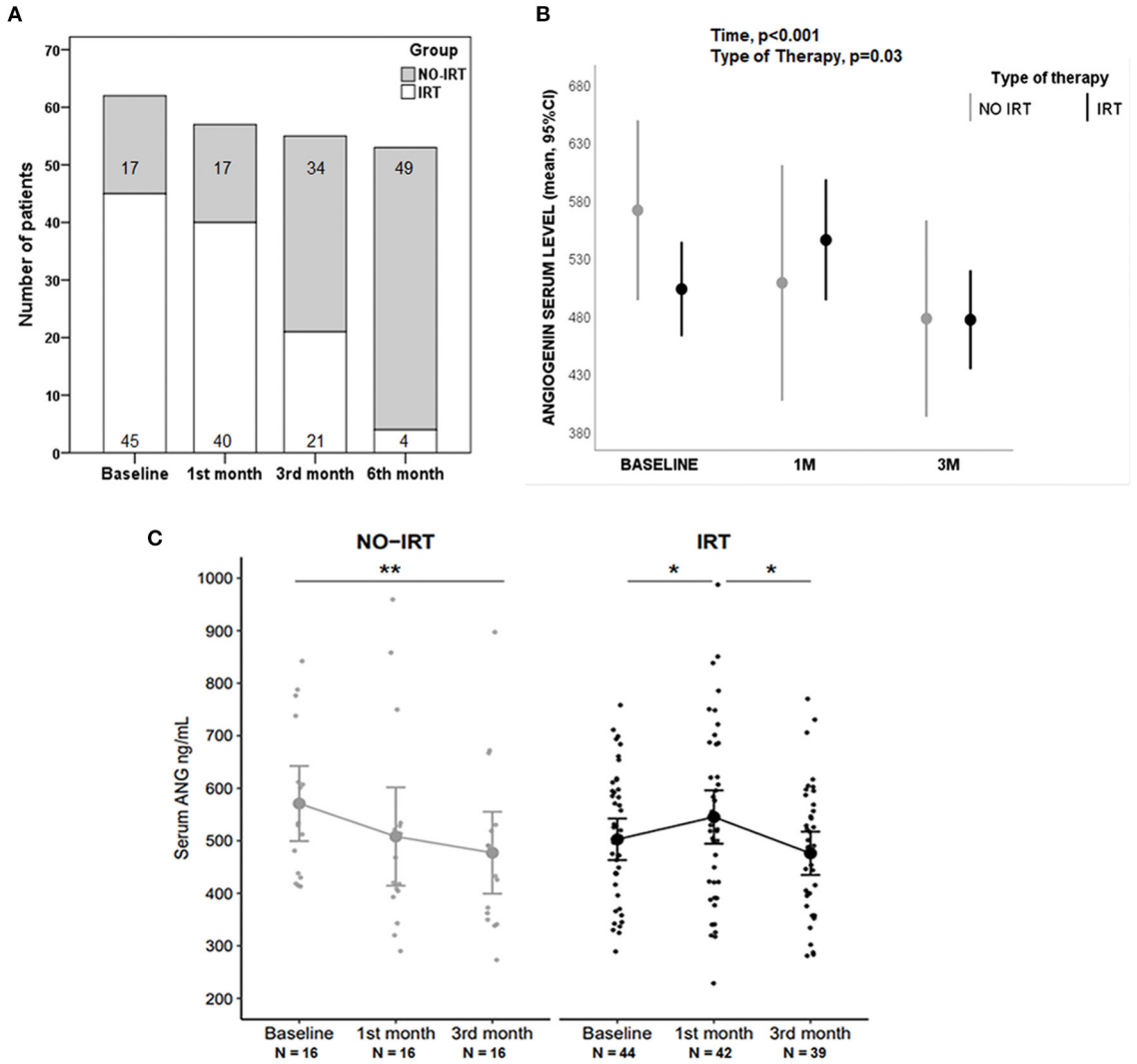

FIGURE 3 | Angiogenin (ANG) blood levels during rehabilitation. **(A)** Bar graph showing the number of patients under IRT and NO-IRT over time, changing according to early improvements in the IRT group. **(B)** Graph comparing how time and type of therapy influenced the serum levels of ANG, assessed with ANOVA for repeated measures. **(C)** Jitter plots showing the temporal profile of ANG levels in NO-IRT and IRT groups; Differences were assessed with Wilcoxon tests, $^{*}p < 0.05$, $^{**}p < 0.01$. Mean with 95% CI are represented in graphs.

independence for the basic activities of daily living. In this regard and following previously reported dependence categories for the BI scale (31, 32), median BI values show that at 1 month IRT lead to a moderate dependence score whereas No-IRT maintained a severe dependence score and later at 3 months IRT lead to a slight independence score whereas No-IRT lead to a moderate dependence score.

Supporting these observations of larger functional gains in the IRT group, Wang and colleagues showed that the daily amount of physical, occupational, and speech and language therapy was also significantly associated with functional improvements (33). Others have previously reported a direct intensity-response between rehabilitation and functional recovery (8, 34). However, the patient's response to rehabilitation is heterogeneous and might depend on the type and amount of therapy received, or on individual endogenous neurorepair responses. In this regard, it is important to elucidate if IRT could further enhance recovery by increasing therapy intensity and/or duration.

A biomarker is an indicator that can be used to measure underlying molecular processes, identify a disease, predict recovery, or monitor treatment responses. In the present study, we show that only patients under IRT presented a significant increase in serum ANG after rehabilitation, which could be linked to the repair process underlying the prompt recovery since this angiogenic factor can trigger a wide range of biological

processes (18). This improvement allowed the reduction of the amount of therapy time that paralleled a decrease of the serum ANG levels at the 3rd and 6th months of therapy. Whether extending the IRT therapy would maintain high ANG and result in larger functional/motor improvements remains to be elucidated in future interventional biomarker studies. Other studies have focused on identifying biomarkers for stroke disease (35, 36), but very few have focused on long-term outcomes or the influence of rehabilitation therapies. Others have explored the use of molecules related to oxidative stress (37) or changes in neurotransmitter levels during post-stroke rehabilitation, reporting a correlation with motor improvement (38). Serum ANG levels were first reported higher in patients with stroke within 48 h and on days 3 and 7, but decreasing at 14 days compared to control subjects (39), but the rehabilitation interventions were not described in this work. Our recent work also in serum ANG reported that blood ANG was increased in stroke patients after IRT (15), which is being confirmed in the present study with a larger cohort. Additionally, in this previous study, experiments in pre-clinical stroke models also described an ANG increase in the ischemic site when performing task-specific exercise, suggesting an association between rehabilitation and molecular changes in the brain. Moreover, another pre-clinical study from our group has recently described that physical exercise rapidly increased the amount of endogenous ANG in the ipsilateral neurogenic subventricular zone after cerebral ischemia (40). All this evidence points to potential connections between ANG, stroke disease, and rehabilitation, although confirmatory investigations are needed.

To our knowledge this is the first time a blood biomarker is described as differentially modulated by the amount of therapy time received during rehabilitation, suggesting the need to include rehabilitation treatments as a co-variable in stroke biomarker analyses, especially in multicenter studies.

As a limitation, our study presents a different number of patients in both rehabilitation cohorts due to different recruitment achieved by the participant centers, which could impact on group comparisons although baseline clinical and stroke characteristics are very similar. Also, in this observational study, the dose of therapy hours decreased over time in the IRT group based on clinical decisions and individual achievements, which could influence the levels of serum ANG between follow-up visits. For these reasons new interventional studies to determine the relationship between the dose of therapy and blood biomarkers are crucial to elucidate the true link with the clinical interventions.

In conclusion, our study shows that designing intensive rehabilitation programs results in earlier improvements, and the monitoring of specific blood biomarkers could be a useful part of the multidisciplinary recovery program.

DATA AVAILABILITY STATEMENT

Requests to access the anonymized datasets should be directed to the corresponding author, anna.rosell@vhir.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee sites [HUVH PR(IR)317/2013-PR(IR)346/2016, PI16/00981/CEI:PI-17-056, Comité de Ética de Investigación de A Coruña-Ferrol 2017-125, Corporació Sanitària Parc Taulí de Sabadell 2017521, Hospital Universitario Politécnico La Fe 2016/0727, Euskadi PI2016168]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NG-R, SR, XB, and AR participated in the design of the study. NG-R, SR, PT, ZM-A, XB, NR, MP-M, MB, JS, LP, MI, SO-V, RM-M, MM, MO-G, and AP participated in patients' recruitment and data collection. NG-R, XB, MQ, AP, and AR participated in data analysis. NG-R, SR, PT, ZM-A, NR, XB, MP-M, MB, JS, LP, MI, SO-V, RM-M, MM, MQ, MO-G, AP, and AR participated in the manuscript draft and/or review. 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.2021.767484/full#supplementary-material

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Recovery of Body Awareness After Stroke: An Observational Study

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Background: Body awareness (BA) is a process that involves sensory awareness originating from the body's physiological states, processes and actions, and is shaped by one's attitudes, perceptions, beliefs and experience of social and cultural context. Impairments in body awareness after stroke are believed to be common and may be an important influence on recovery outcomes. However, recovery of body awareness is poorly understood and receives little consideration in rehabilitation.

Aims: To investigate if body awareness changes over time following stroke; and identify if body awareness after stroke is associated with sensation, motor impairment, self-efficacy and quality of life.

Methods: An exploratory longitudinal observational study was performed. Participants with a stroke diagnosis and associated motor impairment were recruited from an acute stroke unit. An assessment battery consisting of sensory and motor impairment and function, body awareness, self-efficacy and quality of life measures were used at baseline, 1, 3 and 6 months.

Results: A total of 105 people with stroke were recruited. Most recovery in sensation and body awareness occurred within the first month after stroke (all $p < 0.01$). Sensation and body awareness were correlated with other clinical outcomes (motor impairment, self-efficacy and quality of life), demographics, and stroke specific clinical characteristics (all $p < 0.01$).

Conclusions: This is the first study to track recovery of body awareness after stroke and investigate the relationship it may have in recovery of sensation, motor impairment and function, self-efficacy and quality of life. Further research is now warranted to continue investigation of body awareness and to develop effective stroke-specific assessment and intervention strategies.

Keywords: physiotherapy, stroke, rehabilitation, sensation, body awareness

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INTRODUCTION

Body awareness is considered an interactive process that includes awareness of the body's *physiological states, processes (including pain and emotion) and actions (including movement), and is shaped by an individual's attitudes, perceptions, beliefs and social/cultural context experiences* (1) (p.2). The nature of impairments post-stroke would suggest that body awareness may likely be impacted in stroke survivors how this has received little attention in the literature.

Awareness has been proposed to develop from a **body schema** (unconscious representation of the position of the body in space plus the position of sensation on the body surface) (2–31), and **body image** (a conscious representation of one's self) (2, 3, 7–10, 13, 17, 19, 32–34).

Considering recent literature, the triadic model has been proposed to further explain the nature and properties of body representations. The triadic model retains the dyadic (schema and image) notion however subdivides body image into two further representations: body structural descriptions and body semantics. Body structure describes a topological map primarily derived from visual input but also somatic perception. It provides a structural description of the relationships between body parts boundaries, proximity and relative position (2, 9, 12, 15, 25–28, 35–38). Body semantics describes the relationship between words and meaning and represents semantic and lexical information about the body (including functions of body parts, associations between body parts and objects, and body part names) (9, 12, 15, 25–28, 35–40).

The importance of body awareness lies in its' role in constantly monitoring, updating and providing feedback about the position and movement of one's body through space. It is also the main process used in integrating information for perception, decision making and action, making accurate body information essential for the precise control of movements (10, 41). The neuroanatomical basis influencing body awareness is understood to include an integrated system of brain regions and functional networks. The main regions within the somatosensory network (and important for body schema) are found primarily in the parietal cortex (SI and SII) as well as the thalamus, insula and cerebellum (50, 75, 94). A more distributed network, including attention and visual networks, is involved in the conscious processing of somatosensory information (50, 75, 95). Information processing of sensation for perception, and sensation for action, is described to involve both parallel and serial processing (75). It is important to note that all senses (exteroception and interoception) feed into the representation/s. Furthermore, body image involves affective and memory input from the limbic system and the semantic and lexical aspects require input from the language and spatial areas of the parietal lobes in their respective hemispheres.

Intact body awareness is thought to be a major factor that supports motor function and recovery of individuals following stroke (10, 41). One in two people experience impairments in sensation and perception after a stroke which interrupts the representation of the body that is held in the brain (42) and has a profound impact on an individual's body awareness (43–46). Altered motor and sensory cortical processing leads to inaccurate body information which can manifest in many different ways such as altered perception of limb size, position, shape or weight. This impairs the precision and control of one's movements (including postural control, dynamic balance, coordination) and the individual's ability to explore the immediate environment safely (41, 43–45). Subsequently it affects one's functional abilities, execution of daily activities and quality of life (35, 41, 47–49), making simple actions such as preparing breakfast, taking a shower or going for a walk challenging (10, 40). Further, reduced body awareness often interferes with the duration of rehabilitation and discharge destination (43, 45, 50).

Emphasising further the important role of body awareness in stroke recovery, body awareness training has been linked to positive rehabilitation outcomes, particularly with balance and mobility (51–53). However, we currently have little understanding of body awareness during stroke recovery or whether it is important for enabling behavioural restitution. While much work has been focussed on initial motor impairment, structural damage and the neurobiological course of the recovery process (54), little attention has been directed to body awareness (43). Indeed, from sensory and motor impairment studies, research suggests recovery is most marked within the first 3 months after stroke, although ongoing recovery can be observed at 6 months and later (54–56). In particular, evidence from sensory rehabilitation studies have indicated the potential for marked recovery from months to years after stroke (43), and body awareness similarly may continue to evolve over the first 2 years (7, 49). There is some suggestion that individuals within the first 2–6 months direct their attention toward the way their body functions and try to find new ways to manage daily activities and actions. Subsequently from 6 to 12 months the focus shifts to forming an understanding and acceptance of their bodily changes (7).

The purpose of this study was to first investigate if body awareness is impaired after a stroke and if it recovers over time, and second, identify if body awareness is associated with sensation, motor impairment, self-efficacy and quality of life. It was hypothesised that body awareness will initially be impaired after stroke, improve within the first few months and will be associated with improvements in motor, sensory and quality of life measures.

METHODS

Study Design

An exploratory, prospective, longitudinal, observational study was conducted and reported using the STROBE guidelines. Recruitment for this trial commenced September 2017 and

TABLE 1 | Baseline characteristics.

Characteristic	Participants ($n = 89$)
Age (year), mean (SD)	71.9 (12.1)
Gender, *n* (%) female	38 (43%)
TSS to baseline assessment (days), mean (SD)	3.6 (2.1)
Side affected, *n* (%) left	58 (65%)
Stroke type, *n* (%) ischaemic	77 (86.5%)
Premorbid residence (metropolitan), *n* (%)	56 (63%)
NIHSS, mean (SD)	7.8 (5.7)
MOCA, mean (SD)	21.4 (5.9)
FIM, mean (SD)	74.1 (23.1)
MAIA, *n* (%) interoception affected	89 (100)

TSS, time since stroke; NIHSS, National Institutes of Health Stroke Scale; MOCA, Montreal Cognitive Assessment; FIM, Functional Independence Measure.

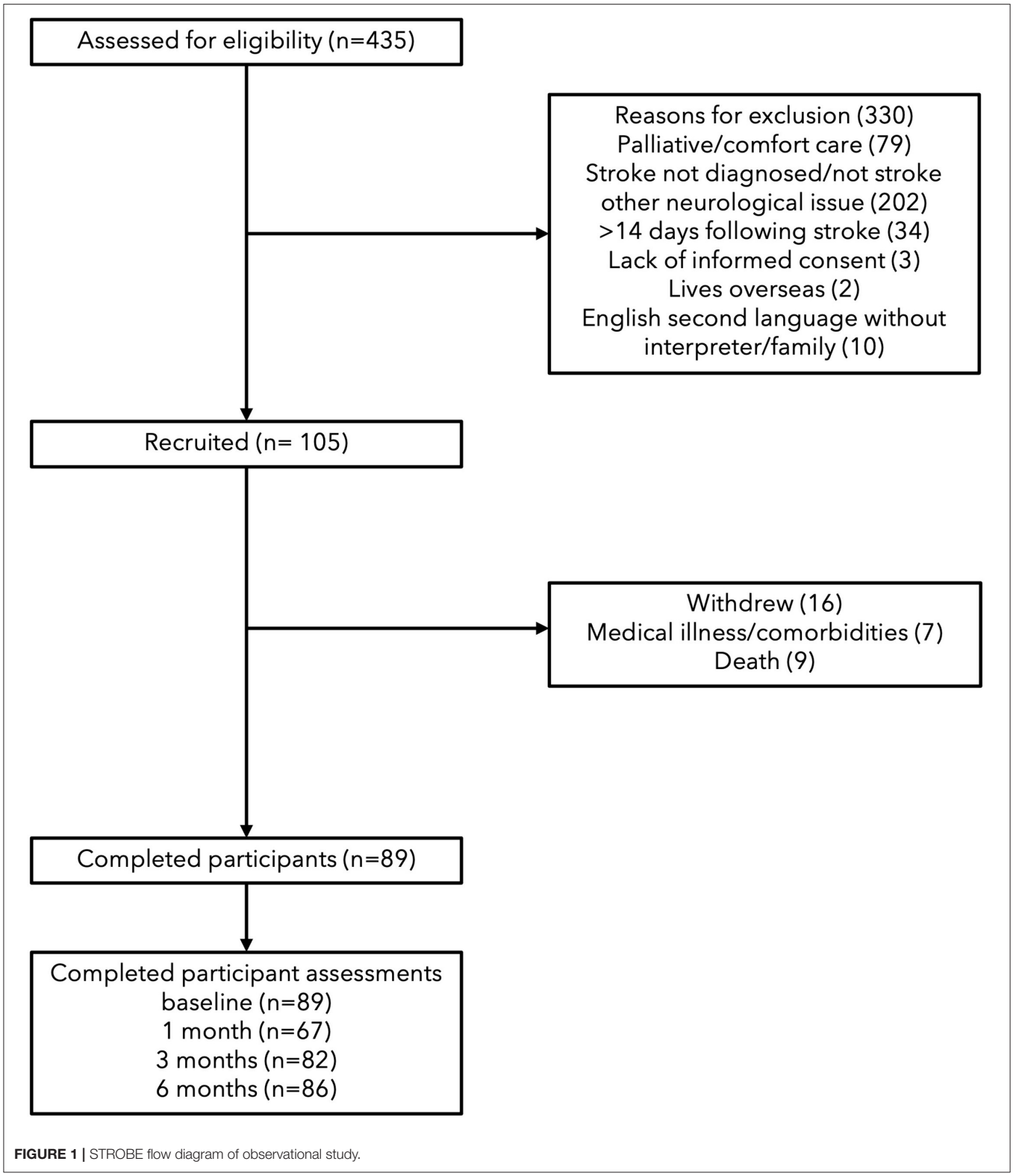

FIGURE 1 | STROBE flow diagram of observational study.

concluded in June 2019. Ethical approval was obtained from the University of South Australia Human Ethics Committee and the governing recruitment site (CALHN). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helinski. All participants provided written informed consent.

Participants

Potential participants admitted to the Royal Adelaide Hospital (RAH) stroke unit were screened for inclusion. The inclusion criteria were: a confirmed diagnosis of stroke on computed tomography and/or magnetic resonance imaging, recruited within 1–14 days of stroke, medically stable, able to provide informed consent (or legal guardian to provide third party consent), any impairment/s (weakness, altered sensation, loss of dexterity, reduced coordination) and ≥18 years of age. Exclusion criteria were patients deemed for palliative or comfort care, an inability to communicate in English (unless a family member was present to interpret) or receptive/expressive aphasia that would interfere with testing. Consecutive recruitment was performed by screening all patients on the Stroke unit daily. With no previous studies to guide sample size calculations and given the exploratory nature of this study, the aim was to maximise recruitment within a period of 8 months.

Outcome Measures

The assessment battery included key outcomes to characterise the cohort [baseline only; National Institutes of Health Stroke Scale (NIHSS), the Montreal Cognitive Assessment (MOCA) and Functional Independence Measure (FIM)] along with repeated assessments at baseline, 1, 3 and 6 months following stroke for sensation, body awareness, self-efficacy, quality of life and motor impairment/function.

Body awareness was assessed with the Body Perception Disturbance (BPD; UL and LL) (measures physical awareness of limb ownership, awareness of limb position, attention required to attend to limb, emotional feelings toward limb, difference in size, temperature, pressure, weight, and the description/mental image of body parts) and the Multidimensional Assessment of Interoceptive Awareness (MAIA) (measures interoceptive awareness, the perception of sensation from inside the body including noticing, distracting, worrying, attention regulation, emotional awareness, self-regulation, body listening and trusting). The MAIA was considered inappropriate to perform in acute phase as some questions were potentially distressing, therefore this measure was only performed at 1, 3, and 6 months after stroke.

Sensation was assessed using the Erasmus Nottingham Sensory Assessment for Upper Limb- EmNSA- UL [measures tactile-light touch, pressure, pinprick, temperature, tactile localisation, bilateral simultaneous touch), kinaesthetic, stereognosis].

Self-efficacy was assessed with the Stroke Self-Efficacy Questionnaire (SSEQ); quality of life with the Stroke Impact Scale (SIS) and Stroke Specific Quality of Life Scale (SSQoL); a comprehensive assessment of motor impairment after stroke using the Fugl-Meyer Upper Extremity (FMA-UE); and the Motor Activity Log (MAL) to observe the amount and quality of motor function. All participants were recruited and assessed within the 14 days following stroke admission. All assessments were performed by a trained and experienced therapist (IS) and all participants received standard stroke and rehabilitation care.

TABLE 2 | Change over time for recovery measures (baseline to 6 months).

	Sensation		Body awareness			Self-efficacy	Quality of life			Motor impairment/function	
Measure (mean, SE) Timepoint	EmNSA-UL Tactile	EmNSA-UL Proprio	BPD-UL	BPD-LL	MAIA	SSEQ	SIS total	SIS %	SSQOL	MAL QOM	MAL AOU	FMA- UE
Baseline	22.0 (12.3)	6.36 (2.90)	11.0 (10.3)	7.41 (9.20)	–	79.3 (38.8)	174.9 (31.8)	53.2 (25.6)	150.7 (33.9)	1.80 (3.77)	1.88 (3.85)	45.0 (22.0)
1 month	25.8 (10.5)	7.60 (1.43)	6.28 (8.86)	3.91 (7.25)	14.1 (6.34)	108.6 (32.5)	225.0 (45.5)	71.5 (20.0)	190.4 (38.4)	3.20 (1.84)	3.23 (1.87)	55.1 (17.9)
3 months	27.0 (9.74)	7.60 (1.50)	6.33 (8.61)	4.66 (7.85)	13.7 (6.25)	106.2 (33.2)	226.1 (46.3)	77.1 (35.6)	189.9 (46.1)	3.29 (1.85)	3.32 (1.88)	55.2 (18.2)
6 months	27.6 (8.72)	7.57 (1.52)	6.38 (8.48)	4.79 (7.22)	13.5 (6.22)	106.9 (32.2)	227.7 (47.4)	74.7 (25.7)	193.9 (43.8)	3.30 (1.79)	3.30 (1.82)	56.6 (16.5)
p-value	<0.001*	<0.001*	<0.001*	<0.001*	0.205	<0.001*	<0.001*	<0.001*	<0.001*	0.002*	<0.001*	<0.001*

*BPD, Body Perception Disturbance Scale; EmNSA UL tactile, Erasmus modified Nottingham Sensory Assessment-Upper Limb; FMA-UE, Fugl-Meyer Assessment- Upper Extremity; MAIA, Multidimensional Assessment of Interoceptive Awareness Questionnaire; MAL QOM/AOU, Motor Activity Log- Quality of Movement/Amount of Use; Proprio. (proprioception); SSEQ, Stroke Self-Efficacy Questionnaire; SIS, Stroke Impact Scale; SSQoL, Stroke-Specific Quality of Life Scale; *significant $p \leq 0.05$.*

Data Analysis

Statistical tests were performed in IBM SPSS Statistics 25 with level of significance set at $p < 0.05$. Data were tested for normality using the Shapiro-Wilk test, and where required, non-parametric tests were used. Descriptive statistics were used to report the mean and standard deviation of clinical characteristics. Linear mixed effects models were used to test for the fixed effect of VISIT (change over time at four assessment points) for all outcomes including sensation (EmNSA), body awareness (BPD, MAIA), self-efficacy (SSEQ) quality of life (SIS, SSQoL) and motor function (FMA, MAL). The estimated means and standard error of the measure at each time point (baseline, 1, 3, and 6 months) were calculated. Where appropriate, pairwise comparisons, adjusting for multiple comparisons using Bonferroni corrections, were then performed to calculate the mean difference, standard error and significance at each time point. The Spearmans rank test (non-parametric) was used to explore bivariate correlations: if body awareness was associated with stroke recovery in terms of sensation, motor impairment and quality of life. As a preliminarily step to investigate possible associations between body awareness and sensation with patient demographics (age, gender, time since stroke, side affected) and clinical outcomes (NIHSS, MOCA, FIM, SSEQ, SIS, SSQoL, MAL, FMA), correlations were performed by averaging clinical outcomes over time.

RESULTS

Participants

A total of 105 participants were recruited, 16 were withdrawn before baseline testing (data not included) due to medical illness or death; with 89 continuing until completion. Participants were aged between 45 and 93 years and were first assessed between zero to 11 days (see **Table 1**). Thrombolysis rates at the recruiting hospital are on average 17% and this sample would reflect that as it is representative (57). At 1 month, 67 participants were tested, followed by 82 at 2 months and 86 at 6 months (see **Figure 1**). The increase in missing assessments at 1 month were due to loss of contact in transition from hospital to rehabilitation, transitional care or home, $n = 22$. In relation to sensation and body awareness, half of the participants exhibited proprioceptive and tactile impairments, while all participants showed impairments in interoceptive awareness.

Change Over Time Comparisons

Each linear mixed model investigating recovery outcomes over time reached significance (all $p < 0.05$, see **Table 2**) except for the MAIA where a significant change over time was not observed ($p = 0.205$) (note, for ethical reasons this measure was not recorded at baseline). In general, for the outcomes that did reach statistical significance, a marked change was observed between baseline and

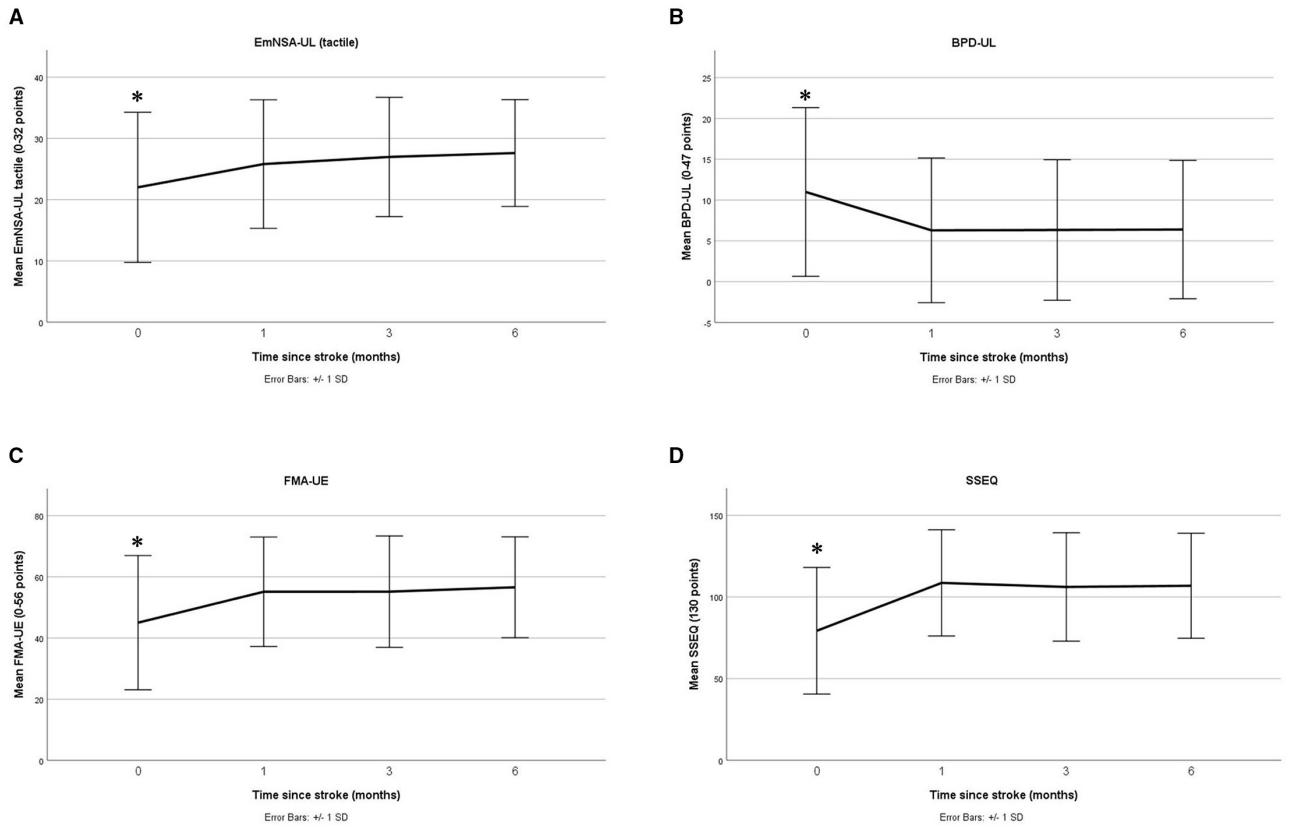

FIGURE 2 | Change over time (mean and standard deviation) for sensation **(A)**, body awareness **(B)**, motor impairment **(C)**, and quality of life **(D)** (baseline to 6 months) * indicates *post-hoc* analysis found significant differences at this timepoint.

one month, with a plateau between months 1 and 3 (see **Figure 2** and *post-hoc* comparisons in **Appendix 1**).

Correlation of Body Awareness and Sensation With Other Variables

Correlation analyses found that higher scores on sensation and body awareness measures were associated with improved clinical outcomes (see **Table 3**). Briefly, correlational analyses found upper limb body awareness (BPDUL) correlated strongly with lower limb body awareness (BPULL), self-efficacy (SSEQ), quality of life (SIS and SSQoL), and motor function/impairment (MALQQM, MALAOU, FMAUE). However, the MAIA body awareness measure showed very weak to weak correlations with body awareness (rho = −0.185 for BPDUL and rho = −0.156 for BPDLL) as well as other recovery measures. This was similar for EmNSA (tactile and proprioception), a measure of sensation which showed very weak to moderate correlations with all body awareness measures (BPDUL, BPDLL and MAIA), and this was further seen with the other recovery measures.

TABLE 3 | Correlational analyses of sensation and body awareness with other recovery measures (Spearmans rho).

	Sensation		Body Awareness		
Parameter	**EmNSA (Tactile)**	**EmNSA (Proprio.)**	**BPD UL**	**BPD LL**	**MAIA**
Gender (M/F)	0.206**	0.065	−0.040	−0.138*	0.063
Age (years)	0.048	−0.090	0.094	0.076	−0.143*
Time since stroke (days)	0.090	0.040	−0.270**	−0.252**	−0.162*
Side affected (L/R)	−0.060	−0.091	−0.028	−0.073	−0.074
NIHSS	−0.269**	−0.084	0.384**	0.191**	−0.049
MOCA	0.064	0.074	−0.266**	−0.174*	0.318**
FIM	0.111*	0.085	−0.444**	−0.241**	0.057
Location (metropolitan/rural)	0.236**	−0.001	0.062	0.111*	−0.186**
EmNSA Tactile	**1.000**	0.517**	−0.288**	−0.188**	0.073
EmNSA Proprio.	0.517**	**1.000**	−0.228**	−0.135*	0.177*
BPDUL	−0.288*	−0.228**	**1.000**	**0.765****	−0.187**
BPDLL	−0.188**	−0.135*	**0.765****	**1.000**	−0.156*
MAIA	0.073	0.177*	−0.187**	−0.156*	**1.000**
SSEQ	0.254**	0.236**	**−0.666****	−0.513**	0.206**
SIS Total	0.301**	0.322**	**−0.696****	−0.516**	0.210**
SIS %	0.334**	0.219**	−0.583**	−0.436**	0.130
SSQoL	0.266**	0.297**	**−0.658****	−0.480**	0.194**
MALQOM	0.328**	0.267**	**−0.723****	−0.493**	0.170*
MALAOU	0.313**	0.283**	**−0.702****	−0.481**	0.193**
FMAUE	0.324**	0.260**	**−0.661****	−0.440**	0.214**

*Correlations: 0.00–0.19 very weak; 0.20–0.39 weak; 0.40–0.59 moderate; 0.60–0.79 strong (bold/underlined); 0.80–1.00 very strong (bold/underlined); * (correlation is significant at the 0.05 level); ** (significant the 0.01 level).*

BPD, Body Perception Disturbance Scale; EmNSA UL tactile, Erasmus modified Nottingham Sensory Assessment-Upper Limb; FMA-UE, Fugl-Meyer Assessment- Upper Extremity; MAIA, Multidimensional Assessment of Interoceptive Awareness Questionnaire; MAL QOM/AOU, Motor Activity Log- Quality of Movement/Amount of Use; Proprio. (proprioception); SSEQ, Stroke Self-Efficacy Questionnaire; SIS, Stroke Impact Scale; SSQoL, Stroke-Specific Quality of Life Scale.

Gender: Male = 1; Female = 2; Side affected: Left = 1, Right = 2; Location: Metropolitan = 1; Rural = 2.

DISCUSSION

Main Findings

To our knowledge, this is the first study to explore impairment of body awareness following stroke and the associated recovery across subsequent months. The main finding of this study was that body awareness was reduced after stroke and improved within the first month, but plateaued with post-stroke gains persisting between 1 and 3 months. This was similar for measures of sensation, motor impairment, function, self-efficacy and quality of life. In addition, greater body awareness was associated with better outcomes for the five mentioned key recovery domains. This is an important finding because it provides insight into understanding the importance of body awareness after stroke. Further, this pattern fits typical stroke and recovery processes. Preclinical studies investigating motor recovery highlight that neural plasticity is enhanced early after stroke, both facilitating and accelerating recovery (56). In humans, behavioural studies suggest motor recovery predominantly occurs within the first 3–6 months before improving further, plateauing or even declining (54, 56). Our current findings suggest a similar pattern may emerge for body awareness (54). These findings are in line with literature concerning other post stroke impairments, possibly because this period of rapid stroke recovery is linked with spontaneous upregulation of plasticity (54). Most recovery was observed within 1 month, this coincides with heightened plasticity and likely delivery of rehabilitation services (54, 56). Alternatively, cost, availability and type of therapeutic input available subsequently required to maintain sufficient levels of therapy dosage may be inadequate.

These findings from this paper highlight the potentially important association that body awareness (using the BPD measure of the upper limb) in particular may have with motor function/impairment (MAL and FMA-UE), self-efficacy (SSEQ) and quality of life (SIS and SSQoL). Although the BPD measure was subjective, the questions directly related to body awareness impairments commonly experienced after stroke and were rated on a numerical scale. It was also time efficient to apply and directly related to symptoms of body awareness post-stroke such as limb size, weight and position (notably both body schema and body image). That the upper limb section appeared to have stronger correlations with other clinical outcomes compared to the lower limb section of the BPD might be explained by the arm having a greater prevalence of sensory loss post-stroke (43, 45, 50). Although other factors beyond sensorial are thought to contribute to body awareness, unexpected findings were found with a poor association between body awareness using the MAIA measure, and all other recovery measures. This may be because this measure was only assessed from 1 to 6 months and did not include a baseline assessment, or perhaps it may not be a useful measure for stroke. Further, the complexity of the questions (e.g., on a scale of zero to five how often do I "listen to my body to inform me about what to do") may have reduced the

accuracy of the responses. It should be noted that the MAIA is only validated in the pain and anxiety literature, and may not translate to this stroke population. Even more surprisingly both measures of body awareness were poorly associated with sensation despite the conceptual models indicating sensation and body awareness are related (10, 41). This finding might suggest body awareness impairments are only partly explained by sensory loss and other perceptual and conceptual processes are more likely to contribute.

A few studies have looked at whether implementing a body awareness training program improves motor impairment and function, however none of these studies measured body awareness (51–53, 58, 59). Only one recent study has looked at this relationship in stroke and reported a positive association between body awareness, balance function (postural control) and independence in activities of daily living (41). This study showed a high level of body awareness was observed in the group with high functional (balance) abilities and independence in daily activities. The focused attention on both the performance and experience during the movements increased the physical and mental aspects of body awareness. Unfortunately, no reports of self-efficacy have yet been assessed (41).

Strengths and Limitations

This study had several strengths including a large sample size; consecutive (representative) case recruitment; heterogeneity in participant demographics and severity of impairments; and the number of follow-up assessments, as well as face validity for the usefulness of the Body Perception Disturbance measure in individuals following stroke. For the limitations of this study we acknowledge not all participants were available at follow-up assessments for a variety of reasons. Therefore, results should be viewed cautiously. The inclusion of a 12-month assessment to review the longer-term pattern of recovery, as well as the inclusion of a baseline neglect measure also may prove beneficial. In addition, all participants were recruited from one main hospital in South Australia potentially reducing the generalisability of this study's findings. Therapy (including thrombolytics) received during the first month and post-discharge from the acute settings was not individually documented and may have been useful to further understand and clarify these findings. Lastly, the BPD (60) and MAIA (1) body awareness measures were sourced from non-stroke literature (pain and anxiety, respectively) because stroke-validated tests could not be identified (in press); therefore they provide only an indication of the importance and impact of body awareness post-stroke.

Future Directions

Future studies should consider lesion characteristics which may help further understand the effects of stroke on body awareness, as well as the relative vulnerability of relevant networks to stroke. A body awareness measure that assesses all constructs of body awareness (image and schema) appropriately for stroke now needs to be developed and piloted in both healthy and stroke populations. The BPD measure appears to have constructs that are most relevant in the stroke population as it covers several aspects of body awareness including body schema and some structural features. However, we do not recommend the MAIA for several reasons: some of the questions in the MAIA were felt to be too distressing for someone in the acute stroke phase, and it also includes hypervigilance (as a result of anxiety) which is not relevant in stroke where hypo-vigilance and neglect are more likely scenarios. In addition the inclusion of neurological imaging could confirm the hypothesised networks regarding body schema and body image.

A further large prospective study is now required to replicate our findings and advance our understanding of the drivers of body awareness, to more definitively understand the role it may play in motor impairment and function, and to develop effective assessment and intervention strategies. The current findings open the door to develop a greater understanding of how body awareness specifically changes following a stroke and how these are modified by the passage of time. It also allows consideration of new treatment approaches such as interventions that might seek to enhance body awareness directly.

CONCLUSION

In summary, this is the first study to document changes in body awareness over time and its association with other key stroke recovery outcomes. We observed body awareness was reduced after stroke, appeared to recover somewhat within the first month and was correlated with clinical outcomes for self-efficacy, quality of life and motor function/impairment. These findings highlight the importance that body awareness may play in stroke recovery. Such information might enable clinicians to intervene more effectively to facilitate recovery either by improving awareness in order to improve activities of daily living or by teaching individuals to find an effective alternative for these difficulties.

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 University of South Australia Human Ethics Committee and the Central Adelaide Local Health Network (CALHN). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.745964/full#supplementary-material

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Efficacy of Scalp Acupuncture in Patients With Post-stroke Hemiparesis: Meta-Analysis of Randomized Controlled Trials

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Huang Y-J, Huang C-S, Leng K-F, Sung J-Y and Cheng S-W (2021) Efficacy of Scalp Acupuncture in Patients With Post-stroke Hemiparesis: Meta-Analysis of Randomized Controlled Trials. Front. Neurol. 12:746567. doi: 10.3389/fneur.2021.746567

Objectives: To conduct a meta-analysis to assess the efficacy of scalp acupuncture (SA) in patients with stroke and consequent hemiparesis regardless of brain infarction or intracerebral hemorrhage.

Methods: A literature search of randomized controlled trials (RCTs) on SA for stroke was performed in five databases up to May 10, 2021. We investigated three types of outcome: motor function, sequelae of poststroke hemiparesis, and adverse effects. Methodological quality was assessed using the revised Cochrane risk of bias tool version 2.0.

Results: Of 1,063 papers, 30 RCTs involving Fugl–Meyer Assessment were selected, among which 10 and four RCTs were selected for evaluation of courses lasting of 1 and 3 months, respectively. The meta-analysis of 1- and 3-month courses revealed significant differences in the motor function of the SA plus Western standard treatment group vs. Western standard treatment only (medication plus rehabilitation; $P < 0.001$). A 3-month course tended to result in better outcomes than a 1-month course.

Conclusions: Our meta-analysis results reveal that SA improves motor function in patients with acute to chronic stroke, regardless of brain infarction or intracerebral hemorrhage. However, because of a lack of methodological quality, thoroughly planned clinical studies are still required.

Keywords: stroke, meta-analysis, randomized controlled trial, scalp acupuncture, revised Cochrane risk of bias assessment

INTRODUCTION

Stroke is the sudden injury of neurons due to lack of blood supply to the brain, leading to the rapid development of a focal neurologic deficit. Globally, stroke is the second leading cause of death and a major cause of disability (1). It can be classified as ischemic (blood vessel occlusion) or hemorrhagic (blood vessel rupture). Common risk factors for ischemic

and hemorrhagic stroke are age, race, sex, hypertension, diabetes, smoking, dyslipidemia, and alcohol use. For ischemic stroke, the specific risk factors are family history, atrial fibrillation, asymptomatic carotid stenosis, cardiac disease, sickle cell anemia, diet (high-sodium, low-potassium diet in overweight or elderly individuals), physical inactivity, obesity, hormone replacement therapy, hyperhomocysteinemia, hypercoagulability, lipoprotein(a), lipoprotein-associated phospholipase A2, inflammation, infection, and geography. For hemorrhagic stroke, the specific risk factors are antithrombolytic use, cerebral amyloid angiopathy, microbleeding, illicit drug use, dialysis, and tumors (2). Stroke incurs a considerable economic burden (3). Rehabilitation is a major part of stroke recovery (4). Furthermore, the use of sensory stimulation (transcutaneous electrical nerve stimulation or acupuncture) was reported to contribute to routine rehabilitation and improve poststroke hemiparesis (5).

Acupuncture has been a mainstream therapy in traditional and complementary medicine for >3,000 years for several diseases and also for poststroke recovery. Among the various methods, scalp acupuncture (SA) is a modern acupuncture technique integrating traditional Chinese needling methods with Western medical knowledge of representative areas of the cerebral cortex. SA is performed based on the functionality of brain areas to stimulate different scalp zones with needles; such stimulation improves the reflexivity of certain nerves and is mostly applied in individuals with acute and chronic central nervous system disorders, especially stroke (6). The mechanisms that are currently considered possible for SA include reducing brain edema, diminishing cerebral vessel permeability, promoting reparation of blood–brain barrier damage, decreasing inflammation, improving energy metabolism, and relieving the inhibitive generalization of the whole brain neuron function (7).

In the past decade, several systematic reviews and meta-analyses have been published that have assessed the effect of SA on acute hypertensive intracerebral hemorrhage (8) and postapoplectic aphasia (9). In addition, a meta-analysis of animal studies reported promising results, finding that SA improved infarct volume and neurological function score (10). Moreover, in Young-Nim et al. (11) obtained similar results in their meta-analysis; however, the intervention methods were mixed (SA and body acupuncture). Therefore, we decided to investigate whether additional SA has benefits for patients with stroke. The purpose of this study was to comprehensively review randomized controlled trials (RCTs) that evaluated the effectiveness of SA for motor dysfunction in stroke. We wanted to obtain a clinically meaningful synthesis of the existing evidence to determine whether SA may be a suitable complementary therapy for the motor sequelae of stroke.

MATERIALS AND METHODS

Types of Studies

Randomized controlled trials (RCTs) evaluating the effect of SA on motor function in stroke with the control group receiving modern standard treatment or conventional treatment were included in this study.

Types of Participants

Randomized controlled trials (RCTs) that included patients of any age or sex with acute or chronic stroke were eligible. SA was administered to patients with stroke as diagnosed through CT or MRI. The control group in these RCTs received only standard Western treatment for stroke in a neurological ward.

Types of Intervention

Randomized controlled trials (RCTs) were included regardless of treatment duration and number of sessions, but acupoint selection was limited to the scalp; ears and body acupoints were excluded. The control group patients received Western standard treatment (medications and rehabilitation). Patients in the trial groups received SA therapy (SA of standard international acupuncture nomenclature) in addition to the same standard treatment as that in the control groups. Concerning SA, acupoints are mostly in the motor areas (the anterior oblique line of the vertex-temporal, MS 6) and sensory areas (the posterior oblique line of the vertex-temporal, MS 7) of the contralateral scalp of hemiplegic limbs. The needle retention time was mostly between 0.5 and 2 h, and the depth of needle insertion was 2–4 cm. The frequency was 5–7 days per week and once a day. The treatment courses ranged from 2 weeks to 6 months. Those who performed SA in these studies were experienced doctors.

Outcomes Measured

We investigated three types of outcome: motor function, sequelae of poststroke hemiparesis, and adverse effects. We evaluated motor function in the upper and lower extremities at the end of the first and third months. The assessment was performed using the Fugl–Meyer Assessment (FMA), a stroke-specific, performance-based impairment index (12, 13). The FMA motor score ranges from 0 (hemiplegia) to 100 (normal motor performance) points, which were divided into 66 points for the upper extremity and 34 points for the lower extremity.

Literature Search

We searched databases, namely, PubMed, Embase, the Cochrane library, Airiti Library, and China National Knowledge Infrastructure (until May 2021) by two reviewers (YJH and CSH). The keywords used for the search were "scalp acupuncture" and "stroke." The type of article searched for was the RCT. We focused on poststroke hemiparesis or hemiplegia and excluded unwanted outcomes (poststroke dysarthria, poststroke dysphagia, poststroke aphasia, central poststroke pain, poststroke depression, poststroke cognitive impairment, etc.). The reference lists of all relevant articles were searched for further studies. There was no language limitation.

Data Extraction and Quality Assessment

Two reviewers (YJH and CSH) independently assessed all studies and independently extracted eligible data from the trial reports by using a data extraction form; data were cross-checked for accuracy before use. Disagreement was resolved through discussion with a third reviewer (SWC) if necessary. The authors of the trials were contacted and requested to provide missing data.

Quality assessment was conducted by revised Cochrane risk of bias tool 2.0 (RoB2.0) to determine whether the trials had the following concerns regarding internal validity: 1) risk of bias arising from the randomization process; 2) risk of bias due to deviation from intended intervention; 3) missing outcome data; 4) risk of bias in outcome measurements; or 5) risk of bias in the selection of the reported results. We conducted the risk of bias of summary and graph by using Review Manager 5.4.

Data Analysis

Heterogeneity between trial results was tested using the standard I^2 test. Results are reported as odds ratios with corresponding 95% CIs for dichotomous data. If continuous data were available, the weighted mean difference or standardized mean difference was calculated. Statistical analysis was performed using the statistical software R version 3.6.0 and the meta package.

RESULTS

Search Strategy and General Information

Based on the search strategy, we manually retrieved 1,062 papers found in the five databases and one from another source (manual search using Google Scholar). These studies were published from 1975 to 2021, and 253 papers had duplicate titles. Of the remaining 810 papers, after screening the abstracts, 18 animal studies, six expert opinions, seven case studies, 57 cohort studies, nine protocols, six systematic reviews or meta-analyses, 56 narrative reviews, 326 relevant articles with an unwanted outcome (poststroke dysarthria, poststroke dysphagia, poststroke aphasia, central poststroke pain, poststroke depression, poststroke cognitive impairment, etc.), and 17 irrelevant articles were excluded; the remaining papers with full text available were selected. Among the 306 RCTs selected, 25 papers with incomplete or insufficient data, one paper regarding noninternational-standard SA (Yamamoto new SA), 212 papers regarding impure SA with rehabilitation, 21 papers comparing different SA types, and 17 papers not including FMA scores were excluded. A total of 30 RCT papers containing FMA scores were finally selected (14–43). The process used for the literature search for the application in the systematic review is summarized in **Figure 1**.

All these 30 RCTs were conducted in China, and the corresponding articles were published from 2007 to 2019 (**Table 1**). Of these RCTs, 15 mentioned 1-month results; five mentioned 6-week results; six mentioned 2-month results; and six mentioned 3-month results. We assessed both upper and lower extremity strengths, so we selected only papers with complete FMA scores (including the upper and lower extremities with a total score of 100). We selected treatment courses of 1 and 3 months and then conducted the meta-analysis. A total of 1,043 patients with acute or chronic stroke from 12 reports were included.

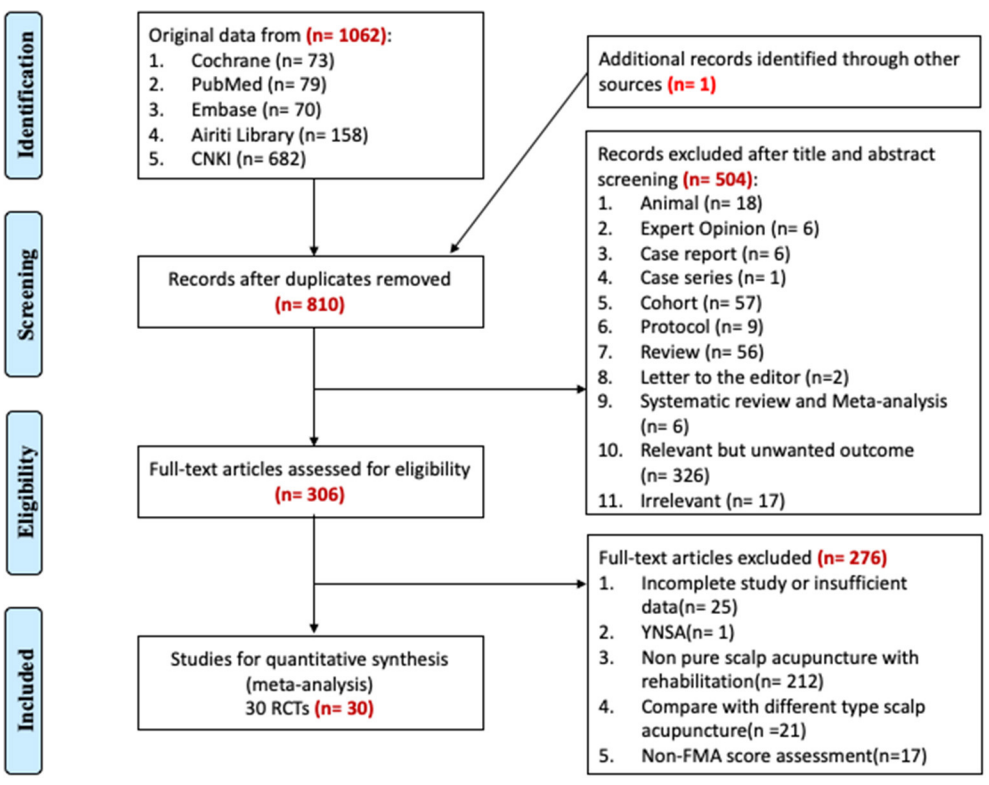

FIGURE 1 | Flow diagram of the literature search.

TABLE 1 | Characteristics of the included RCTs.

Study No.	Author	Year	Journal	Age(years)		Sex (male/female)		Stroke type (infarction/hemorrhage)		Course of treatment	Outcomes FMA U: upper; L: lower (*P*-value); S: sequelae; A: adverse effect
				experimental	control	experimental	control	experimental	control		
1	Xie	2007	Chinese Journal of Rehabilitation Theory and Practice	53 ± 9.3	56.5 ± 6.4	24/17	22/17	41	39	3 months	FMA:U+L ($P < 0.05$)
2	Li	2009	Shanghai J Acu-mox	61 ± 6	63 ± 6	24/21	27/18	34/11	35/10	6 weeks	FMA:U+L ($P < 0.01$), S
3	Ma	2010	Chinese Journal of Rehabilitation	62.1 ± 0.5	61.4 ± 0.2	8/7	9/6	15/0	15/0	3 weeks	FMA:U+L ($P < 0.05$)
4	Fu	2011	Chinese Journal of Traditional Medical Science and Technology	38-81*		37/27*		36/28*		2 months	FMA:U+L ($P < 0.01$)
5	Qin	2013	Journal of Clinical Acupuncture and Moxibustion	59.95 ± 6.35	60.95 ± 7.12	12/8	11/9	20	20	3 months	FMA:L ($P < 0.05$)
6	Kong	2014	Practical Journal of Medicine and Pharmacy	60 ± 9.72	87 ± 9.72	23/10	21/12	33	33	3 months	FMA:U ($P < 0.01$)
7	Zhang	2015	Chinese Medicine Modern Distance Education of China	63 ± 4	62 ± 5	16/14	15/15	18/12	17/13	1 month	FMA:U ($P < 0.05$)
8	Xu	2015	Hebei Medical Journal	58.3 ± 11.2	61.7 ± 9.1	45/15	42/18	48/12	44/16	1 month	FMA:U+L ($P < 0.05$)
9	Qin	2015	Chinese Journal of Gerontology	64.7 ± 5.66	65.3 ± 7.87	39/19	36/22	58	58	3 months	FMA:U+L ($P < 0.05$)
10	Tan	2015	Chinese Journal of Integrated Traditional and Western Medicine	58.4 ± 10.5	59.3 ± 11.5	40/40	42/38	60	60	1 month	FMA:U ($P < 0.01$)
11	Liu	2016	Modern Journal of Integrated Traditional Chinese and Western Medicine	58.6 ± 4.9	60.5 ± 3.9	17/13	20/10	23/7	20/10	1 month	FMA:L ($P < 0.05$)
12	Dou	2016	World Latest Medicine Information	58.7 ± 2.35	59.8 ± 2.77	23/10	22/11	33	33	1 month	FMA:U+L ($P < 0.05$)
13	Chen	2016	Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine	56.1 ± 6.45	55.29 ± 5.86	18/11	16/14	29/0	30/0	1 month	FMA:U+L ($P < 0.01$)
14	Wang	2017	Chinese acupuncture and moxibustion	62 ± 10	63 ± 8	42/18	50/10	21/39	26/34	1 month	FMA:U+L ($P < 0.05$)
15	Yang	2017	China Health Standard Management	47 ± 8.4	48.4 ± 2.5	10/8	11/7	12/6	9/9	1 month	FMA:U+L ($P < 0.05$)
16	Yin	2017	China Health Standard Management	65.2 ± 3.4	64.5 ± 3.2	28/22	26/24	37/13	38/12	2 months	FMA:U ($P < 0.05$)
17	Pan	2017	Information on Traditional Chinese Medicine	64.12 ± 9.69	62.91 ± 10.82	29/24	28/25	53	53	1 month	FMA:U ($P < 0.05$), S

(Continued)

TABLE 1 | Continued

Study No.	Author	Year	Journal	Age(years)		Sex (male/female)		Stroke type (infarction/hemorrhage)		Course of treatment	Outcomes FMA U: upper; L: lower (*P*-value); S: sequelae; A: adverse effect
				experimental	control	experimental	control	experimental	control		
18	Xu	2018	Chinese Medicine Modern Distance Education of China	58.44 ± 8.26	58.28 ± 7.95	12/13	13/12	25	25	1 month	FMA:U+L ($P < 0.01$)
19	Xiao	2018	Jilin Journal of Chinese Medicine	57.14 ± 9.67*		63/45*		54/0	54/0	3 months	FMA:U+L ($P < 0.05$)
20	Hu	2018	Asia-Pacific Traditional Medicine	64.7 ± 6.1*		61/51*		73/39*		2 months	FMA:U+L ($P < 0.05$)
21	Sun	2019	Chinese Journal of Convalescent Medicine	63.26 ± 2.56	63.15 ± 2.15	23/22	22/23	45/0	45/0	6 months	FMA:U ($P < 0.05$), A
22	Zhang	2019	Clinical Education of General Practice	54.49 ± 4.35	52.44 ± 12.13	23/17	21/19	29/11	26/14	6 weeks	FMA:U ($P < 0.05$)
23	Zhang	2019	Chinese Journal of Gerontology	64.3 ± 9.2	64 ± 9.6	18/16	17/17	20/14	20/14	3 months	FMA:U+L ($P < 0.05$)
24	Zhu	2019	Chinese Journal of Rehabilitation Medicine	49 ± 3.7	54 ± 1.9	27/13	17/23	40	40	2 months	FMA:L ($P < 0.01$)
25	Li	2019	China Modern Medicine	67.96 ± 7.98	68.65 ± 8.25	22/16	23/17	38/0	40/0	6 weeks	FMA:U ($P < 0.05$)
26	Hu	2019	Shanghai J Acu-mox	62 ± 10	62 ± 8	19/15	17/17	23/8/3**	26/6/2**	1 month	FMA:U+L ($P < 0.01$)
27	Ye	2019	New Journal of Traditional Chinese Medicine	65.12 ± 7.31	65.03 ± 7.12	33/13	34/12	46/0	46/0	2 months	FMA:U+L ($P < 0.01$)
28	Zhao	2019	Jilin Journal of Chinese Medicine	60.76 ± 7.43	59.89 ± 8.57	27/18	29/16	45	45	2 weeks	FMA:U+L ($P < 0.05$)
29	Chen	2019	Journal of Preventive Medicine of Chinese People's Liberation Army	62.53 ± 11.71	68.63 ± 4.79	12/8	11/9	20	20	6 weeks	FMA:U+L ($P < 0.05$)
30	Ma	2019	New Journal of Traditional Chinese Medicine	67.2 ± 5.7	65.4 ± 4.8	10/10	9/11	20	20	1 month	FMA:U ($P < 0.05$)

**The data was provided by the author before randomization. **Mixed type stroke.*

Quality of the Trials

Based on **Figure 2**, we determined the overall quality of the included studies to be low by RoB2.0. For the first domain (risk of bias arising from the randomization process), the generally unclear risk was indicated. All trials used a randomization method, including a random number generator (calculator) and a sequencing method. One trial (28) described a grade-A level of adequate concealment of randomization in which the patients were allocated according to calculated random numbers sealed in opaque envelopes. For the second domain (risk of bias due to deviation from the intended intervention), the risk was generally high because only one trial (21) included a control group for which sham acupuncture was implemented. The remaining 29 trials did not mention blinding or intention-to-treat analysis. For the third domain (missing outcome data), the risk was generally high because only two trials (21, 28) recorded missing data. For the fourth domain (risk of bias in outcome measurement), the risk was generally unclear because only three trials (14, 28, 37) mentioned that the assessor did not participate in the therapy. For the fifth domain (risk of bias in the selection of the reported results), the risk was generally low. All trials conducted a comparative analysis between the SA group and control group.

Death or Dependency

None of the trials used death or dependency as a primary outcome measure.

Muscle Strength Improvement (FMA)

Among the papers on 30 independent trials, 10 reporting the complete FMA score described the 1-month outcome (**Figure 3**; mean difference, 10.3 [95% CI, 7.43–12.63]; $P < 0.01$), and four reporting the complete FMA score described the 3-month outcome (**Figure 4**; mean difference, 15.18 [95% CI, 8.06–22.31]; $P < 0.01$). Two papers (17, 29) with a 1-month course mentioned that special rehabilitation may diminish the effect of SA; therefore, we removed these papers and reconducted a sensitivity test of the meta-analysis (**Figure 5**; mean difference, 11.16 [95% CI, 8.09–14.23]; $P < 0.01$). There were no homogeneity in the consistency of the trial results (1 month: $I^2 = 78\%$ and 3 months: $I^2 = 83\%$). SA was found to have significantly improved hemiparesis, as represented using the FMA score and when compared with the control group. The outcome after 3 months of SA (mean difference in FMA score: 15.18) seemed to be better than that after 1 month of SA (mean difference in FMA score: 11.16).

Sequelae of Hemiparesis-Associated Symptoms

Only two studies (15, 27) recorded the sequelae of hemiparesis, such as shoulder–hand syndrome, shoulder pain, and muscle atrophy. Only one study (15) recorded complete muscle spasticity and bedsores. After pooling the results of the two papers, we found a significant difference in the incidence of shoulder–hand syndrome (**Figure 6**; odds ratio, 0.39 [95% CI, 0.16–0.94]) between the experimental and control groups, but no difference in that of shoulder pain (**Figure 7**; odds ratio, 0.43 [95% CI, 0.17–1.11]) or muscle atrophy (**Figure 8**; odds ratio, 0.39 [95% CI, 0.13–1.15]).

Adverse Events

Adverse events were mentioned in one trial (38). In the SA groups, the abnormal response rate for dizziness and local skin

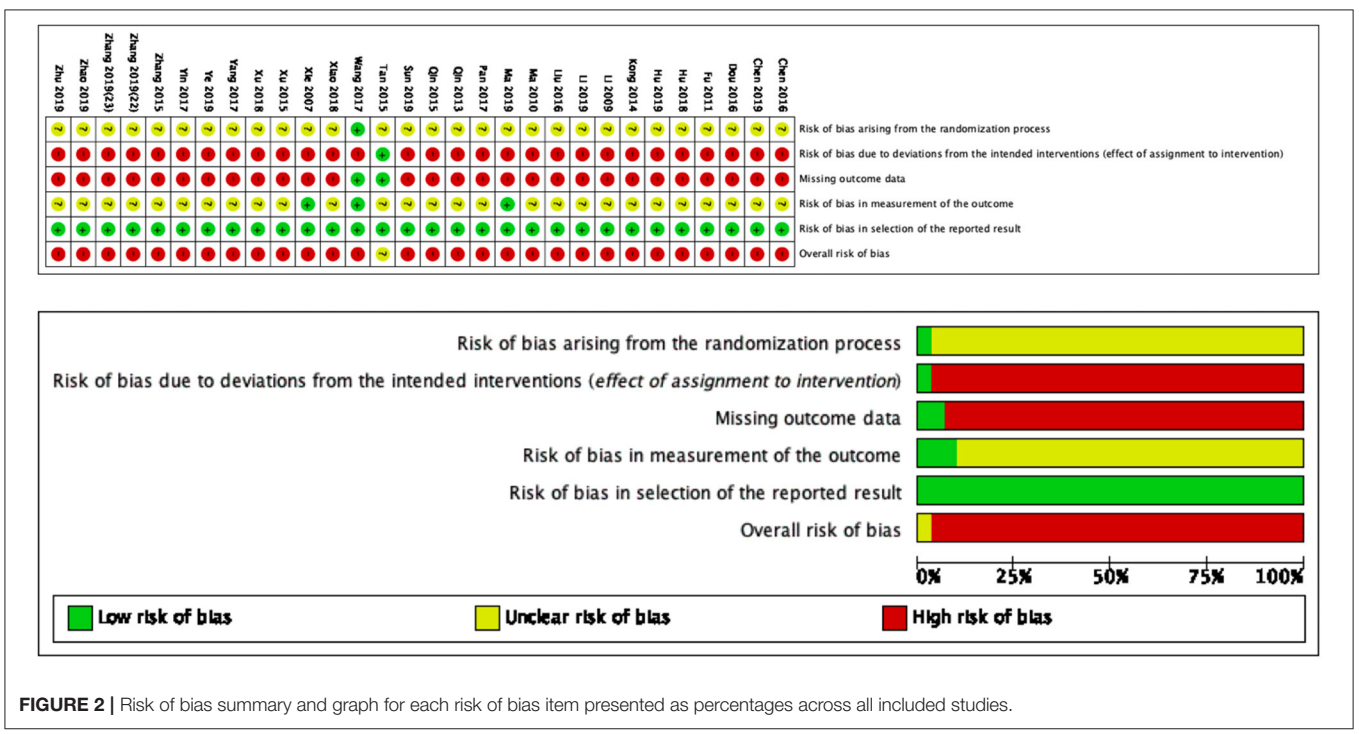

FIGURE 2 | Risk of bias summary and graph for each risk of bias item presented as percentages across all included studies.

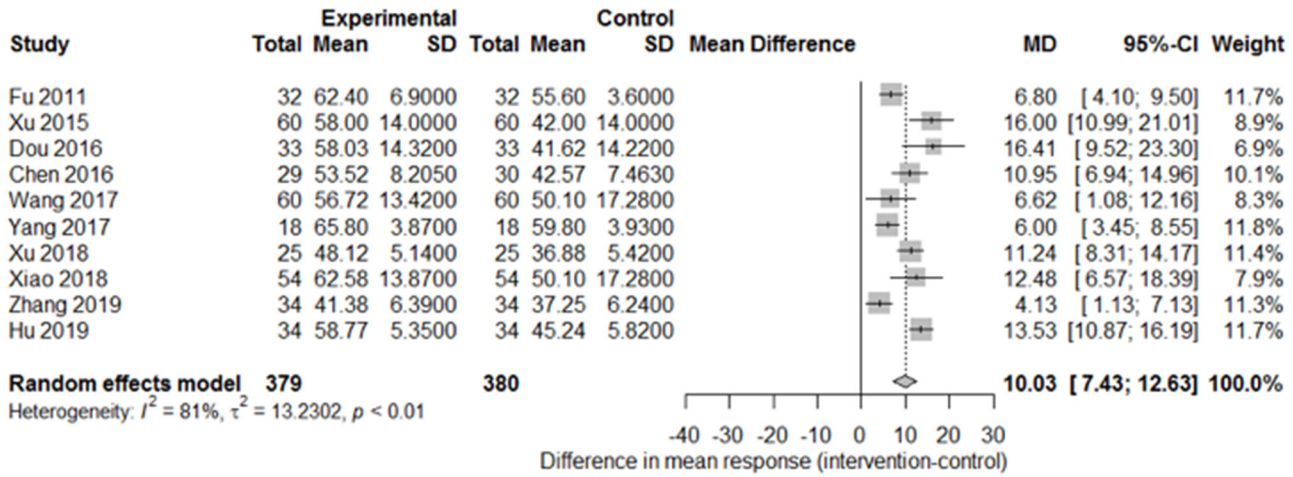

FIGURE 3 | Forest plot of the comparison of mean difference in hemiparesis improvement after treatment with SA vs. control after a 1-month course.

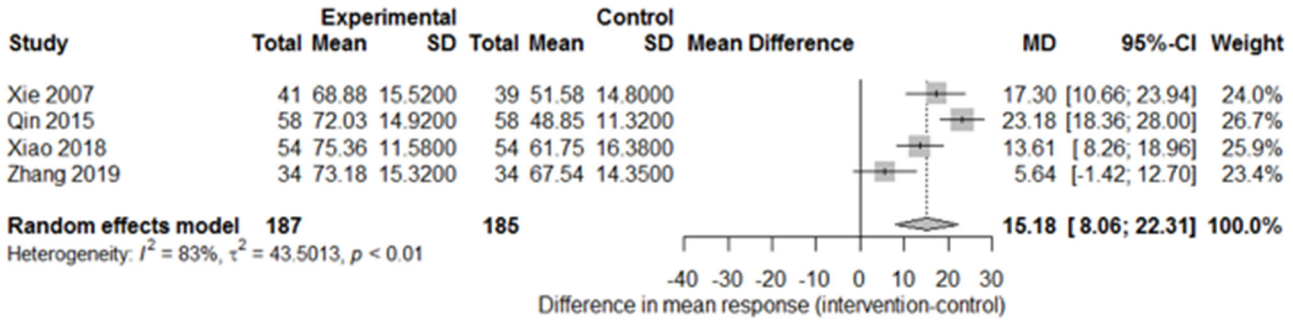

FIGURE 4 | Forest plot of the comparison of mean difference in hemiparesis improvement after treatment with SA vs. control after a 3-month course.

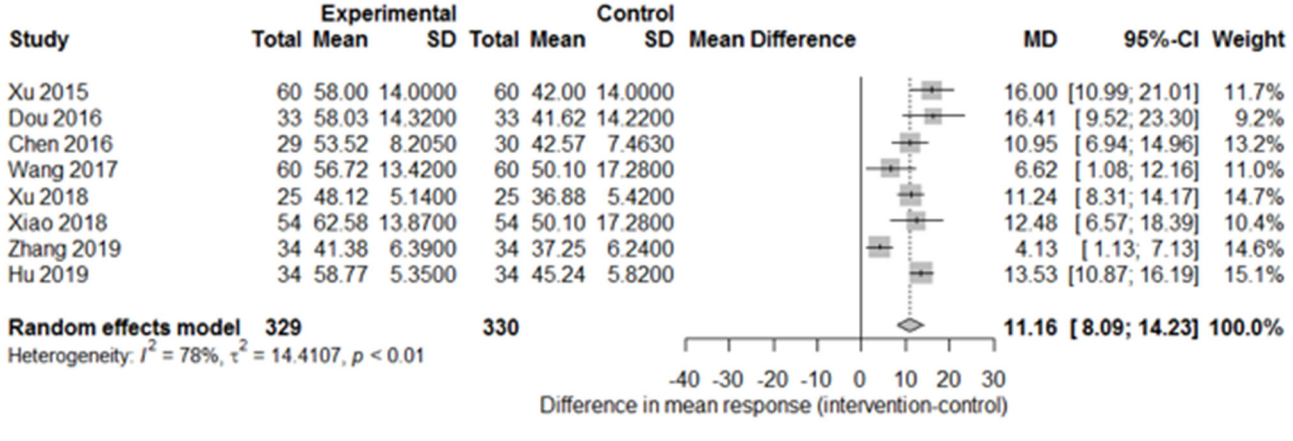

FIGURE 5 | Forest plot of the comparison of mean difference in hemiparesis improvement after treatment with SA vs. control after a 1-month course and removal of two papers on special rehabilitation for the sensitivity test.

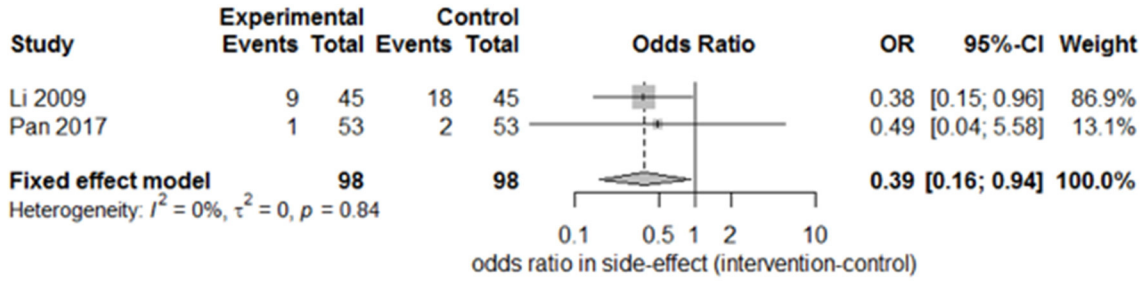

FIGURE 6 | Forest plot of the odds ratio comparison for shoulder–hand syndrome in the SA group vs. the control group.

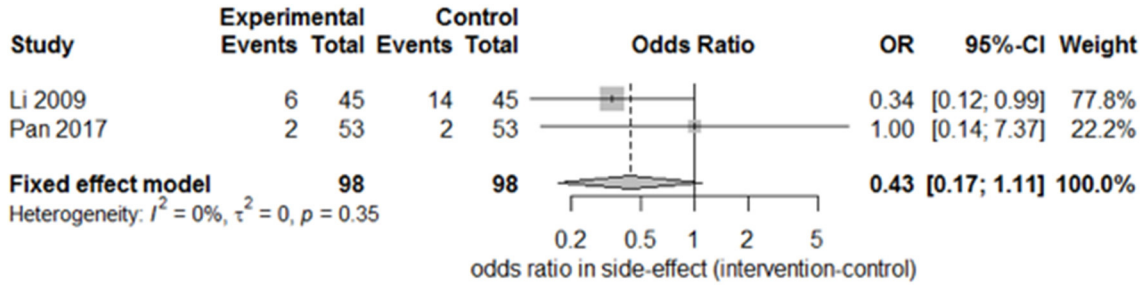

FIGURE 7 | Forest plot of odds ratio comparison for shoulder pain in the SA group vs. the control group.

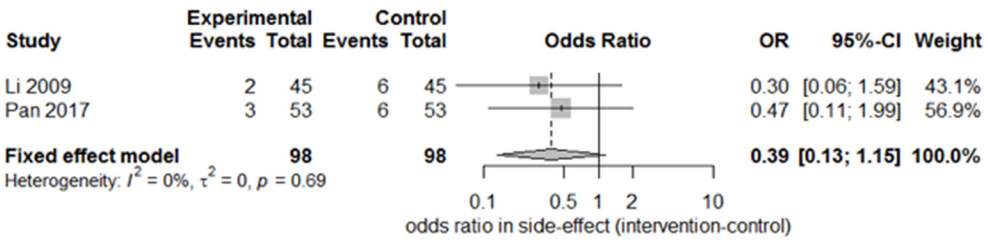

FIGURE 8 | Forest plot of the odds ratio comparison for muscle atrophy in the SA group vs. the control group.

redness was 6.67% (3/45), whereas it was 8.89% (4/45) in the control group. The difference was not significant.

Publication Bias

We used a contour-enhanced funnel plot to differentiate between asymmetry due to publication bias and other reasons. **Figure 9** demonstrates that almost all trials obtained a significant result favoring the experimental group, with $P < 0.01$ (light gray region) in nine trials and $0.01 < P < 0.05$ (dark gray region) in one trial. However, publication bias was noted in five trials from the funnel plot.

DISCUSSION

This is the first meta-analysis to specifically evaluate the clinical outcomes of SA for poststroke hemiparesis, regardless of hemorrhage or infarction. The results indicate that SA is effective for improving motor dysfunction in patients with stroke.

Other clinical studies have suggested that SA therapy may be a suitable complementary treatment for poststroke neurological dysfunctions, namely, dysphagia (44), aphasia (45), central poststroke pain (46), depression (47), and cognitive impairment (48). In this meta-analysis, after searching five databases up to May 2021, 30 RCTs with FMA scores were selected; a systematic review of the clinical research on SA for stroke was conducted, and each study was qualitatively assessed. The disease period investigated in the meta-analysis varied from acute to chronic. We wished to focus only on motor function; therefore, we used the FMA score rather than the National Institutes of Health Stroke Score or Barthel index. Among the 30 RCT papers, 10 described the outcome after 1 month and 4 mentioned the outcome after 3 months. For the sensitivity test, two papers were removed from the 1-month course because of special rehabilitation, which may have influenced the effect of SA therapy. We observed that Zhang (40) reported markedly lower efficacy of SA therapy in contrast to other papers reporting

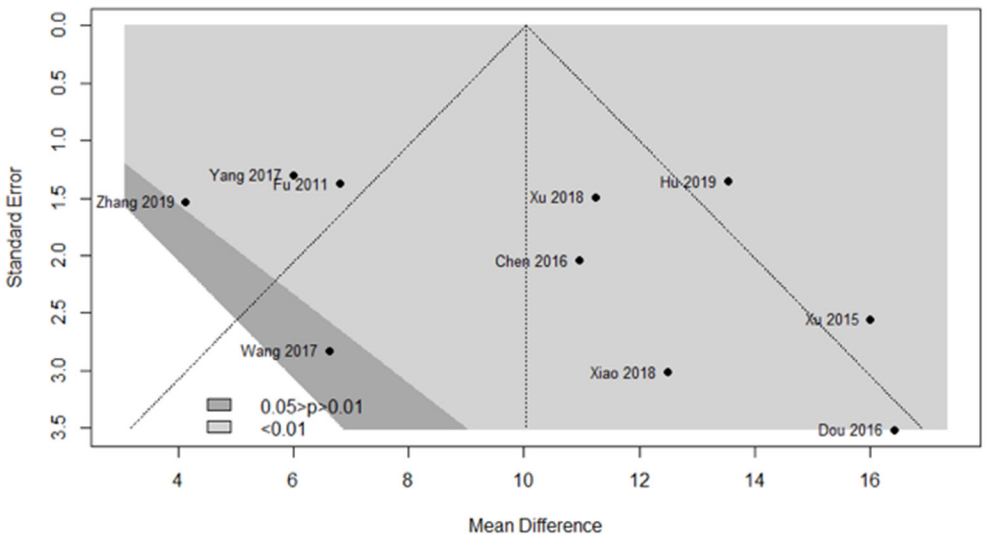

FIGURE 9 | Funnel plot of the clinical effects in the SA group vs. the control group after a 1-month course.

1- or 3-month courses; we speculated that this was related to the different areas of the scalp acupoints used, which were balance areas (MS 14) rather than the motor and sensory areas. When combined with Western standard medicine (medication and rehabilitation), SA obtained significantly better results in the meta-analysis on hemiparesis improvement during the stroke recovery period. A 3-month course tended to be better than a 1-month course. Regarding sequelae of hemiparesis-associated symptoms—namely, shoulder–hand syndrome, shoulder pain, and muscle atrophy—we observed additional SA benefits, although the difference was significant only in the incidence of shoulder–hand syndrome and not in the incidence of shoulder pain or muscle atrophy due to the small sample.

Almost all of the RCTs included in this meta-analysis were conducted without blinding due to the limitation inherent in the acupuncture procedure; thus, confounding factors, such as the placebo effect, may have been present. Only one paper (21) mentioned sham acupuncture as a control. Only two papers (21, 28) reported dropouts, and one paper (38) reported an adverse effect of SA; most papers did not mention these factors, which resulted in low assessment quality when the revised Cochrane risk of bias tool 2.0 was used.

There was no consistency in the rehabilitation method used in the studies in this meta-analysis, which may have affected the results on SA accuracy and efficacy. In most RCTs, physical therapy and occupational therapy were employed as rehabilitation interventions. One RCT added visual scanning and sensory integration training to the rehabilitation (17). Another study used special rehabilitation—constraint-induced movement therapy (29). The different rehabilitation types in these two studies weakened the effect of SA, which indicated that special rehabilitation may have a role in the improvement of poststroke hemiparesis. Different types of rehabilitation with integrated SA therapy as complementary treatment could be used in patients with stroke.

Not all RCTs compared the effect of SA between brain infarction and hemorrhage. The populations in these RCTs were all Asian, and there is a lack of data on Western populations; therefore, whether racial differences affect the outcome of SA must be determined in the future.

Only one study (38) reported the 6-month outcome of SA; significant improvement in poststroke hemiparesis was discovered, which indicated that longer SA duration may result in added benefits in patients with stroke. Another trial (49) assessed the degree of improvement of limb dysfunction by noting the scalp needle retention time in patients with stroke. The scalp needles in the treatment group were indwelled for 7–10 h and in the control group for 30 min. The results indicated greater improvement in limb dysfunction and activities of daily living after stroke when scalp needle retention was longer. The duration effect of SA therapy warrants further 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.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Category 1: Y-JH conception and design of study and acquisition of data. Y-JH, C-SH, K-FL, J-YS, and S-WC analysis and/or interpretation of data. Category 2: Y-JH drafting the manuscript. Category 3: C-SH, K-FL, J-YS, and S-WC revising the manuscript critically for important intellectual content. Y-JH, C-SH, K-FL, J-YS, and S-WC approval of the version of the manuscript to be published. All authors contributed to the article and approved the submitted version.

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Muscle Electrical Impedance Properties and Activation Alteration After Functional Electrical Stimulation-Assisted Cycling Training for Chronic Stroke Survivors: A Longitudinal Pilot Study

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Electrical impedance myography (EIM) is a sensitive assessment for neuromuscular diseases to detect muscle inherent properties, whereas surface electromyography (sEMG) is a common technique for monitoring muscle activation. However, the application of EIM in detecting training effects on stroke survivors is relatively few. This study aimed to evaluate the muscle inherent properties and muscle activation alteration after functional electrical stimulation (FES)-assisted cycling training to chronic stroke survivors. Fifteen people with chronic stroke were recruited for 20 sessions of FES-assisted cycling training (40 min/session, 3–5 sessions/week). The periodically stimulated and assessed muscle groups were quadriceps (QC), tibialis anterior (TA), hamstrings (HS), and medial head of gastrocnemius (MG) on the paretic lower extremity. EIM parameters [resistance (R), reactance (X), phase angle (θ), and anisotropy ratio (AR)], clinical scales (Fugl-Meyer Lower Extremity (FMA-LE), Berg Balance Scale (BBS), and 6-min walking test (6MWT)] and sEMG parameters [including root-mean square (RMS) and co-contraction index (CI) value] were collected and computed before and after the training. Linear correlation analysis was conducted between EIM and clinical scales as well as between sEMG and clinical scales. The results showed that motor function of the lower extremity, balance, and walking performance of subjects improved after the training. After training, θ value of TA ($P = 0.014$) and MG ($P = 0.017$) significantly increased, and AR of X ($P = 0.004$) value and AR of θ value ($P = 0.041$) significantly increased on TA. The RMS value of TA decreased ($P = 0.022$) and a significant reduction of CI was revealed on TA/MG muscle pair ($P < 0.001$). Significant correlation was found between EIM and clinical assessments (AR of X value of TA and FMA-LE: $r = 0.54$, $P = 0.046$; X value of TA and BBS score: 0.628, $P = 0.016$), and between sEMG and clinical scores (RMS of TA and BBS score: $r = -0.582$, $P = 0.029$). This study demonstrated that FES-assisted cycling training improved lower limb function by developing coordinated muscle activation and facilitating an orderly myofiber arrangement. The current study

also indicated that EIM can jointly evaluate lower extremity function alteration with sEMG after rehabilitation training.

Clinical Trail Registration: The study was registered on the Clinical Trial Registry (trial registration number: NCT 03208439, https://clinicaltrials.gov/ct2/show/NCT03208439).

Keywords: cycling, electromyography (EMG), electrical impedance, functional electrical stimulation (FES), stroke

INTRODUCTION

Stroke is a leading cause of disability that impairs sensorimotor and cognitive functions and the activities of daily life (ADL) and contributes to a huge burden on the health, financial, and social resources (1). Gait-related disorders cause significant inconvenience in the ADL of survivors, and persons with stroke meet great challenge to perform smooth ambulation, especially in normal walking and cycling (2). Therefore, a suitable training protocol is desired and essential for them to restore their muscle strength and to regain their motor function (3).

Functional electrical stimulation (FES) and cycling training are common strategies for improving ambulatory function in rehabilitation after stroke. With a positive orthotic effect from FES (4, 5) and symmetrical coordination of muscle contraction during cycling (6), the FES-assisted cycling training was demonstrated in previous studies to bring crucial benefits to chronic stroke survivors by promoting their walking ability (7–11). However, the inherent properties of muscle changes after FES-assisted cycling training are limitedly explored. Besides motor functional deficits, muscle composition and structure significantly alter as stroke proceeds. Those muscle changes include reduction of quantity and proportion of muscle fiber, intramuscular fat infiltration (12), muscle volume, and lean muscle mass dropping (13–15). These muscle changes contribute to a decrease in force production and functional performance of the muscle (16). Therefore, it is necessary to study the muscle composition, structure, and function alterations related to training for stroke survivors, which will reinforce the understanding of the improvement after the intervention.

Electrical impedance myography (EIM) has been considered as a biomarker to assess the neuromuscular disease progression (17) with high repeatability and reliability (18). During EIM assessment, a weak, high-frequency alternating current flows through the muscle that has been evaluated and produces resultant voltage without causing neuron depolarization and muscle contraction (19). The EIM assessment computes electrical impedance parameters of muscles which reflects the inherent properties of the muscle, including resistance (R), reactance (X), phase angle [$\theta = \arctan$ (X/R)], and anisotropy ratio (AR). These parameters are related to muscle volume conduction properties (VCPs) (20). The VCPs are objective physical properties of muscle that are determined by the presence of extracellular and intracellular fluid and by the integrity of cell membranes and tissue interfaces (21–23). Among the EIM parameters, resistance is defined as the inherent resistivity of the assessed muscle, which is influenced by the intracellular and extracellular fluids and fat. Reactance represents the delay in conduction caused by cell membranes, non-ionic substances, and tissue interfaces. The R and X values might be influenced by muscle shape, mass, and tissue integrity (21). To reduce the impact of muscle size on impedance analysis, the θ value is calculated based on the R and X values, which evaluate membrane oscillation properties of the muscle (23). The AR value represents the degree of columnar order in the arrangement of the fibers (24). Higher AR value means a more regular arrangement of myofibers (24–26). In comparison with other muscle property assessment techniques, such as MIR and electromyography, the EIM requires less cooperation from the patients and has shorter time on performing the measurement (27). Lately, Li et al. applied EIM in assessing muscle changes after stroke and demonstrated significant difference in electrical impedance and anisotropic properties of muscle between the paretic side (side dominated by lesional hemisphere) and the nonparetic side (side dominated by contralesional hemisphere) (28). Previous studies also combined EIM with other techniques to further explore the alteration of muscle inherent properties after stroke, including the assessment of ultrasound (29) and compound muscle action potentials (30). In our previous study, EIM parameters, such as X and θ values, were correlated with the muscle structure characteristics assessed by ultrasound in stroke survivors (29), and this pilot ultrasound-EIM combined study revealed that the feasibility of EIM intuitively evaluates the muscle structure alteration with medical images (29). However, there is limited exploration of the application of EIM for assessing the training effects after stroke.

Surface electromyography (sEMG) is widely applied to evaluate muscle activation and muscle contraction pattern. A root mean square (RMS) value of sEMG signal is commonly calculated, which directly reflected the muscle activation ability (31). In addition, the co-contraction index (CI) is computed between two related muscles to identify the muscle contraction pattern during movements (32). The aim of this study was to apply EIM and sEMG to track the muscle inherent properties and activation changes of paretic lower extremity muscles after FES-assisted cycling training for chronic stroke survivors. We hypothesized that muscle impedance properties of paretic muscles would change toward those of the non-paretic muscles, and muscle contraction coordination would also improve after training, and those EIM and sEMG changes might be related to the improvement of clinical scales. The findings of this study could provide insights for clinical evaluation of training effect in muscle weakness and functional deficits on chronic stroke survivors.

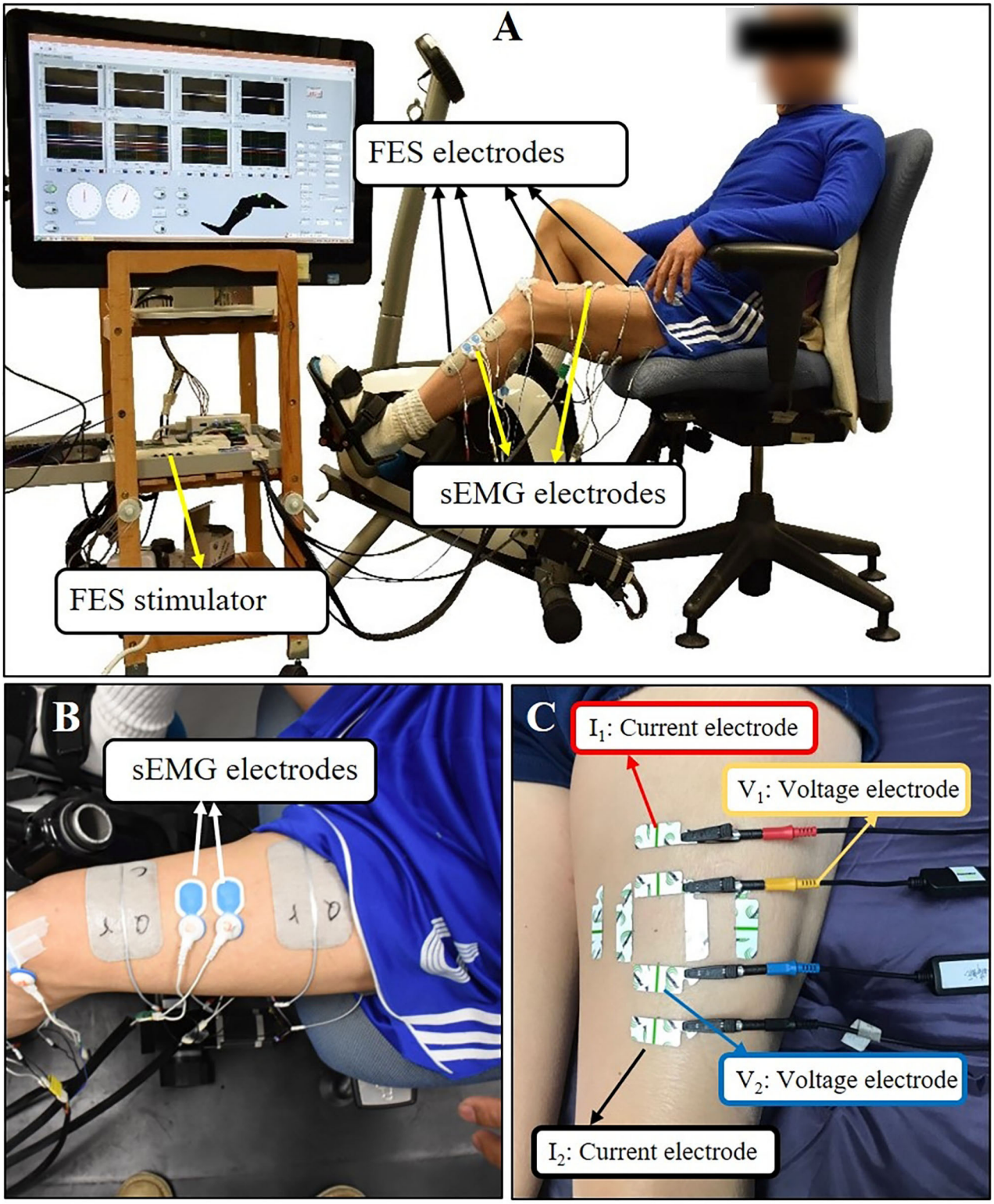

FIGURE 1 | (A) The setup of FES-assisted cycling training system. The pedaling angle was monitored by a goniometer. **(B)** Using quadriceps as an example for sEMG electrodes placement. **(C)** Using quadriceps as an example for EIM electrodes placement. The outer two electrodes (the red and black one) were current electrodes, inner two electrodes (the yellow and blue one) were voltage electrodes. Each test lasted for few seconds and three tests were conducted repeatedly at each direction of the arrangement.

METHODS

Participants and Study Design

Subjects were recruited from primary rehabilitation centers in Hong Kong. After recruitment, they were invited to the lab on the campus for the training. The inclusion criteria were as follows: (1) diagnosed as stroke with hemiplegia; (2) more than 6 months duration after the onset; (3) significant gait deficit (Functional Ambulatory Category, FAC <4). The exclusion criteria were as follows: (1) any additional medical or psychological condition that would affect their ability to comply with the study protocol, e.g., a significant orthopedic or chronic pain condition, major poststroke depression, epilepsy, and artificial cardiac pacemaker/joint; (2) severe hip, knee, or ankle contracture that would preclude passive range of motion of the leg. All of the subjects gave written consent before the experimental procedures. This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster (CUHK-NTEC) Clinical Research Ethics Committee (Ref. no: 2016.093), and all the procedures of this study have been operated in accordance with the Declaration of Helsinki. This study was registered on ClinicalTrials.gov (NCT 03208439). This study utilized a self-controlled design with the combination of clinical scales, EIM, and sEMG assessments on lower extremities after FES-assisted cycling training.

Apparatus and Procedures

FES-Assisted Cycling Training

The cycling equipment includes a pair of pedal meters (PowerTap P1 Pedal Meter, USA) and motor (UIRobot UIM241Co4P-IE/57-76, China). During the cycling training, the subjects were seated on a chair of the cycling system with standardized height of seat and pedaled with voluntary muscle contraction under the assistance of FES. A goniometer was used to measure the angle of pedals (**Figure 1A**). A portable four-channel programmable FES device (Easy Walker, P2-9632 Fine Cure, China) including FES surface electrodes (AXLEGAARD PALS electrodes; Axelgaard Manufacturing Company, CA, USA) were applied. A programmed interface running on the Labview platform was displayed on a computer screen which was viewed by the subjects. Four pairs of electrodes were attached on four paretic lower limb muscle groups and each pair of electrodes was linearly arranged symmetrically on the two sides of sEMG electrodes with a 1 cm interval distance between two neighboring electrodes (**Figure 1A**). For quadriceps (QC), medial head of gastrocnemius (MG), and hamstrings (HS), 5 cm * 8 cm surface electrodes were used, and the 5 cm* 5 cm surface electrodes were also used for tibialis anterior (TA). The parameters for FES were set at a pulse width of 300 μs and the stimulation frequency was set at 20 Hz (8). The FES stimulation pattern was periodically constructed from muscular activation intervals identified on three healthy volunteers (male, 24 ± 2-year-old) during pedaling. The ranges, where FES stimulation happens, were mapped with the muscle activation of healthy subjects in one revolution as illustrated in **Figure 2**. The FES stimulation would be turned "ON" in 340°−190°, 220°−360°, 0°−210°, and 160°−20° on HS, QC, MG, and TA respectively. Every recruited subject received 20 sessions of training (3–5 sessions/week). For every session, firstly, the skin of QC, HS, TA, and MG muscles was exfoliated and cleaned before attaching the electrodes and then, the stimulation intensity was set. The stimulation intensity could be adjusted between 0 and 60 mA and the ideal stimulation intensity produced a visible good contraction of the corresponding muscle to induce a joint movement without any pain and discomfort.

Before pedaling, the angle of the pedals was calibrated, and the 0° of the pedal was set so that the two pedals were in the same line which was vertical to the ground. In each training session, 2 trials were performed and each of them lasted 10 min with a 5-min break between the trials. Each trial included a 2-min warm-up period of voluntary cycling at a cadence of 15 rpm, a 7-min training period of cycling-assisted by FES, and a 1-min cool down period of passive cycling. During passive cycling, the legs of the subjects were passively moved by a motor at a cadence of 15 rpm. Subjects were instructed to normally pedal with their own efforts in the warm-up and training period. One cycling training session took ∼40 min.

Surface Electromyography Assessment

The sEMG parameters were computed to evaluate muscle activation. At first, skin preparation was conducted by using an alcohol pad. Four pairs of sEMG electrodes (Ambu BlueSensor N Electrode, Denmark) were attached parallelly to the muscle fascicles on the paretic muscle groups (**Figure 1B**). An EMG amplifier developed in-house was placed closer to each set of EMG electrodes in order to minimize the amount of motion artifacts picked up and amplified during cycling. The in-house amplifiers have a gain of 1,000 at 3dB, at an input impedance of 10 GΩ. The sEMG baseline and maximum voluntary contraction (MVC) measurements of each muscle group were conducted before pedaling. When performing MVC, the subjects were sitting on the chair of the cycling system and were instructed to fully extend the knee joint for QC MVC, to fully flex the knee joint for HS MVC, to fully dorsiflex the ankle joint for TA MVC, and to fully plantarflex the ankle joint for MG MVC. For the QC and HS MVC measurements, the subjects were instructed to keep flex knee joint at 90° and hip joint at 80°. For the TA and MG MVC measurements, the subjects were instructed to keep knee joint at 160° and to keep the ankle joint at a neutral position. Each measurement lasted for 4 sec, and for each muscle, the MVC was measured twice. Then, the subjects were instructed to conduct pedaling, and at the same time, sEMG recording started. We mainly used the sEMG signal from the constant speed pedaling of the first 2 min (warm-up cycling phase) of the first and the last training sessions for data analysis. The sEMG data were collected at a 2,000 Hz sampling rate. The following standard signal processing procedures were applied: (1) power line artifact removal; (2) stimulus artifact removal; (3) cubic spline interpolation; (4) bandpass filtering with cut off frequencies at 20 Hz and 450 Hz (3-order Butterworth filer); (4) average signal subtraction; (5) full-wave rectification; (6) lowpass filtering (3-order, 5Hz Butterworth filer); (7) signal normalization according to MVC. After performing the above seven steps, the envelope of sEMG in each revolution was generated. In order to illustrate the sEMG-angle results clearly, resampling was done

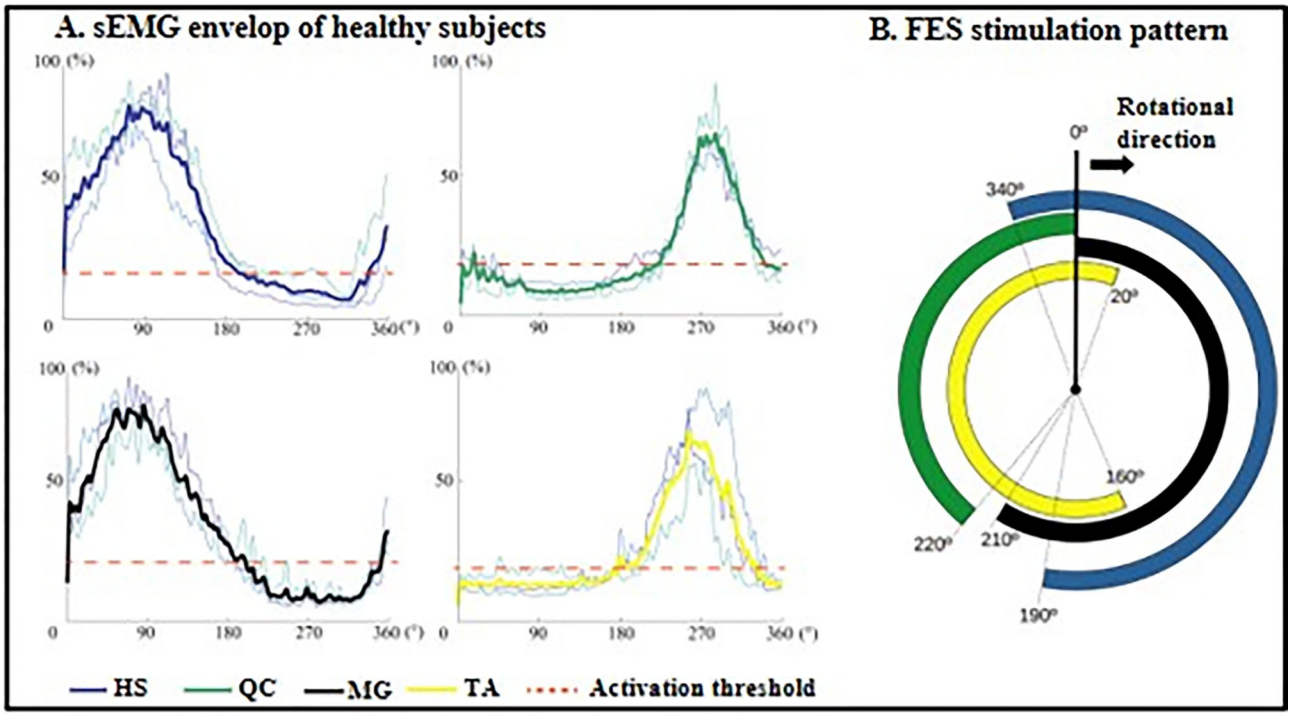

FIGURE 2 | FES stimulation ranges generated from healthy subjects. **(A)** Mean sEMG envelop of three normal subjects: HS, dark blue; QC, dark green; GL, black; TA, yellow. The red dotted lines are the muscle activation thresholds. The y-axis is the contraction level in the range of 0 to 100% normalized by MVC. **(B)** FES stimulation pattern within one revolution: four averaged signals mapping periods of stimulation during cycling. HS, hamstrings; QC, quadriceps; MG, medial head of gastrocnemius; TA, tibialis anterior.

for sEMG to obtain the uniform data size for all parameters in every revolution (10,000 sEMG data points in one revolution). After performing sEGM signal processing and resampling, we acquired angle-related sEMG data from different revolutions; then, we calculated the parameters in each revolution (excluded the first five revolutions) and averaged the parameters from all revolutions for comparison.

Electrical Impedance Myography

Electrical impedance myography (Imp SFB7 Impedimed, Inc., Sydney, NSW, Australia) measurements were performed before the first training and after the last training session on bilateral interest muscle groups. Subjects were instructed to fully relax and lie in supine (for QC and TA) and prone (for HS and MG) positions. The location of the electrodes for each muscle group was marked as a dot: (1) TA: the proximal one-third distance from the proximal fibular head to the center of the medial malleolus; (2) MG: the proximal one-third distance from the medial aspect of the popliteal fossa to the heel; (3) HS: the distal one-third distance from the medial of the popliteal fossa to the ischial tuberosity; (4) QC: the distal one-third distance from the anterior superior iliac spine to the superior border of the patella.

Saline was applied to clean the skin before each test. For the EIM assessment, four electrodes (one pair of voltage electrodes on the inner regions and an outer pair of current electrodes) were linearly arranged parallel to the direction of the myofiber arrangement. Another two pairs of electrodes were linearly arranged perpendicular to the direction of the myofiber arrangement (33). The center-to-center distance of the inner two voltage electrodes was 30 mm and that of the outer two current electrodes distance was 80 mm (34). Each pair of electrodes was distributed symmetrically along the dot that was marked in advance. The dimension of the electrodes was 2.5 cm* 1 cm (**Figure 1C**). Every target muscle was assessed three times at parallel and perpendicular directions, respectively; then the average value of the data was computed for statistical analysis.

Clinical Assessments

The 6-min walk test (6MWT), the Fugl-Meyer Assessment of Lower Extremity (FMA-LE) [FMA for ankle joint and coordination (FMAac), the FMA for knee joint and coordination (FMAkc)], and the Berg Balance Scale (BBS) were carried out to evaluate the ambulation function of the participants, lower limb motor functions, and the balance before and after the training. All these assessments were carried out by a fixed professional physical therapist who was blinded to the training as well as to the EIM and sEMG results.

Data Processing

All the variables of EIM and sEMG were exported for offline analysis. Raw impedance variables were R, X, and θ values across multiple frequencies of alternating current from 5 to 1,000 kHz.

TABLE 1 | Clinical information of subjects.

ID	Gender	Paretic side	Stroke type	Age (year)	Duration (year)	FEMALE*		BBS*		6MWT(m)*		MAS (HS/QC)		MAS (TA/MG)	
						Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	Female	L	I	54	14	24	26	54	53	252	286	0/1	0/0	0/1	0/1
2	Female	L	H	58	2	30	29	50	51	260	331	1/1	1/1	1/1	1/1
3	Female	L	I	68	9	25	26	49	50	224	247	1.5/2	1.5/1.5	1.5/1.5	1.5/1.5
4	Male	L	H	51	1	7	14	14	14	32	29	1/1.5	0/0	0/1	1/0
5	Female	R	H	59	6	24	26	54	55	304	293	1.5/1	1/1	1/2	2/1
6	Male	R	I	37	4	25	25	53	54	295	315	1.5/1	1/1	1/2	1/2
7	Male	R	H	55	6	16	18	50	50	245	278	1.5/1.5	1.5/1.5	1.5/2	1/1.5
8	Female	L	I	72	4	21	28	49	53	173	210	1/1	1/1	1/1	0/0
9	Female	L	I	72	5	17	18	40	45	59	64	1/1	1/1	1/1.5	1.5/1.5
10	Male	L	I	63	2	25	22	56	56	170	127	1/1	1/1	1.5/2	1.5/1.5
11	Male	L	I	57	2	28	29	55	55	366	432	1/1	1/1	1/1	1/1
12	Female	R	U□	40	28	21	28	55	56	340	450	1.5/1.5	1.5/1.5	1.5/2	1/1
13	Male	L	I	61	10	24	23	53	53	192	232	1/1	1.5/1.5	1.5/0	1/1
14	Female	R	I	65	4	16	21	42	51	185	205	1/1	1/1	1/1	1/1
15	Female	R	I	60	3	20	25	55	56	264	323	1.5/1.5	1.5/1	1.5/1.5	1/1
		Mean		58.1	6.67	21.5	23.9	48.6	50.1	224	255	1.13/1.20	1.03/1.00	1.07/1.37	1.03/1.07
		SE		2.6	1.8	1.5	1.6	2.7	2.6	24.1	25.5	0.10/0.08	0.12/0.12	0.13/0.15	0.13/0.14

*FML-LE, Fugl-Meyer Assessment of Lower Extremity; Pre, pretraining; Post, post-training; L, left; R, right; I, ischemic; H, hemorrhagic; U, unknown. *Significant difference between pre and posttraining. □This subject suffered from paralysis due to stroke; however, she forgot the type of stroke and the diagnose recording was missing, and she dropped out of the trial after 11 sessions of the training because of personal reasons.*

Raw EIM data collected at the frequency of 50 kHz was analyzed and compared (28) because the frequency of 50 kHz has been widely used as a standard for single-frequency analysis in EIM (35). The AR of R, X, and θ (AR of R, X, and θ) were computed based on the raw variables.

The AR of X, R, and θ was computed by the following Equation (1):

$$AR_V = \frac{V_{Perp}}{V_{Para}} \tag{1}$$

where V represents the X, R, and θ values, respectively; V_{Perp} and V_{Para} represent these variables collected from perpendicularly and parallelly arranged electrodes, respectively.

The RMS and CI were used to characterize muscle activation and coordination.

We calculated the normalized RMS value by Equation (2):

$$RMS_i = \sqrt{\frac{1}{T}\int_0^T [EMG_i(t)]^2 dt} \tag{2}$$

Where i is the assessed muscle, including QC, HS, TA, and MG. RMS_i is the normalized RMS value of muscle i in one revolution. T is the length of the signal. A decrease in the RMS value represented the improvement of muscle activation volume, which means the subjects can perform the same task with lower efforts.

The CI value was calculated by the following Equation (3):

$$CI_{ij} = \frac{1}{T}\int_0^T A_{ij}(t)\, dt \tag{3}$$

TABLE 2 | Comparison of EIM parameters before training.

Muscle	EIM parameters	Paretic side (mean ± se)	Non-paretic side (mean ± se)
QC	R	76.93 ± 6.73	75.00 ± 6.38
	X*	8.74 ± 0.74	10.21 ± 0.66
	θ*	7.42 ± 1.17	8.69 ± 1.15
TA	R*	44.39 ± 2.88	47.99 ± 2.8
	X*	9.83 ± 0.62	11.11 ± 0.88
	θ*	12.83 ± 1.12	13.73 ± 1.14
HS	R	64.01 ± 5.83	61.10 ± 5.39
	X*	8.30 ± 0.52	8.71 ± 0.51
	θ*	8.54 ± 1.2	9.34 ± 1.24
MG	R*	50.79 ± 4.47	54.55 ± 4.85
	X*	8.86 ± 0.76	10.79 ± 0.95
	θ*	11.04 ± 1.5	12.46 ± 1.5

**Significant difference of EIM parameters between paretic and non-paretic sides. HS, hamstrings; QC, Quadriceps; MG, medial head of gastrocnemius; TA, tibialis anterior.*

Where A_{ij} is the overlapping area of sEMG linear envelops for the muscles i and j in the warm-up cycling phase, and T is the length of the signal. The CI value varied from 0 (non-overlapping of the muscle pair activation in a specific movement) to 1 (the two muscles' activation totally overlapped with both normalized sEMG activation levels kept at 1 during the movement) (36). The reduction of CI after intervention revealed a more coordinated muscle contraction pair during cycling. Only CI values of agonist

and antagonist muscle pairs (TA and MG, QC and HS) were calculated in the current study, to precisely analyze muscle coordination within one joint movement.

Statistical Analysis

The clinical scores (FMALE, FMAac, FMAkc, 6MWT, and BBS), EIM variables (AR, R, X, and θ), and sEMG parameters (CI and RMS) were reported using mean and standard error. The "1+" score in MAS was coded as "1.5" for statistics (37, 38). Comparisons of EIM parameters between paretic and nonparetic sides as well as before and after all the training were conducted by the paired *t*-test if the data set was normally distributed. Comparison of clinical scores and sEMG variables between pretraining and posttraining was conducted by the paired *t*-test for the normally distributed data set. Data normality was verified by the Shapiro–Wilk test. Wilcoxon signed ranks test was performed for non-normally distributed data set (28). Pearson correlation was conducted on EIM, sEMG, and clinical scores if the data sets were normally distributed; otherwise, the Spearman correlation was applied. Statistical significance was defined as $P < 0.05$, two-tailed for all calculations. Statistical analysis was conducted by SPSS23 (IBM Inc., WA, USA),

RESULTS

Fifteen subjects with hemispheric stroke (9 women and 6 men, aged 58.1 ± 10.1 years, duration 1–28 years) were recruited in this study (**Table 1**). All subjects claimed no history of taking anti-spastic medication half-a-year before the training and during the training. One subject (a 40-year-old woman) dropped out from the training after 11 sessions because of personal reasons. We conducted a clinical assessment on this subject after 11 training sessions; however, the sEMG signal was not recorded; therefore, an intention to treat was conducted to do the statistical analysis. **Table 1** shows the demographic and clinical information of the cohort.

EIM Parameters

The EIM variables of R, X, θ, and AR of four measured muscle groups were compared between the paretic and non-paretic sides. The θ value of paretic muscles were significantly lower than that of the non-paretic side (QC: $P = 0.004$, TA: $P = 0.009$, HS: $P = 0.002$, MG: $P = 0.004$). The X values were significantly lower in the paretic muscles of QC ($P < 0.001$), TA ($P = 0.007$), and MG ($P = 0.002$). The R values were significantly lower in the paretic muscles including TA ($P = 0.014$) and MG ($P = 0.027$) (**Table 2**). After 20 training sessions, statistical results revealed that the θ value significantly increased in paretic TA ($P = 0.014$, pretraining: 12.6 ± 1.22, post-training: 13.64 ± 1.08), and MG ($P = 0.017$, pretraining: 11.04 ± 1.56, posttraining: 12.14 ± 1.68) (**Figure 3**). AR value comparison showed that only paretic TA presented a significant increase in the AR of θ value ($P = 0.041$, pretraining: 1.283 ± 0.062, posttraining: 1.339 ± 0.069) and AR of X value ($P = 0.004$, pretraining: 1.275 ± 0.054, posttraining: 1.374 ± 0.046) after training (**Figure 4**). QC and HS showed no significant alterations of EIM parameters after training ($P > 0.05$).

sEMG Parameters

For sEMG parameters, RMS value of paretic TA significantly decreased after training ($P = 0.022$, pretraining: 0.24 ± 0.01, posttraining: 0.2 ± 0.01). The CI between paretic TA and MG significantly reduced after the training ($P < 0.001$, pr-training: 0.21 ± 0.01, posttraining: 0.16 ± 0.01) (**Figure 5**). **Figure 6** demonstrates muscle contraction pattern alteration during three

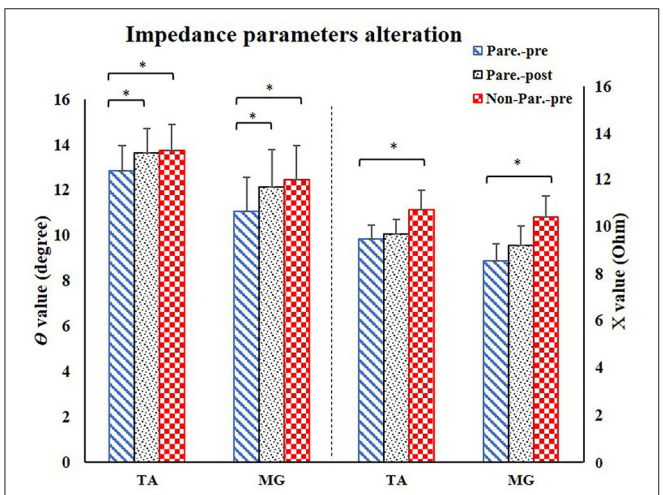

FIGURE 3 | EIM parameters alteration after training. For comparison between paretic and non-paretic muscles, there is a significant reduction of θ and X value in paretic TA and MG. After training, the paretic TA and MG both presented significant increase of θ value. TA, tibialis anterior; MG, medial head of gastrocnemius; X, reactance; θ, phase angle. *$P < 0.05$.

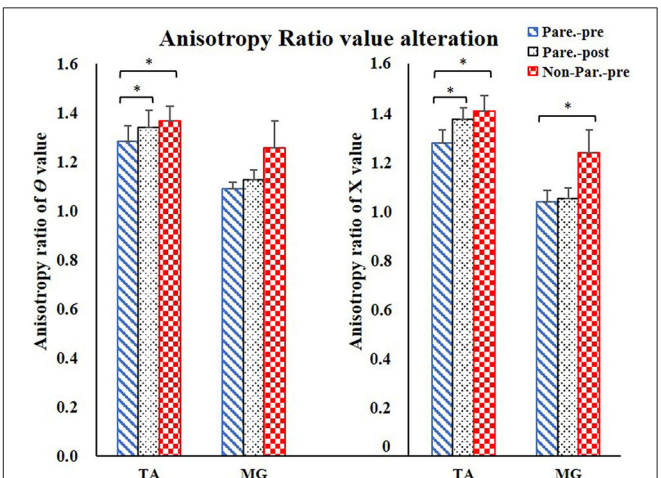

FIGURE 4 | Anisotropy Ratio parameter comparison. For comparison between paretic and non-paretic muscles, significantly lower AR of θ value was shown in TA, significantly lower AR of X value was shown in TA and MG. After training, only TA presented significant increase on the AR of θ and AR of X values. AR, anisotropy ratio; X, reactance; θ, phase angle; TA, tibialis anterior; MG, Medial head of gastrocnemius. *$P < 0.05$.

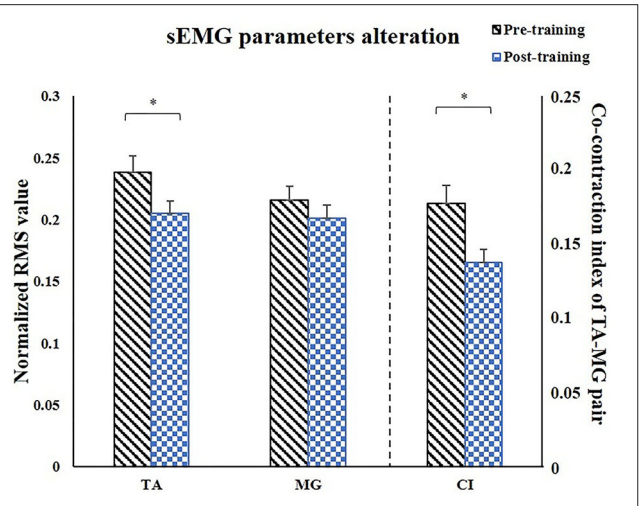

FIGURE 5 | Comparison of the paretic muscles using sEMG parameters. After training, RMS of TA significantly decreased, CI of TA/MG muscle pair significantly decreased. sEMG, surface electromyography; TA, tibialis anterior; MG, medial head of gastrocnemius; CI, co-contraction index; X, reactance; θ, phase angle. *$P < 0.05$.

revolutions of cycling of one recruited subject, in which the contraction of TA and MG was more coordinated after training with less overlapping area under the curves (CI value of TA and MR muscle pair: pretraining: 0.168, posttraining: 0.139) (**Figure 6**). QC and HS showed no significant alteration of RMS and CI value after training ($P > 0.05$).

Clinical Assessments and Correlation Analysis

Significant increases in clinical scores (FMA-LE: $P = 0.013$, FMAac: $P = 0.02$, 6MWT: $P = 0.009$, BBS: $P = 0.038$) (**Table 1**) were observed after the training. Mean MAS scores decreased after training, while the differences were not significant (Ps > 0.05). There was no significant alteration of FMAkc score after training ($P = 0.058$) (**Figure 7**). Significant correlation was demonstrated between EIM parameters and clinical scores, including AR of X value for TA and clinical score (AR-X-TA and FMA-LE score: $r = 0.54$, $P = 0.046$, AR-X-TA and FMAac score: $r = 0.594$, $P = 0.025$), as well as the X value of TA and clinical scores (TA-X and FMAac: $r = 0.692$, $P = 0.006$; TA-X and BBS: $r = 0.628$, $P = 0.016$). Significant correlation was indicated between sEMG and clinical scores, including RMS of TA and BBS score ($r = -0.582$, $P = 0.029$), RMS of MG and FMA-LE ($r = -0.618$, $P = 0.019$), and RMS of MG and FMAac ($r = -0.653$, $P = 0.011$) (**Figure 7**).

DISCUSSION

In this study, EIM and sEMG measurements were conducted in stroke survivors before and after FES- assisted cycling training. The application of EIM and sEMG analysis for evaluating the changes in the inherent property of the muscle and the level of muscle activation after FES-assisted cycling training is relatively a novel application. The results demonstrated that after training, muscle activation increased and muscle contraction coordination within ankle joint movements improved. Muscle inherent properties of paretic muscles changed in the non-paretic muscles. Significant correlations were found between EIM and clinical scores as well as between sEMG and clinical scores. The lower extremity motor function improved after training, and the subjects acquired better balance and ambulation performance.

Bilateral Difference

All paretic muscles presented lower θ values compared to the non-paretic muscles. The X value was reduced only in paretic QC, HS, and TA compared to the non-paretic side. The R value was decreased only in TA and MG. These outcomes were consistent with the previous study by Li et al. which reported that θ can be a more sensitive biomarker than X and R values in assessing the inherent muscle property of Biceps Brachii after stroke (28). We also observed significant lower AR values in paretic TA and MG. Reduced AR of X value and θ value after stroke was related to the loss of muscle fibers, increased fat, and connective tissue infiltration (24, 25). Previous histological studies also revealed muscle atrophy and fat tissue accumulation after stroke (12). This cross-sectional result supported that the EIM assessment could also be applied to muscle composition and structure evaluation of lower extremity muscles in chronic stroke survivors.

Training Effects From EIM and sEMG Measurements

Previous studies reported that the increase in the CSA of muscle, muscle fiber hypertrophy, and intramuscular fat consumption were considered to be a longstanding effect after stroke rehabilitation intervention. Increased muscle mass and decreased intramuscular fat were related to the improvement of muscle strength (16, 39). Ryan et al. and Chae et al. found that muscle CSA and muscle fiber size increased and the intramuscular fat reduced after FES and cycling training (5, 40). Walls et al. and Herrero et al. found that the muscle fiber size and muscle CSA increased after FES intervention (41, 42). Natsume et al. (43) reported that FES could result in muscle hypertrophy because of recruiting both slow- and fast-twitch muscle fibers (43). Therefore, due to these factors, muscle fiber size increased and myofiber cytomembrane area enlarged, which increased the charge storage capability of the cytomembrane (22). This led to a higher time shift in this study when alternating current passed through the muscle in EIM evaluation, and resulted in the elevation of θ value after training (**Figure 3**). On the other hand, the AR value of TA increased after training in the current study, which further suggested a more regular myofiber arrangement after training compared to the one before training. In a fixed muscle volume, the increase of muscle fiber size caused the myofibers to arrange more tightly, which improved the characteristic of muscle anisotropy and made the electrical current flow tougher in the direction perpendicular to the fiber than in the longitudinal direction (29). In addition, the isotropic intramuscular fat reduction would increase muscle anisotropy

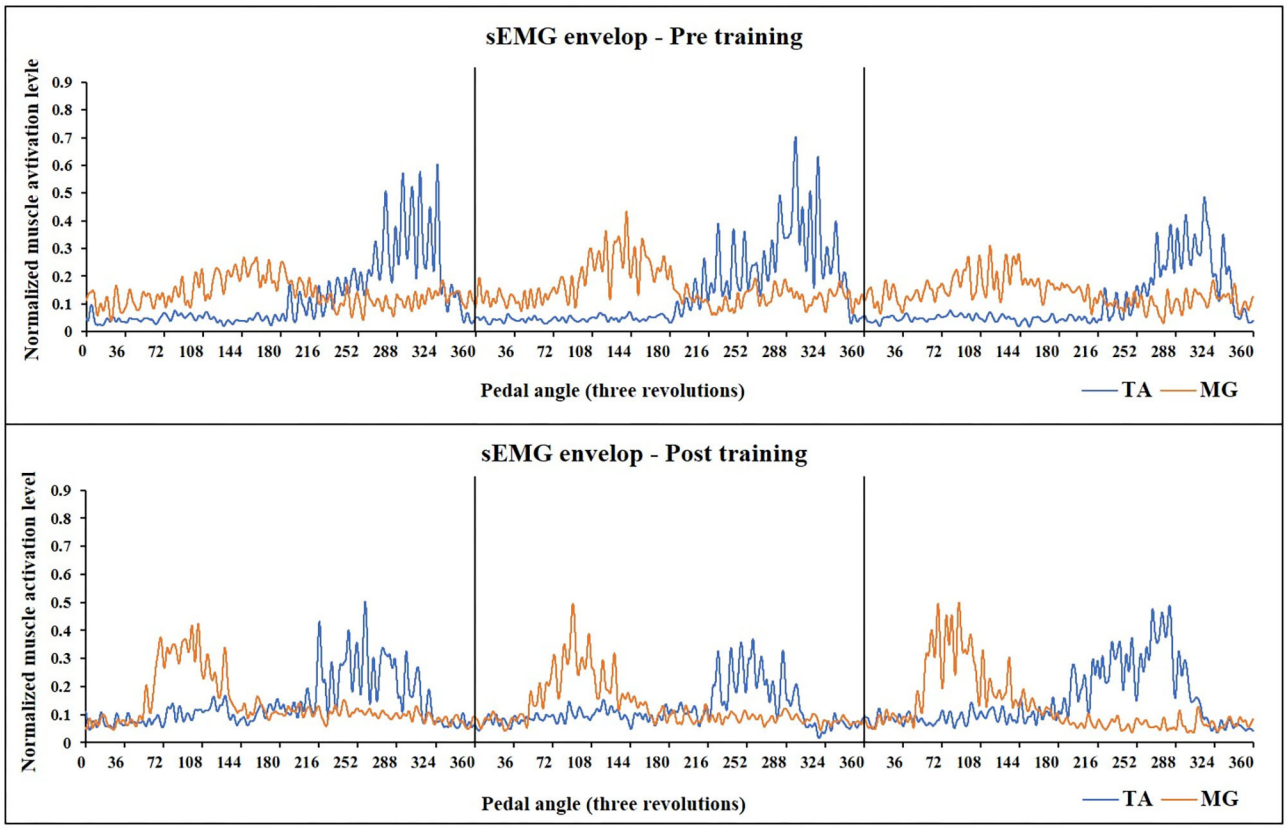

FIGURE 6 | Muscle activation alteration of TA and MG before and after training in one subject (Subject No 12). The sEMG-enveloped signal during the middle three revolutions of cycling is demonstrated. X-axis represents the cycling angles of the pedals. The zero degree of the pedal was set so that the two pedals were in the same line which was vertical to the ground. Yellow curve: sEMG envelope of MG, Blue curve: sEMG envelope of TA. After training, the activation of both two muscle pairs decreased, and MG muscle presented a more independent and rhythmic activation pattern (CI value of TA and MR muscle pair: pretraining: 0.168, posttraining: 0.139). TA, tibialis anterior; sEMG, surface electromyography; MG, medial head of Gastrocnemius.

property in return. These two points might be the reason for the increase in AR value after the training (**Figure 4**).

From a perspective of myofiber structure, ultrasonography was widely applied to evaluate muscle structure alteration after training. Liu et al. used B-mode ultrasound to assess TA and MG architecture alteration after 3 weeks of body weight-supported treadmill training in stroke survivors (44). Significant increases in pennation angle and muscle thickness after the training were reported in FES- assisted lower extremity training (44–47). In our previous cross-sectional study, EIM and ultrasound were jointly applied to explain muscle composition and structure alteration during passive muscle stretch for subacute stroke survivors. In paretic TA, the lower pennation angle and muscle thickness value might contribute to the reduction of the X and θ values compared to the non-paretic TA muscle (29). Therefore, in the current study, the increase of X and θ values on TA could be related to the higher pennation angle and muscle thickness value after FES-assisted cycling training. The elevation of the pennation angle suggested that more muscle fibers and contractile materials are attached to the tendon and contributed to more muscle fibers packed in the same cross-sectional area, which promoted force transfer to the tendon (48). Greater pennation angle and higher muscle thickness contributed to higher AR value because under these conditions, muscle fibers are arranged more perpendicularly, and the current would transversely flow through more muscle fibers in a fixed distance of two voltage electrodes during EIM assessment; ultimately, the AR value increased.

Functional electrical stimulation combined with cycling or gait training was widely used to facilitate gait performance by relieving the subjects from "drop foot" (11, 49–51). It induced coordinated function assistance during ankle dorsi-flexion and reduced the energy consumption for stroke survivors during ambulation. Recently, Rouse revealed that muscle activation is improved in an FES cycling study; however, the performance of the clinical function was not evaluated (52). Previous studies reported that the absolute RMS value of paretic TA during maximum dorsi-flexion increased after FES intervention, which revealed that the capacity of the muscle output increased after training (53). In our study, the decrease of the normalized RMS value of TA after training might be attributed to the increase in maximum activation during MVC or less activation during pedaling, which could both reflect development in

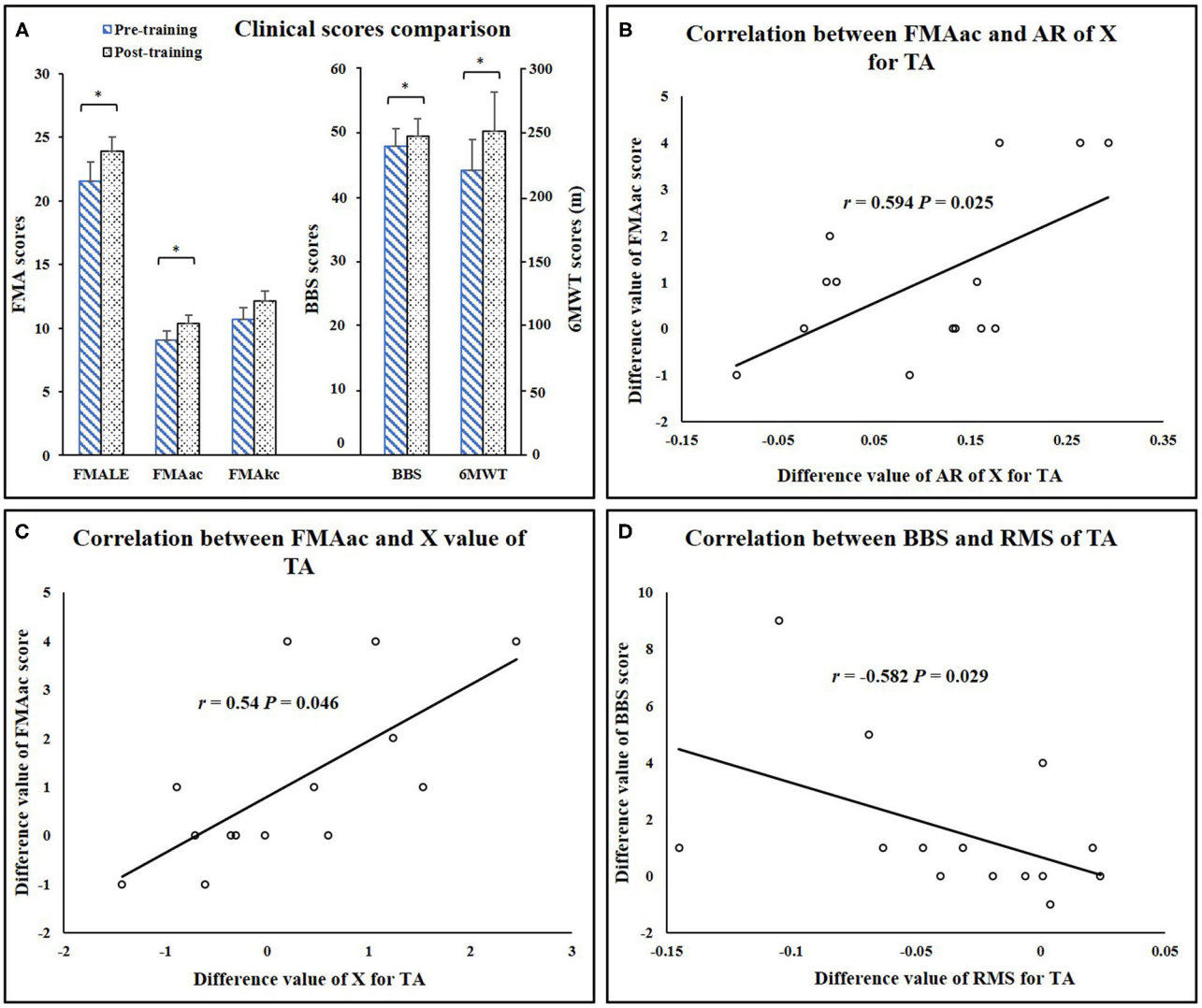

FIGURE 7 | (A) Clinical score comparisons. **(B)** Correlation between FMAac and AR of X value for TA. **(C)** Correlation between FMAac and X value of TA. **(D)** Correlation between BBS and RMS value of TA. AR, anisotropy ratio; RMS, root mean square; TA, tibialis anterior; FMA-LE, Fugl-Meyer assessment of lower extremity; FMAac, Fugl-Meyer assessment of ankle joint and coordination segments; FMAkc, Fugl-Meyer assessment of knee joint and coordination segments; BBS, Berg Balance Scale; 6MWT, 6-minute Walking Test. *$P < 0.05$.

the muscle activation capacity of TA (54). In addition, the decrease of normalized RMS after training also suggested reduced excessive muscular activities of TA during pedaling tasks (55, 56). Furthermore, the reduction of excessive muscular activation indicated the development in voluntary motor controls (56). Yan et al. found a significant decrease of co-contraction ratio during dorsiflexion of the paretic ankle joint after FES intervention (without cycling) (51). It was explained and cross-validated that frequently repeated movements, induced by FES in this study, might reinforce network connection patterns. The FES-assisted cycling in our study allowed for continuous repetition of movements during pedaling. The assists from FES simulated and synchronized with normal muscle activation pattern from healthy subjects during cycling. Therefore, this synchronized stimulation and repetitive muscle contraction reminded the subjects how to pedal voluntarily and coordinately. An fMRI study reported that the repetitive FES-induced movements facilitated motor learning according to cortical mechanisms and spinal mechanisms (57), which revealed a more independent control of muscle contraction after training. Our study also demonstrated significant muscle co-contraction reduction within ankle movements during cycling (**Figure 4**). In addition, as shown in **Figure 6**, the sEMG enveloped signals of TA and MG were more rhythmic after training, the overlapping area of muscle activation decreased obviously. In Brunnstrom's theory, the reduction of TA/MG co-contraction could induce the separation movements of ankle joint and result in function improvement (58). This also explained our clinical results that

the FMALE score increased, and the ambulation performance improved after training.

Our study combined EIM and sEMG techniques to jointly evaluate the FES-assisted cycling training effect. The increase of θ and AR value of TA after training may partly reflect that muscle cross-sectional area and muscle mass increased and might be related to the decrease in the intramuscular fat tissue, and the myofiber is arranged more regularly after training (17, 24, 25). Similarly, the current study proved that muscle activation from sEMG and muscle structure changes from EIM were both improved after the FES-cycling training. These results revealed the alteration of muscle properties after training from different points of view, which help us understand the training effect from different aspects.

Clinical Consideration of Training Effects

Results of clinical scales indicated improvements in motor functions of lower extremity, gait, and balance after 20 sessions of training (**Table 1**). The walking distance in 6MWT improved 13.8% and the FMALE score increased 11.2% after training compared to that before training, which was similar to previous studies (59). In the study by Janssen, it was found that after FES-induced cycling training, the BBS score increased from 40 to 44.2 (10%) and 6MWT increased from 160 to 185 (15.7%) (11). However, the improvement of balance function after training was relevantly lower than that of the ambulation performance (6MWT) and motor function (FMALE) in the current study. Because most of the recruited subjects presented high BBS scores before training as shown in **Table 1**, the ability of balance control was not mainly required during cycling exercise (60). Thus, the subjects in this study presented limited improvement in balance function.

Another interesting result was that all the parameters of EIM and sEMG revealed that TA muscle presented the most significant improvement after training, and it was noticed that FMA scores of ankle segment presented a significant increase while no significant alteration was revealed by the FMA scores of knee segment. This outcome might be due to the higher stimulation intensity applied to the TA muscle as compared to the rest of the muscle groups according to our experiment records (**Supplementary Material**). This can be reasonable because the reduced innervation of TA was the leading cause of drop foot (61). Our correlation analysis also partly explained this unique improvement on TA. As shown in **Figure 7**, EIM, sEMG, and clinical scores significantly correlated with each other on TA. Therefore, our results partly reveal that after the training, muscle composition, and structure property of TA change toward the direction of nonparetic side of TA, and myofibers might be arranged more regularly and extra tissues (fat and connective tissues) are reduced (partly indicated by EIM), which might facilitate the increase of muscle activation volume during ankle dorsi-flexion (revealed by sEMG). Those alterations in some way possibly promoted ankle joint motor function and enhanced the walking performance. Based on the results, we may speculate that after the repetitive muscle contraction during FES-assisted cycling, the subjects might learn to coordinately control muscle activation (revealed by CI of sEMG), and this motor relearning procedure allowed subjects to perform better in ambulation and balance assessment.

LIMITATIONS

There were some limitations in the current study which needed cautions to interpreting the results. First, no control group was designed, which might inevitably neglect some substantial information to demonstrate the unique characteristics of FES-assisted cycling. The motor function of the lower extremity of the subjects in the current study was moderate to high, which partly affected the improvement after the training; in the future study, the subject pool should cover stroke survivors with different motor function levels. In addition, EIM changes only indirectly reflect the muscle architecture alteration after the training. In the future study, we may utilize ultrasound as an assessment tool to discuss muscle structural alteration along with EIM changes based on our recent findings on paretic TA muscle of stroke survivors (29).

The current pilot study applied only FES on the paretic side muscle and then EIM and sEMG data were not measured at the nonparetic muscles after training, which might be due to lack of some training effect comparison since the cycling training involved both the lower extremities. In future studies, the EIM and sEMG assessment should also be conducted on the non-paretic muscles to provide a full picture of the training effects. Our study found no significant alterations of impedance properties on HS and MG, which might be due to the thicker subcutaneous fat compared to TA and MG. In future studies, ultrasound can be used to measure the thickness of the subcutaneous fat, which might provide more information about its effect on impedance properties measurement. In the current study, only the motor function assessment of the lower extremity was assessed, while the assessments of ADL is not performed. In the future study, the ADL performance (Barthel Index, etc.) will also be recorded, which will help us understand the training effect. Our study did not analyze frequency domain sEMG data, which might give information about the loss in the muscle fiber firing rate information as well as the fatigue status. In the future study, the frequency domain sEMG will be calculated to provide more information regarding muscle function.

CONCLUSION

Our study demonstrated the feasibility to combine EIM and sEMG to assess the muscle inherent properties and activation changes in subjects with chronic stroke after FES-assisted cycling training. The motor function improvement of the lower extremity was related to increased muscle impedance properties (intramuscular fat consumption, more regular myofiber arrangement, etc.), higher muscle activation capacity, and better muscle coordination during ankle joint movements. The TA and MG benefited greatly in the FES-assisted cycling training. This study provided insights for clinical

evaluation in muscle weakness, functional deficits, and clinical rehabilitation therapy on stroke survivors.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Joint Chinese University of Hong Kong-New Territories East Cluster (CUHK-NTEC) Clinical Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CH, RK-YT, and LL conceived and designed the study. CH, TW, and KL performed the experiments. CH and TW wrote the paper. RK-YT and LL reviewed and edited the manuscript. All authors had read and approved 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.2021.746263/full#supplementary-material

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Retrospective Robot-Measured Upper Limb Kinematic Data From Stroke Patients Are Novel Biomarkers

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Background: The efficacy of upper-limb Robot-assisted Therapy (ulRT) in stroke subjects is well-established. The robot-measured kinematic data can assess the biomechanical changes induced by ulRT and the progress of patient over time. However, literature on the analysis of pre-treatment kinematic parameters as predictive biomarkers of upper limb recovery is limited.

Objective: The aim of this study was to calculate pre-treatment kinematic parameters from point-to-point reaching movements in different directions and to identify biomarkers of upper-limb motor recovery in subacute stroke subjects after ulRT.

Methods: An observational retrospective study was conducted on 66 subacute stroke subjects who underwent ulRT with an end-effector robot. Kinematic parameters were calculated from the robot-measured trajectories during movements in different directions. A Generalized Linear Model (GLM) was applied considering the post-treatment Upper Limb Motricity Index and the kinematic parameters (from demanding directions of movement) as dependent variables, and the pre-treatment kinematic parameters as independent variables.

Results: A subset of kinematic parameters significantly predicted the motor impairment after ulRT: the accuracy in adduction and internal rotation movements of the shoulder was the major predictor of post-treatment Upper Limb Motricity Index. The post-treatment kinematic parameters of the most demanding directions of movement significantly depended on the ability to execute elbow flexion-extension and abduction and external rotation movements of the shoulder at baseline.

Conclusions: The multidirectional analysis of robot-measured kinematic data predicts motor recovery in subacute stroke survivors and paves the way in identifying subjects who may benefit more from ulRT.

Keywords: robot-assisted therapy, stroke rehabilitation, motor recovery, upper extremity, kinematics

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INTRODUCTION

More than 70% of stroke survivors suffer from upper limb impairment and from a kind of disability in the activities of daily living (1, 2). For these reasons, the recovery of the upper limb motor function and the reintegration into the real-life context have always been the main goals of post-stroke rehabilitation (3, 4). A Cochrane review of 2014 showed that any approach of high dose physical rehabilitation is more effective than usual care in improving motor functions (5). This outcome has been subsequently confirmed by Mehrholz et al. who reviewed the literature on the efficacy of upper limb Robot-assisted Therapy (ulRT) in improving activities of daily living, arm function, and arm muscle strength (6). The efficacy (7–11), acceptability (12), safety (13), and cost-effectiveness (14) of ulRT in stroke patients are well-established in literature.

Traditionally, the effects of ulRT are reported by using standardized clinical assessments [such as, the upper extremity subscale of the Fugl-Meyer Assessment (15), the upper limb Motricity Index (16, 17), or the Action Research Arm Test (18)] and biomechanical measurements of upper limb movements (19–22). Specifically, a multiplicity of kinematic parameters has been applied for upper limb evaluations, such as movement accuracy, speed, and smoothness, and some of them have been correlated to the clinical outcome measures (21, 23). Interestingly, a number of publications analyzed the Robot Measured Kinematic (RMK) data (i.e., the trajectories for movements) registered by the robot (20, 24–28) assessing the biomechanical changes induced by ulRT, and thus the patient progress, in terms of motor control and coordination. Moreover, these robotic measurements allow monitoring the time course of motor recovery during ulRT (24–27), showing that it is movement direction-dependent (20, 28). The robot-measured data have been processed not only for assessing the efficacy of ulRT, but also for predicting the clinical scales (29–31). Krebs et al. found that measurements of kinematics and kinetics recorded by a robot may predict the clinical outcomes registered on a given day (29), thus suggesting that the robotic measurements can be biomarkers of motor impairment. These findings were confirmed by Grimm et al. who showed that exoskeleton-based kinematics correlated to clinical outcome measures (30). More recently, Agrafiotis et al. analyzed the RMK data and developed predictive models of the clinical outcomes with the aim to remove inter- and intra-rater variability and reduce the sample size in stroke clinical trials (31). Even though the literature on clinical predictors after ulRT is well-established (32–36), only Duret et al. analyzed the RMK data with the aim to predict the upper limb recovery at the end of ulRT (37). However, the results obtained on 46 subacute stroke subjects evidenced that selected RMK parameters, calculated from the overall trajectory, do not predict the total upper limb Fugl-Meyer Assessment scores at the end of the treatment (37).

Nevertheless, considering the importance of evidence-based practice in stroke rehabilitation (38), the identification of patients who may benefit more from a robotic treatment (34) is needed. Especially, the pre-treatment motor status of subject should be analyzed in detail, considering the recent findings on the time course of motor recovery and the variations of the workspace exploration skills of a patient during ulRT (20, 39). In particular, movements characterized by elbow extension and shoulder flexion and by the abduction and external rotation of the shoulder are the most demanding to be executed by stroke subjects (40, 41) since these are against the abnormal flexor strategy. For these reasons, the recovery of these movements should be monitored as post-rehabilitation outcomes.

The aim of this study was to calculate a set of kinematic parameters from RMK data and to identify reliable predictors of upper-limb motor performance following ulRT in subacute stroke subjects. Specifically, the ability to execute point-to-point reaching movements in different directions has been considered as representative of motor impairment and of motor synergies in stroke survivors. Therefore, we hypothesized that the analysis of pre-treatment kinematic parameters would allow us to find predictors of upper limb recovery and, thus, to identify individuals who can benefit more from ulRT.

MATERIALS AND METHODS

An observational retrospective study was carried out on stroke subjects who had conducted ulRT in addition to the conventional therapy. This secondary analysis considered the RMK data for assessing the time course of motor recovery during ulRT (19). The data covered by this paper were acquired and processed by the IRCCS San Raffaele Roma (Rome, Italy).

Selection of Patients

The study was conducted on a database of 271 inpatients who underwent ulRT with the planar end-effector InMotion 2.0 robot (Bionik Laboratories, Watertown, MA, USA) at the IRCCS San Raffaele Roma (Italy) between January 2011 and December 2017. Data were selected from patients who satisfied the following inclusion criteria: age between 18 and 80 years; first event of unilateral hemiparetic stroke; subacute phase (ulRT started within 30 ± 7 days post-stroke); upper limb Chedoke-McMaster scores between 2 and 5; Motricity Index affected Upper Limb <100; and ulRT for 20 sessions. The exclusion criteria were the following: bilateral impairment; chronic phase; ulRT for less than 20 sessions; interruption of the ulRT for more than 3 consecutive days; the presence of other severe medical conditions; and incomplete data in the database.

Rehabilitative Protocol

All subjects conducted 20 sessions (5 times/week) of InMotion2-based ulRT with an "assist as needed" strategy. The InMotion 2.0 device is an integrated system for interactive upper limb motor training and the simultaneous kinematic data registry (42). Each session of treatment lasted 45 minutes and consisted of the execution of a sequence of point-to-point reaching movements in the horizontal plane (16, 34). Each task involved the training of different muscle synergies, moving the end-effector from a central target to 8 peripheral targets, equally spaced on a 0.14 m radius circumference and vice versa (**Figure 1**). Visual biofeedback was delivered from a monitor placed in front of the subject. In addition, the subjects

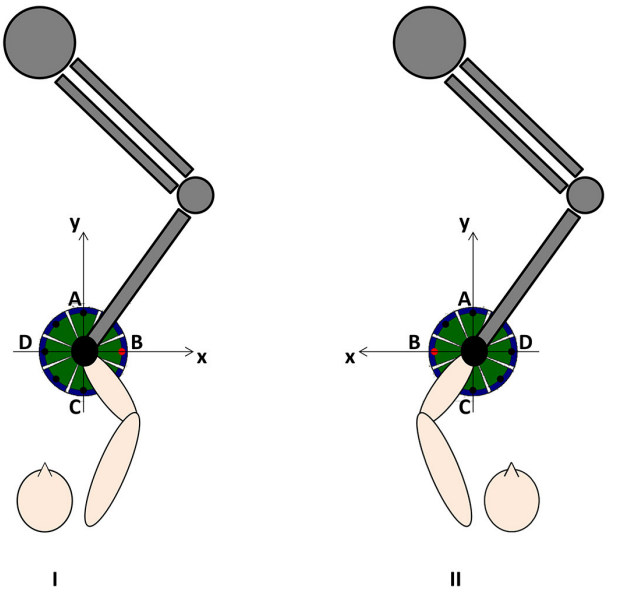

FIGURE 1 | Experimental setup and reference system in case of right (I) or left (II) affected limb.

underwent conventional physiotherapy sessions according to the standardized rehabilitation protocol for subacute stroke patients: assisted stretching, shoulder and arm exercises, and functional reaching tasks. Detailed and relevant information on ulRT is available in the previous paper of the authors (20).

Data Extraction

The demographic and clinical data have been extracted from the electronic medical records, such as age, gender, affected side, time since stroke, and etiology. The clinical and kinematic assessments were registered at the beginning (T1) and at the end (T2) of the ulRT. The privacy of patient was preserved by identifying each record in the database by means of a unique alphanumeric code.

The clinical outcomes are the following: modified Barthel Index (mBI) (4), Motricity Index of the affected Upper Limb (MI_{UL}) (43), and the Motricity Index sub-items assessing the elbow flexion (MI_{ELBOW}) and the shoulder abduction ($MI_{SHOULDER}$). The item related to the pinch grip was not considered in this study because the InMotion2-based ulRT typically involves the elbow and shoulder joints.

The kinematic parameters were calculated from the trajectories recorded by the robot at 200 Hz, as detailed in the previous study of the authors (20). Specifically, the end-effector trajectory has been expressed with respect to a reference system consistent with the lesion side (**Figure 1**) and the following kinematic parameters have been calculated for each trajectory from the central target to the peripheral ones (directions of movement A, B, C, and D): Movement Path Error in centimeters (MPE); mean Movement Speed in centimeters/second (MS); and the number of Peaks Speed (nPS). The MPE is the mean absolute value of the minimum distance of each point of the actual path traveled by the subject from the ideal one (i.e., the straight line connecting the targets): the value is 0 if the trajectory lies exactly on a straight line connecting the targets. The MPE means how much the trajectory is far from the ideal straight line. The MS is the mean value of the resultant velocities in the plane where the trajectory lies. The nPS is defined as the number of peaks of the resultant velocity and it is a metric used for assessing the smoothness of the movement: low nPS values derive from few accelerations and decelerations, i.e., smooth movement.

The kinematic parameters computed in this study describe functional abilities and are in the "body function and structure" ICF domain as described by Tran et al. (24). They are considered as "performance metrics" for assessing the quality of the movement by assuming that the physiological reaching movements are straight, fairly quick, and smoothed (23, 29). Since the reference system is consistent with the lesion side (**Figure 1**), the directions of movement corresponded to the following major anatomical joint movements: A (elbow extension and shoulder flexion), B (abduction and external rotation of the shoulder), C (elbow flexion and shoulder extension), and D (adduction and internal rotation of the shoulder). Therefore, the ability to execute point-to-point reaching movements in different directions described by the kinematic parameters has been considered as representative of different synergies involved in the execution of the reaching tasks (51).

Ethical Considerations

Since March 2012, the Italian Data Protection Authority (Garante per la protezione dei dati personali) declared that IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico - Institute for scientific research and healthcare) are authorized to perform retrospective studies without the approval of the local Ethical Committee, and mandatory formal communication is sufficient. Such communication relative to this study was registered by the Ethical Committee of the IRCCS San Raffaele Roma on February 22, 2017 (code number: 06/17).

Data Analysis and Statistical Analysis

The statistical analyses were performed on SPSS, Version 27.0 (SPSS Inc., Chicago, IL, USA, 2020). Descriptive statistics were computed to appropriately explain the characteristics of the sample. Data are represented as frequency (with the relative percentage), mean value with Standard Deviation (SD), and median value with Interquartile range (IQR) for the categorical, continuous, and ordinal variables, respectively. The Kolmogorov–Smirnov test with the Lilliefors correction was used to evaluate the normality of distribution. The statistically significant difference between T1 and T2 was assessed with paired *t*-test if the data were normally distributed, while Wilcoxon signed-rank test for other comparisons.

The regression analysis was applied for assessing the relationship between a dependent variable and a set of independent variables. The following analyses were conducted:

A. Dependent variable: MI_{ELBOW} at T2. Independent variables: age, kinematic parameters at T1.

B. Dependent variable: $MI_{SHOULDER}$ at T2. Independent variables: age, kinematic parameters at T1.
C. Dependent variable: MI_{UL} at T2. Independent variables: age, kinematic parameters at T1.
D. Dependent variable: MPE A at T2. Independent variables: kinematic parameters at T1.
E. Dependent variable: MPE B at T2. Independent variables: kinematic parameters at T1.
F. Dependent variable: MS A at T2. Independent variables: kinematic parameters at T1.
G. Dependent variable: MS B at T2. Independent variables: kinematic parameters at T1.
H. Dependent variable: nPS A at T2. Independent variables: kinematic parameters at T1.
I. Dependent variable: nPS B at T2. Independent variables: kinematic parameters at T1.

The MI_{ELBOW} and $MI_{SHOULDER}$ are categorical variables composed of six classes, as defined by Wade (43). The MI_{UL} has been transformed into a categorical variable, by grouping the possible MI_{UL} values into the following six classes: $class_0 = 1–27$; $class_1 = 29–40$; $class_2 = 41–54$; $class_3 = 55–66$; $class_4 = 67–77$; and $class_5 = 78–100$.

The choice of considering, as dependent variables, the kinematic parameters calculated from the trajectories executed in direction A and B, was made taking into account that the motor tasks in these directions were the most challenging after stroke, as confirmed by the literature (20, 44).

In the regression analysis, the general linear model or the Generalized Linear Model (GLM) has been applied in the case of dependent variables with normal distribution or with non-normal distribution, respectively. Specifically, in the case of GLM, the following models have been used: Poisson model with a log link function, for categorical variables; Gamma model with a log link function, or Linear link identity for continuous variables; and multinominal cumulative logit for ordinal variables. The Pearson's χ^2 and the deviance statistics were evaluated to assess the model's goodness of fit. The partial slope β was reported to measure the influences of each predictor. All tests were considered significant at a $p < 0.05$.

RESULTS

Starting from a database of 271 inpatients, 66 subacute stroke subjects satisfied the inclusion criteria and were included in the study (**Figure 2**). The mean age was 64.97 years (SD 12.75 years); 44 (66.7%) patients were male; and 39 (59.1%) subjects had the right upper limb impairment. **Table 1** shows the demographic characteristics of the sample at baseline, the clinical scores (mBI, MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL}), and the kinematic parameters (MPE, MS, and nPS: directions A, B, C, and D) calculated at T1 and T2. At the end of ulRT, all clinical outcomes significantly improved ($p < 0.05$). The kinematic outcomes registered significant changes between T1 and T2 in all parameters except the MPE calculated from the trajectories executed in direction B ($p = 0.159$).

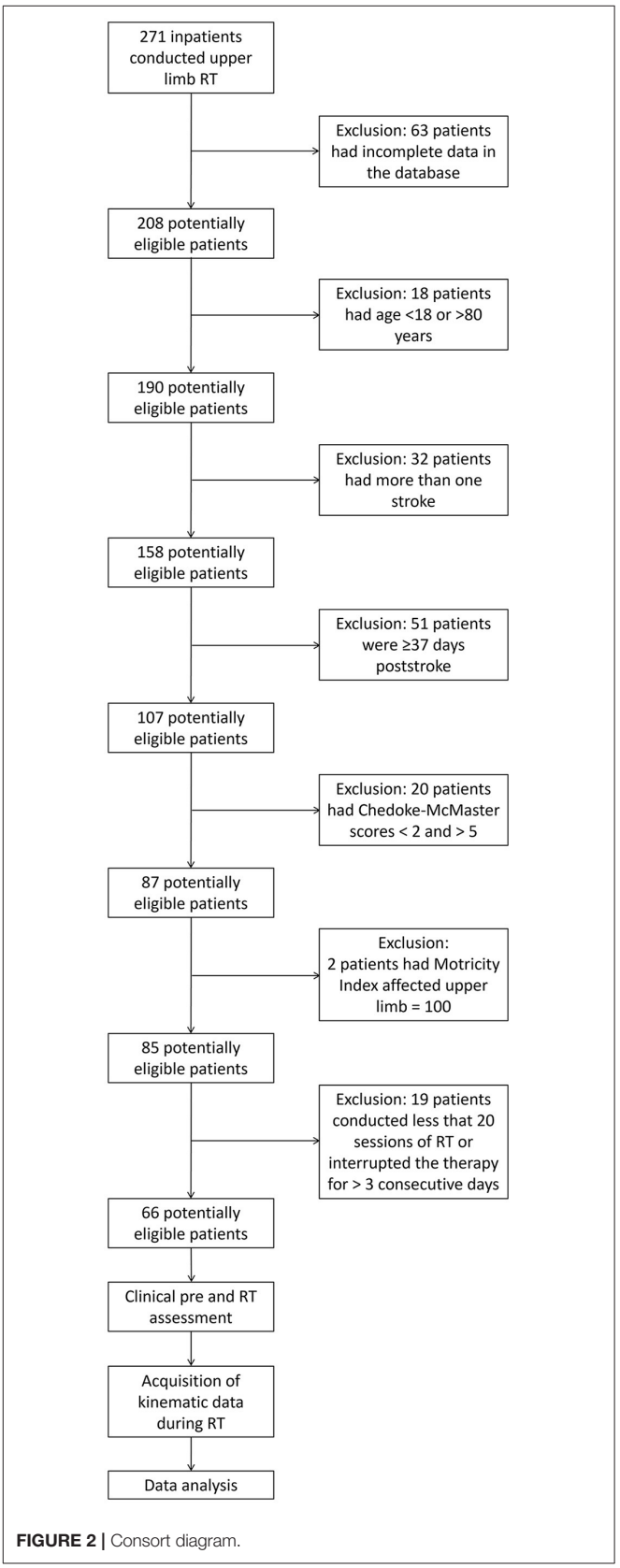

FIGURE 2 | Consort diagram.

TABLE 1 | Summary of the sample characteristics before (T1) and after (T2) the upper-limb robot-assisted therapy (ulRT).

	N (%)	T1	T2	*p*-value
Age (years)		64.97 ± 12.75		
Gender, male/female	44 (66.7)/22 (33.3)			
Side, right/left	39 (59.1)/27 (40.9)			
Time since stroke (days)		15.27 ± 18.07		
Etiology, ischemic/hemorrhagic	47 (71.2)/19 (28.8)			
mBI		26.0 (14.75–40.25)	79.5 (64.25–92.25)	<0.001*
MI_{ELBOW}		14.0 (9.0–19.0) 14.2 ± 9.6	25.0 (17.75–33.0) 23.8 ± 10.3	<0.001*
$MI_{SHOULDER}$		14.0 (9.0–19.0) 14.0 ± 9.1	25.0 (17.75–33.0) 23.5 ± 9.8	<0.001*
MI_{UL}		42.0 (19.0–62.0) 42.6 ± 27.8	77.0 (47.25–93.0) 69.4 ± 30.2	<0.001*
MPE A (m)		0.021 (0.012–0.043)	0.014 (0.010–0.028)	0.004*
MPE B (m)		0.016 (0.007–0.026)	0.013 (0.007–0.022)	0.159*
MPE C (m)		0.017 (0.012–0.029)	0.010 (0.01–0.02)	0.002*
MPE D (m)		0.017 (0.011–0.030)	0.010 (0.01–0.02)	0.002*
MS A (m/s)		0.061 ± 0.043	0.085 ± 0.040	<0.001+
MS B (m/s)		0.074 ± 0.049	0.112 ± 0.054	<0.001+
MS C (m/s)		0.058 (0.031–0.095)	0.10 (0.08–0.14)	<0.001*
MS D (m/s)		0.074 ± 0.050	0.108 ± 0.048	<0.001+
nPS A		6.0 (4.0–9.0)	2.0 (1.0–3.0)	<0.001*
nPS B		4.0 (2.0–7.0)	2.0 (1.0–3.0)	<0.001*
nPS C		4.0 (2.0–8.0)	2.0 (1.0–4.0)	<0.001*
nPS D		4.0 (2.0–7.0)	1.5 (1.0–3.0)	<0.001*

*Data are shown as mean ± SD or median (interquartile range [IQR]). *Wilcoxon signed-rank tests. +Paired t-test. mBI, modified Barthel Index; MI_{ELBOW}, Motricity Index affected elbow flexion; $MI_{SHOULDER}$, Motricity Index affected shoulder abduction; MI_{UL}, Motricity Index affected Upper Limb; MPE, Movement Path Error; MS, mean Movement Speed; nPS, number of Peaks Speed. T1: before the ulRT; T2: after the ulRT. Directions of movement: A, B, C, D.*

Table 2 presents the results of the regression analysis of factors associated with the upper limb motor impairment: the model used for the analysis was the GLM with multinomial cumulative logit since the dependent variables (MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL}) were ordinal. The age, the path errors (MPEs in directions A, C, and D), and the speed (MS in direction B) at T1 were significant predictors of MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL} at T2. Specifically, older subjects were less likely to increase the Motricity Index of the affected upper limb: all subjects improved their level of impairment at T2 but for each year of age, the probabilities to increase of one class in the MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL} diminished by 7.0, 5.8, and 7.3%, respectively. The MPEs calculated from the trajectories executed in direction A and C were significant positive predictors of MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL}: the less accurate the trajectories were at baseline (i.e., high MPE values), the more the MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL} increased at the end of the treatment. Conversely, the MPE (direction D) and the MS (direction B) were negative prognostic factors for motor impairment at the end of the ulRT: less accurate trajectories in direction D and quick movements in direction B at T1 negatively interfere with the increase of MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL} at T2. The remaining independent variables did not significantly contribute in predicting the clinical assessment of motor impairment at T2.

The regression analysis of MPE and MS was executed with the GLM with the Gamma distribution (with a log link function) and with Linear link identity, respectively. Since the response of the nPS is a count, the nPS A and nPS B respected the assumptions to perform the GLM with Poisson distribution (with a log link function). The histograms of MPE, MS, and nPS and the corresponding distributions are showed in **Appendix**.

Table 3 (I) shows the results of the GLM for MPE direction A at T2. The MPE direction B was not considered as a dependent variable because it did not significantly change between T1 and T2 (as shown in **Table 1**). The analysis revealed that the nPS direction A was a significant protective factor of MPE direction A (odds ratio [OR] = 1.088; 95% CI = 1.020–1.159). Expressly, having one peak more in the resultant velocity (direction A) at T1 increases 8.8% of the probability to have a higher path error (i.e., MPE) in executing point-to-point movements in direction A at T2.

Table 3 (II) depicts the predictors of MS direction A and direction B at T2. The results show that the MPE direction C and the nPS direction B were negative prognostic factor for MS direction A and B, respectively. For each one-unit increase in MPE direction C, the expected value of the dependent variable (MS direction A) increases by $\beta = -0.478$, assuming all other variables constant. Therefore, the greater the MPE direction C at baseline, the smaller the MS direction A at the end of the treatment. For each one-unit increase in nPS B, the expected value of MS direction B decreases at T2 ($\beta = -0.006$): the more fluid movements are performed toward B (against the

TABLE 2 | Results of the regression analysis of factors associated with the upper limb motor impairment at the end of ulRT.

Modeled using GLM with Multinominal cumulative logit	**MI_{ELBOW} T2**					**$MI_{SHOULDER}$ T2**					**MI_{UL} T2**				
	β	**SE**	**OR**	**95%CI**		**β**	**SE**	**OR**	**95%CI**		**β**	**SE**	**OR**	**95%CI**	
Age	−0.072*	0.023	0.930	0.890	0.972	−0.059*	0.0225	0.942	0.902	0.985	−0.076*	0.0237	0.927	0.885	0.971
MPE A T1	0.003*	0.001	1.003	1.001	1.006	0.004*	0.0014	1.004	1.001	1.007	0.003*	0.0013	1.003	1.001	1.005
MPE B T1	0.001	0.002	1.001	0.998	1.004	0.002	0.0013	1.002	0.999	1.004	0.001	0.0013	1.001	0.998	1.003
MPE C T1	0.006*	0.002	1.006	1.003	1.009	0.006*	0.0015	1.006	1.003	1.009	0.005*	0.0015	1.005	1.002	1.008
MPE D T1	−0.007*	0.002	0.993	0.989	0.997	−0.007*	0.0021	0.993	0.989	0.997	−0.006*	0.0022	0.994	0.989	0.998
MS A T1	−0.001	0.001	0.999	0.998	1.001	−0.001	0.0007	0.999	0.998	1.001	−0.001	0.0008	0.999	0.998	1.001
MS B T1	−0.002*	0.001	0.998	0.996	0.999	−0.002	0.0010	0.998	0.996	1.000	−0.002	0.0011	0.998	0.996	1.000
MS C T1	0.002	0.001	1.002	0.999	1.004	0.001	0.0011	1.001	0.998	1.003	0.001	0.0012	1.001	0.999	1.003
MS D T1	0.001	0.001	1.001	0.999	1.003	0.002	0.0008	1.002	1.000	1.003	0.001	0.0009	1.001	0.999	1.003
nPS A T1	0.012	0.094	1.013	0.841	1.218	0.018	0.0970	1.018	0.841	1.231	−0.011	0.0967	0.989	0.818	1.195
nPS B T1	0.124	0.097	1.132	0.9360	1.370	0.021	0.0902	1.021	0.855	1.218	0.125	0.0965	1.133	0.938	1.369
nPS C T1	−0.012	0.060	0.988	0.879	1.111	0.002	0.0601	1.002	0.890	1.127	−0.022	0.0606	0.979	0.869	1.102
nPS D T1	0.067	0.102	1.069	0.875	1.306	0.154	0.1086	1.167	0.943	1.443	0.132	0.1081	1.141	0.923	1.410
Threshold															
Class score 1	0.049	1.6914	1.050	0.038	28.911	2.269	1.7729	9.673	0.300	312.33	−0.948	1.7491	0.387	0.013	11.940
Class score 2	−1.010	1.6645	0.364	0.014	9.513	1.155	1.7232	3.173	0.108	92.946	−1.981	1.7656	0.138	0.004	4.391
Class score 3	−1.829	1.6706	0.161	0.006	4.243	−0.117	1.7146	0.889	0.031	25.617	−2.649	1.7840	0.071	0.002	2.335
Class score 4	−2.560	1.6788	0.077	0.003	2.077	−1.173	1.7071	0.309	0.011	8.782	−3.254	1.7901	0.039	0.001	1.290
Class score 5	−3.987*	1.7098	0.019	0.001	0.529	−2.334	1.6961	0.097	0.003	2.691	−3.900*	1.7932	0.020	0.001	0.680
Deviance	0.552					0.568					0.571				
Pearson's Chi Square/gdl	1.998					1.163					1.273				
AIC	208.270					213.251					214.105				
Likelihood ratio	33.134*					32.74*					28.329*				

MI_{ELBOW}, Motricity Index affected elbow flexion; $MI_{SHOULDER}$, Motricity Index affected shoulder abduction; MI_{UL}, Motricity Index affected Upper Limb; MPE, Movement Path Error; MS, mean Movement Speed; nPS, number of Peaks Speed. T1: before the ulRT; T2: after the ulRT. Directions of movement: A, B, C, and D. $^{*}p < 0.05$.

pathological pattern) at T1, the more rapid movements are performed toward B at T2.

Table 4 presents the outcomes of the GLM with Poisson distribution (with a log link function) with the nPS direction A and direction B at T2 as dependent variables. The MPE direction A at baseline was found to be a significant predictor of both dependent variables (nPS direction A: $OR = 1.001$, 95% $CI = 1.001$–1.002; nPS direction B: $OR = 1.001$, 95% $CI = 1.000$–1.001). Thus, the greater the MPE direction A at T1, the greater the nPS direction A and direction B at T2. On the other hand, having higher MS direction B at baseline decreases the probability to have high nPS in the same direction at the end of ulRT ($OR = 0.999$, 95% $CI = 0.999$–1.000): the greater the MS direction B the smaller the nPS in the same direction.

DISCUSSION

This observational retrospective study analyzed the upper limb kinematics and the clinical characteristics of subacute stroke subjects, who received ulRT, to find potential inferences on the degree of impairment with motor outcomes at the end of the treatment. To this aim, data from 66 subjects were analyzed by GLMs to explore all potential relations between the dependent variables and every independent variable as predictive biomarkers. Although the literature on the clinical predictors after ulRT is well-established (32–36), a limited number of studies aimed to find predictors from data registered by a robot for rehabilitation (31, 37): however, the published studies aimed to predict the clinical outcomes and calculated the RMK features from complex trajectories composed by a set of movements having different directions in the workplace, thus did not discriminate the performance in executing movements with different directions. To the best of our knowledge, this is the first attempt at a multidirectional analysis of RMK data to find potential predictive biomarkers of motor outcomes after an intensive rehabilitation protocol that combined ulRT with conventional rehabilitation.

In our study, all the clinical and RMK outcomes (except the trajectories executed in direction B) significantly improved at the end of the treatment, in accordance with studies on the efficacy of ulRT in stroke survivors (9, 16). The obtained improvement could depend on the high dose physical rehabilitation, since

TABLE 3 | Results of the regression analysis of factors associated with: (I) the movement path error (MPE) direction A at the end of ulRT; (II) the movement speed (MS) direction A and direction B at the end of ulRT.

I)	*Modeled using GLM with Gamma link log*	MPE A T2				
		β	SE	OR	95%CI	
	MS A T1	−0.894	2.554	0.409	0.003	61.073
	MS B T1	−0.315	3.161	0.729	0.001	35.790
	MS C T1	2.630	3.811	13.871	0.008	24354.400
	MS D T1	1.309	2.818	3.704	0.015	928.756
	nPS A T1	0.084*	0.033	1.088	1.020	1.159
	nPS B T1	−0.003	0.029	0.997	0.942	1.056
	nPS C T1	0.023	0.021	1.023	0.982	1.066
	nPS D T1	0.025	0.027	1.025	0.973	1.081
	Intercept	−4.844*	0.418	0.008	0.003	0.018
	Deviance	0.561				
	Pearson's Chi Square/gdl	0.556				
	AIC	−379.092				
	Likelihood ratio	10.313*				

II)	*Modeled using GLM with linear link identity*	MS A T2				MS B T2			
		β	SE	95%CI		β	SE	95%CI	
	MPE A T1	−0.349	0.198	−0.738	0.039	−0.270	0.274	0.447	1.305
	MPE B T1	0.158	0.213	−0.260	0.576	0.409	0.294	0.846	2.681
	MPE C T1	−0.478*	0.241	−0.949	−0.006	−0.366	0.332	0.362	1.329
	MPE D T1	0.461	0.309	−0.144	1.066	0.219	0.426	0.540	2.868
	nPS A T1	0.003	0.002	0.999	1.006	0.003	0.002	−0.002	0.007
	nPS B T1	−0.001	0.002	0.995	1.002	−0.006*	0.002	−0.010	−0.001
	nPS C T1	−0.001	0.001	0.997	1.001	−0.001	0.001	−0.003	0.002
	nPS D T1	−0.002	0.002	0.994	1.001	−0.001	0.002	−0.006	0.003
	Intercept	0.101*	0.013	0.076	0.126	0.137*	0.017	0.103	0.171
	Deviance	0.001				0.003			
	Pearson's Chi Square/gdl	0.001				0.003			
	AIC	−236.621				−194.145			
	Likelihood ratio	18.853*				17.144*			

MPE, Movement Path Error; MS, mean Movement Speed; nPS, number of Peaks Speed. T1: before the ulRT; T2: after the ulRT. Directions of movement: A, B, C, and D. * $p < 0.05$.

the patients conducted a highly intensive ulRT (20 sessions, 5 times/week), considering the literature on the topic (5).

The results obtained from the regression analysis of upper limb motor impairment showed that age was a significant negative prognostic factor, in agreement with the literature on predictors of upper limb recovery following stroke (45). Furthermore, a subset of kinematic parameters calculated at baseline evidenced significant effects on motor impairment after ulRT, thus suggesting a correlation between upper limb kinematics and clinical outcomes. The trajectory accuracy is a significant positive predictor of upper limb recovery, and the analysis of the MPEs at baseline may suggest the pattern of motor recovery at the end of ulRT. Adduction and internal rotation movements of the shoulder are known as the typical abnormal strategy of stroke survivors (28, 40). Consolidated literature, in fact, described the stereotyped movement patterns characterized by simultaneous shoulder abduction and elbow flexion as flexor synergy (41). In our study, patients with good ability to perform these movements were more likely to recover upper limb motor function at the end of the treatment: as shown in **Table 2**, less accurate trajectories toward D and quick movements toward B at baseline negatively interfere with the increase of MI_{ELBOW}, $MI_{SHOULDER}$, and MI_{UL} at the end of ulRT. Conversely, the ability to perform trajectories characterized by flexion-extension movements of the elbow negatively affects motor recovery: subjects who executed less accurate and controlled elbow movements at baseline were more likely to recover upper limb functions at the end of the treatment. These results are in accordance with Dipietro et al. (41) who described the changes in the motor performance of the circle drawing task executed by chronic stroke subjects with the same robot, finding a correlation with the process of tuning of motor synergies that underlies stroke recovery. Our findings suggest that more severely compromised patients appear to have a better chance of recovery after ulRT. Indeed, it is worth to mention that this outcome could be the result of a ceiling effect of

TABLE 4 | Results of the regression analysis of factors associated with the number of peaks speed direction A and direction B at the end of ulRT.

Modeled using GLM with Poisson link log	nPS A T2					nPS B T2				
	β	SE	OR	95%CI		β	SE	OR	95%CI	
MPE A T1	0.001*	0.0003	1.001	1.001	1.002	0.001*	0.0003	1.001	1.001	1.002
MPE B T1	0.000	0.0003	1.000	0.999	1.000	−0.083	0.0003	1.000	0.999	1.001
MPE C T1	0.000	0.0003	1.000	1.000	1.001	0.001	0.0003	1.001	1.000	1.001
MPE D T1	0.000	0.0004	1.000	0.999	1.001	0.000	0.0004	1.000	0.999	1.000
MS A T1	0.000	0.0002	1.000	0.999	1.000	−0.001*	0.0003	0.999	0.998	0.999
MS B T1	0.000	0.0003	1.000	0.999	1.000	−0.001*	0.0003	0.999	0.998	0.999
MS C T1	0.000	0.0004	1.000	0.999	1.000	0.081	0.0004	1.000	0.999	1.001
MS D T1	0.000	0.0002	1.000	1.000	1.001	0.000	0.0003	1.000	1.000	1.001
Intercept	1.277*	0.199	3.585	2.429	5.292	1.298*	0.221	3.663	2.375	5.650
Deviance	1.115					1.119				
Pearson's Chi Square/gdl	1.128					1.344				
AIC	268.739					255.541				
Likelihood ratio	51.871*					43.666*				

MPE, Movement Path Error; MS, mean Movement Speed; nPS, number of Peaks Speed. T1: before the ulRT; T2: after the ulRT. Directions of movement: A, B, C, and D. $p < 0.05$.*

RMK measurements for the less severely damaged patients, as Agrafiotis et al. claimed (31).

Considering the evidence on the time course of kinematic parameters during the ulRT (28), the movements characterized by elbow extension and shoulder flexion (target A) and by the abduction and external rotation of the shoulder (target B) are the most difficult to be executed at the end of ulRT (20). The ability to perform good elbow extension and shoulder flexion movements after ulRT is significantly dependent on the ability to execute accurate and smooth elbow flexion-extension movements at baseline. Moreover, good control of movements toward B at the end of the treatment depends on the ability to perform accurate elbow extension movements at baseline. On the other hand, the smoothness and speed of abduction and external rotation movements of the shoulder are correlated to good levels of the same kinematic parameters at baseline. Subjects who did not present upper limb spastic co-contraction and abnormal motor synergies at T1 and, as a result, executed smooth and accurate movements toward A, had a higher probability to recover a more physiological motor control (i.e., direction A and B) characterized by high accuracy and smoothness. This outcome is in accordance with the literature on clinical aspects of upper limb motor impairment after stroke (46, 47). Specifically, Rohrer et al. (46) analyzed the movement smoothness changes using RMK features from the same robot and found a significant difference between the subacute and chronic patients, and a moderate correlation to the Fugl-Meyer Assessment score. In addition, the smoothness and submovement changes in chronic stroke patients have been analyzed by Dipietro et al. (47) who found that by the end of the training movements became smoother and that it could be explained by changes in increasingly overlapping submovements, which became fewer, longer, and faster during recovery. These outcomes suggested that recovery starts first by regaining the ability to generate submovements and then, over a longer time-period, by reacquiring the means to combine them.

The kinematic parameters calculated from the trajectories toward the target C can be representative of upper limb spastic co-contraction (48, 49). Therefore, the less accurate the trajectory in C (meaning that the flexion of the elbow is not well-controlled), the lower the speed in A (stimulating the extension of the elbow), which could represent the spasticity level. Similarly, the smoothness (nPS direction C) can be a predictor of accurate trajectories at T2 toward B. These outcomes are in accordance with the literature on upper limb kinematics, showing that the movements of stroke patients are characterized by slow and segmented trajectories (50, 51), and that motor recovery increases movement smoothness and decrease the number of velocity peaks (48). The kinematic parameters calculated from the trajectories toward target D (toward the hemiparetic side) are not predictive of any kinematic parameter at the end of ulRT.

This study presented some limitations that deserve to be discussed. The retrospective design of the research is associated with the presence of potential confounding factors, with the limited number of subjects, and with the absence of an assessment of spasticity. However, environmental influences are minimized considering that the recruited subjects underwent additional conventional physiotherapy according to the standard rehabilitative protocol for subacute stroke patients. In future studies, an assessment of spasticity, joint sensory and proprioception, and a description of any flexion synergy should be included in the study design. Another limitation is that the motion kinematics was assessed from RMK data, which could have biased the results. Moreover, the study considered a planar end-effector robot, while robotic exoskeletons for ulRT are available. The future research agenda should consider longitudinal large studies, involving different types of robots for rehabilitation, and could assess the motion kinematics with motion capture systems, such as stereophotogrammetry or inertial sensors (22).

Nevertheless, the obtained results showed that the ability to execute point-to-point reaching movement in different

directions can be considered as representative of motor recovery and that a multidirectional analysis of pre-treatment RMK data may help to identify subjects who could benefit more from ulRT. In fact, although the studies on ulRT evidenced that robotic training is effective in stroke patients (6), the literature on the impact of characteristics and abilities of patients on the motor performance outcomes is not consistent.

CONCLUSIONS

The multidirectional analysis of pre-treatment RMK data allows predicting motor recovery after ulRT in subacute stroke survivors. Specifically, kinematic parameters calculated at baseline can help the clinicians in defining the rehabilitative program, tailoring the ulRT to the characteristics and abilities of patients at baseline. Specifically, an additional ulRT training in the elbow extension and shoulder flexion and in the abduction and external rotation of the shoulder may help reduce the upper limb flexion synergies and could be a good rehabilitation strategy in the subjects with negative predictors. The end-effector ulRT could be considered more effective for severely compromised patients who appear to have a greater chance of recovery and reduce their impairment. On the other hand, less impaired stroke patients have a higher probability to recover a more physiological motor control characterized by point-to-point reaching movements with high accuracy and smoothness.

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 IRCCS San Raffaele Roma. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG, MF, and FP have made substantial contributions to conception and design. SPo and AG participated in the enrolment phase and carried out the treatment. MG and SPo carried out the clinical and kinematic assessments. MG and SPr designed the algorithm for data analysis. MG, SPo, SPr, AG, FP, and MF participated in the study design and coordination and statistical analysis. SP and FP participated in the manuscript revisions. MG and MF gave the final approval of the version. 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.2021.803901/full#supplementary-material

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Early Deterioration and Long-Term Prognosis of Patients With Intracerebral Hemorrhage Along With Hematoma Volume More Than 20 ml: Who Needs Surgery?

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Background and Purpose: The treatment of patients with intracerebral hemorrhage along with moderate hematoma and without cerebral hernia is controversial. This study aimed to explore risk factors and establish prediction models for early deterioration and poor prognosis.

Methods: We screened patients from the prospective intracerebral hemorrhage (ICH) registration database (RIS-MIS-ICH, ClinicalTrials.gov Identifier: NCT03862729). The enrolled patients had no brain hernia at admission, with a hematoma volume of more than 20 ml. All patients were initially treated by conservative methods and followed up ≥ 1 year. A decline of Glasgow Coma Scale (GCS) more than 2 or conversion to surgery within 72 h after admission was defined as early deterioration. Modified Rankin Scale (mRS) ≥ 4 at 1 year after stroke was defined as poor prognosis. The independent risk factors of early deterioration and poor prognosis were determined by univariate and multivariate regression analysis. The prediction models were established based on the weight of the independent risk factors. The accuracy and value of models were tested by the receiver operating characteristic (ROC) curve.

Results: After screening 632 patients with ICH, a total of 123 legal patients were included. According to statistical analysis, admission GCS (OR, 1.43; 95% CI, 1.18–1.74; $P < 0.001$) and hematoma volume (OR, 0.9; 95% CI, 0.84–0.97; $P = 0.003$) were the independent risk factors for early deterioration. Hematoma location (OR, 0.027; 95% CI, 0.004–0.17; $P < 0.001$) and hematoma volume (OR, 1.09; 95% CI, 1.03–1.15; $P < 0.001$) were the independent risk factors for poor prognosis, and island sign had a trend toward significance (OR, 0.5; 95% CI, 0.16-1.57; $P = 0.051$). The admission GCS and hematoma volume score were combined for an early deterioration prediction model with a score from 2 to 5. ROC curve showed an area under the curve (AUC) was 0.778 and cut-off point was 3.5. Combining the score of hematoma volume, island sign,

and hematoma location, a long-term prognosis prediction model was established with a score from 2 to 6. ROC curve showed AUC was 0.792 and cutoff point was 4.5.

Conclusions: The novel early deterioration and long-term prognosis prediction models are simple, objective, and accurate for patients with ICH along with a hematoma volume of more than 20 ml.

Keywords: intracerebral hemorrhage, risk factors, prediction model, early deterioration, long-term prognosis

INTRODUCTION

An intracerebral hemorrhage is a serious form of stroke with high mortality (30–40%) and disability (70–80%) (1). In recent years, many studies have proposed that the specific signs displayed on initial CT, such as black hole sign, island sign, swirl sign, and blood-fluid level in hematoma, are related to early hematoma expansion (HE) (2, 3). In addition, coagulation abnormalities, the interval from onset to initial CT, hematoma volume, intraventricular hemorrhage (IVH), are also associated with the expansion of the hematoma or perihematomal edema (PHE) (4). However, whether these signs can be used to predict the early deterioration or poor prognosis for patients with intracerebral hemorrhage (ICH) and as reliable indicators for early surgical intervention remains controversial.

The results of Surgical Trial in Intracerebral Hemorrhage (STICH) trials and minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE) trials suggested that there were no significant differences between the prognosis of the early surgery group and the initial conservative treatment group in patients with ICH (5, 6). However, the subgroup analysis of the STICH II study showed that patients with the evacuation of hematoma within 21 h might have a better clinical prognosis (3). A meta-analysis of 8 studies with 2,186 patients demonstrated that surgery for hematoma removal within 8 h after a stroke can significantly improve the prognosis of patients with ICH (7). Theoretically, evacuating the hematoma before deterioration, eliminating the mass effect, and removing blood degradation products, could improve the prognosis of patients with early ICH. However, the treatment of patients with ICH along with hematoma volume more than 20ml and without cerebral hernia at admission is still controversial (8–11). Early screening and stratification may be helpful to identify patients with a high risk of deterioration and poor prognosis. Therefore, this study aimed to explore the risk factors and to establish a practical prediction model for early deterioration and poor prognosis.

METHODS

Patients

This study recruited patients from our prospectively maintained patients-with-ICH database (RIS-MIS-ICH ClinicalTrials.gov Identifier: NCT03862729) between January 2015 and October 2019. The criteria for enrollment were as follows: (1) ICH diagnosed by emergent CT or computed tomographic angiography (CTA) within 24 h; (2) no cerebral hernia at admission and hematoma volume more than 20 ml; (3) no obstructive hydrocephalus caused by IVH; (4) patients with GCS score > 8 at admission; (5) initially treated by conservative approaches and no emergency surgical intervention was arranged. Ethical approval was obtained through the relevant ethics committee of the First Affiliated Hospital of Fujian Medical University (Ethical Approval Number: MRCTA, ECFAH of FMU [2018] 082-1). Additionally, this study also followed the relevant Chinese laws, regulations, and guidelines, as well as international laws and regulations.

Treatment

The patients in this study were treated according to two guidelines, namely Chinese multidisciplinary expert consensus: Diagnosis and Treatment of Spontaneous Cerebral Hemorrhage (2015) and Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association (2015) (12). For patients with ICH along with hematoma volume more than 20 ml, with neurological dysfunction but without cerebral hernia, conservative treatment and minimally invasive surgery (MIS) were recommended as the first-line treatment. The consciousness and neurological functions of patients treated by conservative therapy were closely observed. If the GCS decreased 2 or more scores or the functional defect worsened, conversion to surgical treatment was recommended. CT scanning was performed in the conservative treatment group at the 6, 12, 24, 48, and 72 h after stroke.

Data Collection and Endpoint

All the data retrieved from our prospective ICH patient registration database including: (1) personal information: gender, age, etc.; (2) history of present illness: time of onset, initial symptoms, pre-hospital management; (3) past medical history: hypertension, diabetes, anticoagulants, antiplatelet drugs, antihypertensive drugs, and other drugs; (4) physical examination: vital sign (blood pressure/respiration rates/temperature/heart rates), neurological examination (pupillary reflex, GCS, the strength of contra-lesional extremities, etc.); (5) laboratory assay: coagulation function, blood routine test, etc.; (6) radiological imaging: (a) initial CT: hematoma location, depth of hematoma, whether with IVH or not, hematoma volume, PHE, hematoma shape and density categorical scales score (13), black hole sign, island sign, swirl sign, blood-fluid level in a hematoma (2, 3). Additionally, hematoma shape and density categorical scales scores include 2 novel 5-point categorical scales, ranging from Category 1 (most regular shape and most homogeneous density) to Category 5 (most irregular shape and most heterogeneous density) (13);

(b) repeat CT: expansion of hematoma and/or PHE, whether cerebral infarction occurred, whether hydrocephalus occurred; (7) post-hospitalization assessments: neurological examination daily, and mainly focused on GCS score and functional deficits; (8) follow-up data: all patients were followed up every 6 months after a stroke at the outpatient department or by the phone call. This study focused on mRS score, all-cause mortality, and follow-up events (re-hemorrhage, cerebral infarction, seizures, etc.) 1 year after stroke. Thus, HE was defined as a 33% increase in hematoma volume or an absolute increase of 6 ml in a repeat CT scan. Similarly, expansion of PHE was defined as an increase in the ratio of PHE volume to hematoma volume or an absolute increase of 5 ml in the repeat CT scan. The early deterioration was defined as a sudden decline of GCS more than 2 or conversion to surgical treatment within 72 h after admission. The poor prognosis was defined as mRS $\geq$ 4 at 1 year after stroke.

Data Management and Quality Control

For data collection, data management, and quality control, refer to the registration information of the RIS-MIS-ICH study on the ClinicalTrials.gov website, which is as follows: https://www.clinicaltrials.gov/ct2/show/NCT03862729?term=fuxin$+$lin&draw=2&rank=2. The project-related data was collected through the electronic data registry system (Real Data Medical Research Inc.). (eRDDM syestem, Ningbo, Zhejiang Province, China) And the radiological image information and follow-up data were determined by two neuroradiologists with consensus.

Statistical Analysis

Demographic and clinical characteristics were descriptively summarized as mean (*SD*) for continuous variables and as number (%) for categorical variables. The chi-square test and Fisher's exact test were used for categorical variables, while Student's *t*-test was used for continuous variables. Only the variables with a $P < 0.1$ on univariate analysis were enrolled in multivariate analysis. The independent risk factors of early deterioration and poor prognosis 1 year after stroke were determined by multivariate analysis, respectively. The corresponding scores were assigned based on the weights of each independent risk factor. Accordingly, a prediction model of early deterioration and prognosis 1 year after stroke was established. The receiver operating characteristic (ROC) curves were drawn and analyzed, to find the cut-off point and calculate the AUC. $P < 0.05$ was considered significant.

RESULTS

Baseline Patient Characteristics and Outcomes

A total of 632 patients with ICH were screened (**Supplementary Figure 1**), of which only 376 patients were within 24 h from the onset to the initial CT. The results showed that 158 patients were without cerebral hernia at admission and with a hematoma volume of more than 20 ml. Among them, 35 patients chose surgical treatment as the primary treatment modality, while other 123 patients preferred the initial conservative treatment. However, only 86 (70%) patients from the initial conservative treatment group had complete follow-up data.

Among 123 patients who received initial conservative treatment, the average age was 58.1 $\pm$ 13 years old, including 93 men (75.6%) and 30 women (24.4%). The average admission GCS score was 11.7 $\pm$ 2.6, and the average time from onset to the initial CT scan was 11.5 $\pm$ 8.3 h. The initial CT showed that 89 patients (72.4%) had basal ganglia hemorrhage (deep), 38 patients (30.9%) had hematoma less than 1 cm from the cortex (superficial), and 46 patients (37.4%) had IVH. The average hematoma volume was 37.7 $\pm$ 14.6 ml, and the average PHE volume was 14.9 $\pm$ 14.4 ml. According to the previously published literature (13), the results of hematoma shape categorical scale scores were as follows: 21 (17.1%) scored 1, 44 (35.8%) scored 2, 35 (28.5%) scored 3, 17 (13.8%) scored 4, and 6 (4.9%) scored 5. The hematoma density categorical scale score of 1 to 4 were 56 (45.5%), 42 (34.1), 18 (14.6%), and 7 (5.7%), respectively. Based on morphologic features of hematoma on initial CT, the number of patients with black hole sign, island sign, swirl sign, the blood-fluid level was 36 (29.3%), 61 (49.6%), 20 (16.3%), and 7 (5.7%), respectively. During 72 h after admission, 62 (50.4%) were converted to surgical treatment, 67 (54.5%) suffered from early deterioration. The average GCS score at discharge and mRS score at discharge was 12.6 $\pm$ 3.3 and 3.3 $\pm$ 1.2, respectively. Among the 86 (70%) patients with complete follow-up data at 1 year, 27 (31.4%) had seizures, 3 (3.5%) had re-hemorrhage, and 1 (1.2%) had cerebral infarction. The 1-year-follow-up mRS score showed as follows: 15 (17.4%) scored 1, 22 (25.6%) scored 2, 9 (10.5%) scored 3, 27 (31.4%) scored 4, 6 (7%) scored 5, and 7 (8.1%) scored 6. Therefore, 40 patients (46.5%) had poor prognosis (mRS $\leq$ 4) (**Table 1**).

Risk Factors for Early Deterioration and Prediction Model

The univariate analysis indicated that admission GCS score (OR (odds ratio), 1.35; 95% CI,1.16-1.58; $P < 0.001$), time from onset to initial CT (OR, 1.04; 95% CI, 0.1–1.09; $P = 0.061$), hematoma volume (OR, 0.91; 95% CI, 0.88–0.95; $P < 0.001$), volume of hematoma and PHE (OR, 0.97; 95% CI, 0.95–0.98; $P < 0.001$), hematoma shape categorical scale score (OR, 0.66; 95% CI, 0.46–0.94; $P = 0.021$), black hole sign (OR, 2.05; 95% CI,0.91-4.6; $P = 0.083$), island sign (OR, 2.84; 95% CI, 1.36–5.92; $P = 0.005$) were the risk factors for early deterioration of patients with ICH. Then, these factors were included in the Logistic multiple regression model. The results showed that admission GCS score (OR, 1.43; 95% CI, 1.18–1.74; $P < 0.001$) and hematoma volume (OR, 0.9; 95% CI, 0.84–0.97; $P = 0.003$) were the independent risk factors (**Table 2**). Given the statistical analysis results and facilitating clinical practice, 13 $<$ GCS $\leq$ 15 was assigned a score of 1, 10 $<$ GCS $\leq$ 13 was assigned a score of 2, and 8 $\leq$ GCS $\leq$ 10 was assigned a score of 3. Additionally, hematoma volume $\leq$ 30 ml was assigned a score of 1, and volume of hematoma $>$ 30 ml was assigned a score of 2. A scoring model for early deterioration was constructed to predict disease progression of patients with ICH at the early stage (**Table 3**). ROC curve analysis indicated that the prediction model is strongly associated with the early deterioration of patients with ICH, with an AUC of 0.778 and a cut-off point of 3.5 (**Supplementary Figure 2**). In brief, for the

TABLE 1 | Clinical characteristics of patients with intracerebral hemorrhage (ICH).

Clinical characteristics	Number(proportion,%)
Patients number	123
Age (year)	58.1 ± 13.0
Gender	
Male	93 (75.6)
Female	30(24.4)
Hypertension	
Yes	89 (72.4)
No	34(27.6)
Diabetes	
Yes	12 (9.8)
No	111(90.2)
Oral anticoagulants	
Yes	3 (2.4)
No	120 (97.6)
Oral antiplatelet drugs	
Yes	2(1.6)
No	121(98.4)
SBP (mmHg)	157.1 ± 25.9
DBP (mmHg)	90.3 ± 15.0
Admission GCS score	11.7 ± 2.6
INR	1.0 ± 0.1
APTT	29.6 ± 8.1
Time from onset to initial CT (h)	11.5 ± 8.3
Hematoma Location	
Basal ganglia	89 (72.4)
Lobar	34 (27.6)
Hemisphere	
Left	61(49.6)
Right	62(50.4)
Depth of Hematoma	
>1 cm	85(69.1)
≤1 cm	38(30.9)
IVH	
Yes	46 (37.4)
No	77 (62.6)
Hematoma volume (ml)	37.7 ± 14.6
PHE Volume (ml)	14.9 ± 14.4
Volume of hematoma+PHE (ml)	52.5 ± 22.9
Hematoma shape categorical scale score	
1	21 (17.1)
2	44 (35.8)
3	35 (28.5)
4	17 (13.8)
5	06 (4.9)
Hematoma density categorical scale score	
1	56 (45.5)
2	42 (34.1)
3	18 (14.6)
4	7 (5.7)
5	0 (0.0)
Black hole sign	
Yes	36 (29.3)
No	87 (70.7)
Island sign	
Yes	61 (49.6)
No	62 (50.4)
Swirl sign	
Yes	20 (16.3)
No	103 (83.7)
Blood-fluid level in hematoma	
Yes	7 (5.7)
No	116 (94.3)
Converted to surgical intervention	
Yes	62 (50.4)
No	61 (49.6)
Pulmonary infection	
Yes	66 (53.7)
No	57 (46.3)
Cardiac events	
Yes	6 (4.9)
No	117 (55.1)
Seizures	
Yes	2 (1.6)
No	121 (98.4)
GCS score at discharge	12.6 ± 3.3
mRS score at discharge	3.3 ± 1.2
Disease deterioration during hospitalization	
Yes	67 (54.5)
No	56 (45.5)
Follow-up	
Number of registered follow-up	86 (70.0)
Number of lost to follow -up	37 (30.0)
Follow-up events	
Seizures	27 (31.4)
Rehemorrhage	3 (3.5)
Cerebral infarction	1 (1.2)
mRS score in 1 year after hemorrhage	
1	15 (17.4)
2	22 (25.6)
3	9 (10.5)
4	27 (31.4)
5	6 (7.0)
6	7 (8.1)
Prognosis in 1 year after hemorrhage	
Good	46 (53.5)
Poor	40 (46.5)

(Continued)

patients with ICH with a score of 2 (13.3%) or 3 (36.4%), the risk of deterioration during hospitalization was low, but for patients with a score of 4 (67.6%) or 5 (86.7%), the risk of deterioration during hospitalization was higher (**Figure 1**).

TABLE 2 | Univariate logistic regression and multiple logistic regression of correlation between initial CT and an early deterioration.

Variable	Univariate logistic regression			Multiple logistic regression		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.01	0.98–1.04	0.493			
Gender	1.27	0.56–2.89	0.572			
Hypertension	0.78	0.32–1.74	0.550			
Diabetes	2.74	0.71–10.67	0.146			
Oral anticoagulants	1.69	0.15–19.17	0.671			
Oral antiplatelet drugs	1.37	0.21–9.06	0.744			
SBP	0.99	0.98–1.01	0.857			
DBP	1.02	0.99 −1.04	0.201			
Admission GCS score	1.35	1.16–1.58	<0.001	1.43	1.18–1.74	<0.001
INR	2.10	0.04–17.24	0.717			
APTT	1.01	0.949–1.07	0.808			
Time from onset to initial CT (h)	1.04	0.10–1.09	0.061	1.03	0.97–1.09	0.418
Hematoma location	1.51	0.68–3.34	0.309			
Hemisphere	0.97	0.48–1.97	0.934			
Depth of hematoma	0.96	0.44–2.06	0.906			
IVH	1.14	0.55–2.38	0.724			
Hematoma volume	0.91	0.88–0.95	<0.001	0.90	0.84–0.97	0.003
PHE Volume	0.99	0.96–1.01	0.368			
Volume of hematoma and PHE	0.97	0.95–0.98	<0.001	1.00	0.97–1.04	0.943
Hematoma shape categorical scale score	0.66	0.46–0.94	0.021	0.90	0.54–1.50	0.681
Hematoma density categorical scale score	0.74	0.49–1.12	0.153			
Black hole sign	2.05	0.91–4.60	0.083	0.83	0.28–2.49	0.736
Island sign	2.84	1.36–5.92	0.005	1.53	0.52–4.50	0.436
Swirl sign	1.03	0.39–2.69	0.959			
Blood-fluid level in hematoma	2.18	0.41–11.68	0.364			

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; GCS, Glasgow Coma Scale; INR, International normalized ratio; APPT, Activated partial thromboplastin time; IVH, Intraventricular hemorrhage; PHE, Perihemotomal edema.

TABLE 3 | Early deterioration prediction model and prognosis prediction model.

Early deterioration prediction model		Prognosis prediction model	
Admission GCS score	Score	Hematoma volume	Score
13<GCS≤15	1	≤25	1
10<GCS≤13	2	>25	2
8≤GCS≤10	3	Island sign yes/no	1/0
Hematoma Volume	Score	Hematoma location	Score
≤30	1	Lobar	1
>30	2	Basal ganglia	3

GCS, Glasgow Coma Scale.

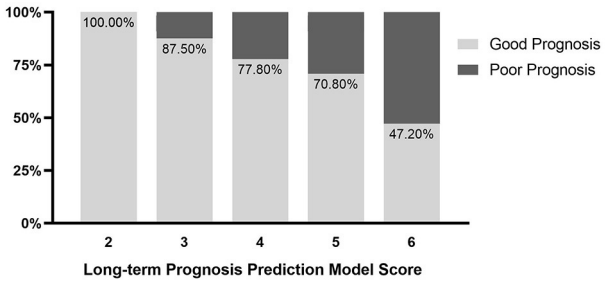

FIGURE 1 | Probability distribution for early deterioration of patients with intracerebral hemorrhage (ICH) with different scores.

Risk Factors for Poor Prognosis and Prediction Model

The univariate logistic regression analysis indicated that with a history of hypertension (OR, 0.36; 95% CI, 0.13–1; $P = 0.049$), admission GCS score (OR, 0.8; 95% CI, 0.67–0.95; $P = 0.012$), hematoma location (OR, 0.07; 95% CI, 0.02–0.32; $P = 0.001$), depth of hematoma (OR, 0.28; 95% CI, 0.1–0.79; $P = 0.016$), hematoma volume (OR, 1.04; 95% CI, 1–1.08; $P = 0.032$), island sign (OR, 0.35; 95% CI, 0.15–0.85; $P = 0.019$) were the risk factors for the poor prognosis at 1 year after stroke. Then, these factors above were included in the multiple logistic regression model, and the results showed that hematoma location (OR, 0.027; 95% CI, 0.004–0.17; $P < 0.001$) and hematoma volume (OR, 1.09; 95% CI, 1.03-1.15; $P < 0.001$) were independent risk factors. The island sign (OR, 0.5; 95% CI, 0.16–1.57; $P = 0.051$) had a trend to

TABLE 4 | Univariate logistic regression and multiple logistic regression of correlation between initial CT and prognosis in 1 year after stroke.

Variable	Univariate logistic regression			multiple logistic regression		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.03	0.99–1.07	0.112			
Gender	0.76	0.29–1.97	0.576			
Hypertension	0.36	0.13–1.00	0.049	0.19	0.04–0.86	0.235
Diabetes	0.54	0.14–2.07	0.368			
Oral anticoagulants	0.88	0.05–14.32	0.920			
Oral antiplatelet drugs	0.86	0.05–14.32	0.920			
SBP	1.01	0.99–1.02	0.374			
DBP	1.01	0.98 −1.04	0.435			
Admission GCS score	0.80	0.67–0.95	0.012	0.995	0.76–1.20	0.690
INR	0.09	0.00–11.04	0.328			
APTT	0.97	0.90–1.05	0.433			
Time from onset tolnitial CT (h)	0.97	0.93–1.03	0.316			
Hematoma location	0.07	0.02–0.32	0.001	0.027	0.004–0.17	<0.001
Hemisphere	1.90	0.81–4.49	0.143			
Depth of hematoma	0.28	0.10–0.79	0.016			
IVH	0.54	0.22–1.28	0.161			
Hematoma Volume	1.04	1.00–1.08	0.032	1.09	1.03–1.15	<0.001
PHE Volume	1.00	0.97–1.03	0.978			
Volume of hematoma and PHE	1.01	0.99–1.03	0.197			
Hematoma shape categorical scale score	1.31	0.87–1.98	0.197			
Hematoma density categorical scale score	1.27	0.78–2.08	0.342			
Black hole sign	1.15	0.45–2.94	0.765			
Island sign	0.35	0.15 −0.85	0.019	0.50	0.16–1.57	0.051
Swirl sign	0.60	0.19–1.91	0.386			
Blood–fluid level in hematoma	1.33	0.21–8.36	0.764			

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; GCS, Glasgow Coma Scale; INR, International normalized ratio; APPT, Activated partial thromboplastin time; IVH, Intraventricular hemorrhage; PHE, Perihemotomal edema.

significant (**Table 4**). Based on the statistical analysis results and to facilitate clinical use, hematoma volume $\leq$ 25 ml was assigned a score of 1, and hematoma volume $>$ 25 ml was assigned a score of 2. The lobar hematoma was assigned a score of 1, but basal ganglia hematoma was assigned a score of 3. Additionally, the appearance of the island sign on the initial CT scan was assigned a score of 1. Then, a scoring model for predicting the prognosis 1 year after stroke was constructed (**Table 3**). ROC curve analysis indicated that the prediction model was strongly associated with the prognosis of patients with ICH 1 year after stroke, with an AUC of.792 and a cut-off point of 4.5 (**Supplementary Figure 3**). In brief, for the patients with a score of 2 to 4, the risk of poor prognosis in 1 year after stroke was low, but for the patients with a score of 5 (29.2%) or 6 (52.8%), the risk of poor prognosis in 1 year after stroke was higher (**Figure 2**). To facilitate the clinical evaluation, the various types of prognostic scores were summarized in **Figure 3**.

DISCUSSION

The STICH trails are the milestones in the field of surgical invention study for ICH. STICH-I study did not find that early surgical treatment (within 72 h from onset) can benefit patients with supratentorial ICH but only suggested that patients with superficial hematoma (within 1 cm from the brain surface) may benefit from surgery (8). However, the STICH-II study focused on cerebral lobe hemorrhage revealed that early surgical treatment of patients within 12 h from onset did not reduce the death and disability rate of patients with lobar ICH. Therefore, the 2015 AHA/ASA guideline for the treatment of spontaneous ICH is recommended as follows: for most patients with supratentorial ICH, the usefulness of surgery is not well established; a policy of early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate. In recent years, a series of studies involved in MIS treatment for ICH had been conducted (8, 9). The MISTIE-II study verified the safety of MIS combined with rt-PA perfusion in the treatment of supratentorial patients with ICH with hematoma greater than 20 ml and within 72 h from a stroke. However, the results of the MISTIE-III study showed that for moderate to large intracranial hematomas, MIS combined with rt-PA perfusion did not improve the overall functional prognosis at 1 year after stroke (9). But, in our opinion, MIS plus rt-PA perfusion treatment seems not to be superior to conventional treatment modalities might be due to the failure of accurate stratification of enrolled patients. Accurate stratification of patients with ICH to identify

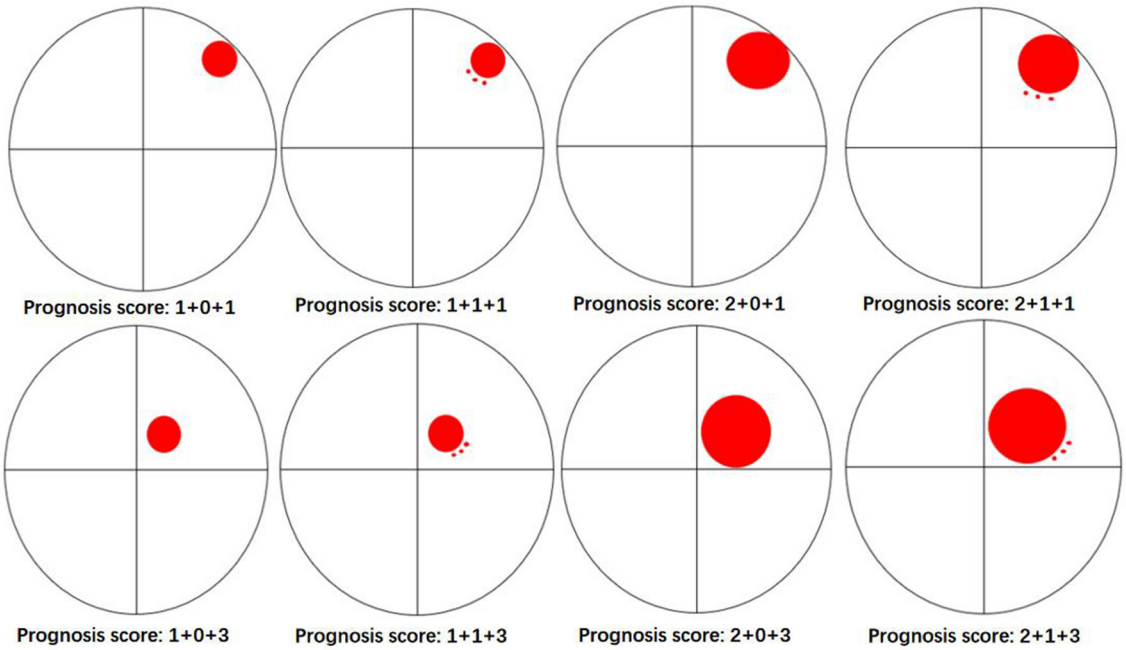

FIGURE 2 | Probability distribution for poor prognosis of patients with ICH with different scores.

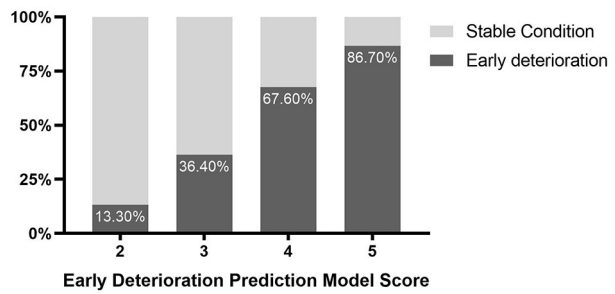

FIGURE 3 | Schematic diagram of different scores in the prognosis prediction model.

the patients with a high risk of early deterioration and destined poor prognosis is important to invasive surgery decisions. Applying appropriate minimally invasive surgical methods to suitable subgroups of patients to interrupt the vicious circle after cerebral hemorrhage may be able to improve the functional prognosis for this subgroup of patients. Given that a hematoma volume < 20 mL manifested in little mass effect (14), the patients with ICH along with hematoma volume more than 20 ml without cerebral hernia were enrolled in this study.

Previous studies suggested that HE is associated with worse outcomes (15–17). Risk factors for the expansion of hematoma have become a major topic of hemorrhagic stroke research. In 2007, Wada R et al. proposed the correlation between early CTA imaging punctate enhancement (spot sign) and expansion of hematoma (18). From 2015 to 2017, blend sign, black hole sign, and island sign-on non-contrast CT were successively identified as predictors of the expansion of hematoma (19–21). In recent years, reduced perihematomal cerebral blood volume (CVB) by computed tomography perfusion (CTP) has been confirmed to be associated with HE (22). Compared with the spot sign on CTA, the specific radiological signs on non-contrast CT are more convenient in clinical. Some researchers hypothesized that the specific radiological signs may be associated with prognosis and could be used as evidence for early surgical intervention. In 2016, Gregoire B et al. suggested that low density of hematoma on emergency CT was related to the prognosis of patients with ICH (23). In 2018, Peter B. S et al. confirmed black hole sign, blend sign, island sign, hypodensities, and heterogeneous densities were reliable predictors of poor outcomes in patients with ICH (24). These findings are consistent with our results. We determined that the island sign was associated with the poor prognosis at 1 year after stroke and was used as an independent risk factor in the prognosis prediction model. However, the CT signs were directly related to the expansion of hematoma, but not directly related to the deterioration of the patients. This indirect relationship weakened the correlation between the CT sign and the patient's deterioration. Therefore, as the results of this study, the directly related factors such as admission GCS score and hematoma volume were more weighted than CT signs in the early deterioration prediction model.

According to the novel prediction models proposed in this study, patients with ICH with a score of 4 or 5 in the early deterioration prediction model will have a higher risk of early deterioration during hospitalization. Similarly, the patients with

ICH with a score of 5 or 6 in the prognosis prediction model will suffer from a higher risk of poor prognosis at 1 year after stroke. In 2019, after integrative analysis of STICH trials and STITCH study patients, Gregson BA et al. found patients with a GCS score from 10 to 13 or a large ICH are likely to benefit from surgery (25). By comparing the patients from the ERICH study (test group) and ATACH-II study (validation group), Audrey C Leasure et al. concluded that 8 ml in thalamic and 18 ml in basal ganglia ICH as an optimal cut-off point for predicting the poor prognosis (26). These researches also supported our study results partly. GCS score $<$ 13, hematoma volume $>$ 25 ml, and basal ganglia hematoma were all independent risk factors and accounted for larger weights in our prediction models. Therefore, early MIS may be beneficial for patients with ICH with disorders of consciousness (GCS score $\leq$ 13), hematoma volume more than 25 ml, and elevated risk of hematoma expansion (island sign).

CONCLUSIONS

The early deterioration and prognosis prediction model of the patients with ICH with hematoma volume more than 20 ml has the advantages of simplicity, objectivity, and accuracy, which may be helpful for clinicians to select treatment methods and prognosis consultation. Patients with an early deterioration score of 4 or 5 may have a higher risk of deterioration during hospitalization. Patients with a prognosis score of 5 or 6 may have a higher risk of poorer prognosis at 1 year after stroke. The prediction models will be validated by prospective multicenter large-sample-size data at the next step by the RIS-MIS-ICH study.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Fujian Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DK has obtained research funding and is the principal investigator of the study. LD, FL, QH, YT, DK, and WF have developed this study, including ensuring ethical principles, designing study methodology, and drafting and revising the manuscript. MZ, GY, ZG, WH, and LC have participated in this study for data collection and follow-up. FW, DW, and YL have provided helpful feedback for all aspects of the work and participated in the final design of the study.

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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.2021.789060/full#supplementary-material

Supplemental Figure 1 | Flow chart of patient selection. ICH, intracerebral hemorrhage; CT, Computed tomography.

Supplemental Figure 2 | ROC curve analysis between admission GCS score and early deterioration, AUC was.703,cutoff point was 9.5 (green line). ROC curve analysis between hematoma volume of initial CT and early deterioration, AUC was.765, the cutoff point was 31.6ml (blue line). ROC curve analysis between hematoma volume of the early deterioration prediction model, AUC was.778, the cutoff point was 3.5 (red line).

Supplemental Figure 3 | ROC curve analysis between hematoma volume and poor prognosis in 1 year after stroke, AUC was.627,cutoff point was 24.8 ml (blue line). ROC curve analysis of prognosis prediction model, AUC was.792, the cutoff point was 4.5 (green line).

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

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Effect of Cognition Recovery by Repetitive Transcranial Magnetic Stimulation on Ipsilesional Dorsolateral Prefrontal Cortex in Subacute Stroke Patients

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Objective: To demonstrate the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) over the ipsilesional dorsolateral prefrontal cortex (DLPFC) on neurological recovery in patients with subacute phase stroke.

Methods: Patients with supratentorial hemispheric stroke who were hospitalized for intensive rehabilitation in the subacute phase were enrolled for this retrospective analysis. Two groups of patients were selected: the rTMS group who received high-frequency (20 Hz) rTMS $\geq$ 5 times over the ipsilesional DLPFC, and a control group who did not receive any rTMS. The patients were further divided into groups with right- or left-side brain lesions. Functional measurements for cognitive ability, mood, speech, and activities of daily living, which were assessed at baseline and at the 1-month follow-up as a routine clinical practice, were used for analyses.

Results: Among 270 patients with available clinical data, 133 (women, 51; age, 61.0 $\pm$ 13.8 years) met the inclusion criteria and were enrolled for analysis. There were no differences in demographic data and functional scores at baseline between the rTMS ($n = 49$) and control ($n = 84$) groups. The rTMS group showed a higher gain in the mini-mental status examination (MMSE) total score and subscores of all domains, forward digit span, and FIM-cognition than the control group ($P < 0.05$). Among the patients with left hemispheric lesions ($n = 57$), the rTMS group showed better outcomes in cognition and depression through scores of total and "attention and concentration" subscores of MMSE, FIM-cognition, and the geriatric depression scale ($P < 0.05$). Among the patients with right hemispheric lesions ($n = 76$), the rTMS group showed better outcomes in cognition through the MMSE total score and subscores of "attention and concentration," "registration," and "recall," and scores of both forward and backward digit spans ($P < 0.05$).

Conclusion: High-frequency rTMS over the ipsilesional DLPFC has beneficial effects on the recovery of cognition on both sides as well as mood in patients with left-sided hemispheric lesions.

Keywords: stroke, repetitive transcranial magnetic stimulation, cognition, DLPFC (dorsolateral prefrontal cortex), neurorehabilitation, ipsilesional dorsolateral prefrontal cortex, subacute stroke

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INTRODUCTION

Cognitive impairment and depression are common complications after stroke (1) which lead to slow recovery in activities of daily living (ADL) (2). Although various rehabilitation techniques and medications are constantly being attempted, their therapeutic effects have been limited (3). Repetitive transcranial magnetic stimulation (rTMS) has emerged as an alternative therapeutic avenue for neurological recovery from stroke sequelae (4) and its beneficial effects are becoming increasingly evident (5). It has been demonstrated that rTMS activates neural plasticity by shifting synaptic weighting, sprouting new dendritic connections, and forming new synapses (6). Adaptive neural plasticity induced by rTMS, including changes in synaptic connectivity and excitability in surviving neural cells in lesions and peri-lesions, is directly related to functional recovery in patients with stroke (7, 8). Previous research revealed temporary recovery from post-stroke cognitive impairment by applying rTMS to the left dorsolateral prefrontal cortex (DLPFC) (9) and various attempts have already proven its effect on psychiatric symptoms in patients with completed stroke (5, 10, 11). In particular, rTMS therapy on the left DLPFC was approved for the treatment of depression in USA in 2008 (12) and has been widely used for treatment-resistant depression in many countries (13).

It is well known that the DLPFC in the bilateral hemisphere plays a key role in various cognitive processes, such as attention, working memory, cognitive flexibility, planning, inhibition, and abstract reasoning (14, 15). However, the precise role of each DLPFC in cognition has not been clearly identified (16). Many previous therapeutic approaches for patients with stroke have focused on the left DLPFC, mostly when it was proposed to ameliorate cognitive impairment and depression (17–19). Treatments with rTMS over the left DLPFC has been reported to enhance working memory and executive functioning in patients with stroke (20, 21). However, clinical studies investigating the effects of rTMS over the right DLPFC are relatively insufficient, and there is still controversy regarding the role of the right DLPFC (22) and transcallosal connections between the left and right DLPFC (23). Meanwhile, there are reports that indicate involvement of the right DLPFC in the retrieval of information from episodic memory (24, 25).

According to our clinical experience of rTMS application in several ways for cognitive enhancement, high-frequency stimulation of the ipsilesional DLPFC was effective in patients with supratentorial hemispheric stroke. Functional and structural studies have indicated that the DLPFC is connected to a variety of brain areas, including the thalamus, basal ganglia, and primary and secondary association areas of the neocortex, including the posterior temporal and parietal areas (26) and the connectivity was significantly correlated with the corresponding cognitive performance (27). To the best of our knowledge, no studies have evaluated the therapeutic efficacy of ipsilesional rTMS. Moreover, no reports have compared the effects on cognition according to the applied hemispheric side of the DLPFC, left *vs.* right. Therefore, we conducted a retrospective study investigating the effect of high-frequency rTMS on cognition when it was applied to the ipsilesional DLPFC and analyzed the effect on each side of the lesion in patients with supratentorial hemispheric stroke during the subacute phase.

MATERIALS AND METHODS

Patients

This retrospective analysis was conducted at the rehabilitation center of a university-affiliated general hospital in charge of intensive stroke rehabilitation immediately after being stabilized from acute care. The study was approved by the institutional review board of the study hospital (IRB file No: 2017-09-060 and 2021-12-039). All the corresponding patients were enrolled without exception according to the following inclusion criteria: (1) subacute period of the first ever completed stroke, 15–90 days after the onset; (2) unilateral supratentorial hemispheric stroke lesion; and (3) over 18 years of age who were admitted and received intensive rehabilitation for at least 4 weeks between March 2014 and December 2019 (**Figure 1**). Exclusion criteria were: (1) brainstem or cerebellar lesion, (2) involvement of the lesion in the contralateral cerebral hemisphere, (3) signs suggestive of degenerative neurological diseases such as Parkinson's disease or Alzheimer's disease, (4) patients with severe cognitive impairment who were incapable of assessment with the Mini-Mental Status Examination (MMSE) score, (5) no remarkable impairment of cognition with MMSE score > 26 points, and (6) patients who received rTMS over cortices other than the DLPFC or received rTMS 1–4 times.

The rTMS treatment was performed at least three times a week for four consecutive weeks for each patient. According to a meta-analysis that referred 5–10 times of high-frequency rTMS on the DLPFC as a therapeutic intervention (5), this study analyzed the therapeutic effect of rTMS by comparing outcomes in two groups of patients: rTMS-treated group, who received ≥ 5 times of rTMS treatment, and the control group, who never received rTMS.

All the patients in this study received intensive rehabilitation consisting of 30–40 min of physical therapy twice and 30–40 min of occupational therapy per day, 5 days a week for weekdays, and once on weekends. While physical therapy targets gross motor recovery, occupational therapy aims to enhance various cognitive abilities, facilitates the use of disabled upper extremities, and promotes independent ADL. Although an individualized therapeutic approach was applied to each patient, the overall framework was based on the standardized protocol of the trained rehabilitation team of the university hospital (28). And occupational therapy was implemented as soon as rTMS was finished (in a 10 mins), with the exception of a few due to urgent events.

Repetitive Transcranial Magnetic Stimulation

The rehabilitation center has provided rTMS as an optional therapy to facilitate the rehabilitation of patients. A patient or legal guardian may choose the therapy on their own after being informed by the physician about rTMS.

Stimulation was performed using a biphasic stimulator (MagPro® Dantec, Denmark; from March 2014 to May 2018

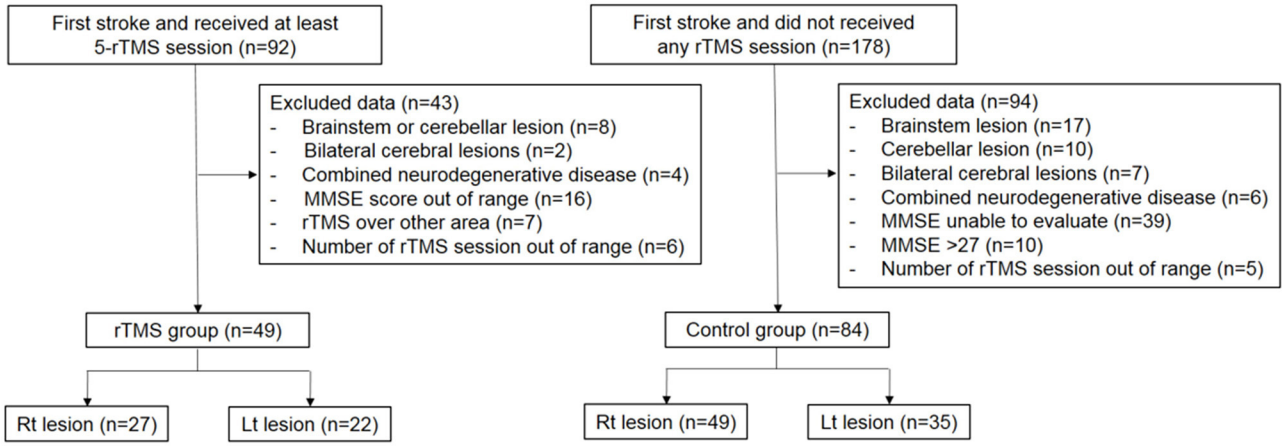

FIGURE 1 | Flow chart of subject selection for analyse. rTMS, repetitive Transcranial Magnetic Stimulation; MMSE, Mini-Mental State Examination.

and ALTMS® Remed, Republic of Korea; from May 2018 to December 2019) and a 70-mm figure-eight coil. The routine stimulation procedure is described as follows. First, the resting motor threshold was measured for each patient. At the lowest stimulus output, a stimulus was applied to the M1 cortex of the uninjured hemisphere aiming at the site that caused the largest visible twitch in the participant's thumb. The resting motor threshold was defined as the intensity required to generate a motor-induced potential of > 50 μV in the contralateral abductor pollicis brevis muscle at least 5 out of 10 times with 30 s of inter-stimulus time interval (29, 30).

According to the prescription, rTMS was administered by trained physicians over the ipsilesional DLPFC, which approximately corresponds to Brodmann area 9/46, 5 cm forward along the parasagittal line at the M1 cortex location where the abductor pollicis brevis muscle was activated. The angle of the coil was inclined 45° relative to the sagittal line of the head (18, 31). Stimulation was given at 80% of the resting motor threshold stimulator output: 20 Hz, 5-s train duration, 55-s inter-train interval, and a total number of stimulations of 1,000 pulses per session for 20 min (5). Any side effects were monitored during rTMS treatment and up to 10 min after treatment in the therapy room.

Assessment of Outcome and Side Effects

All data were obtained from electronic medical records according to the medical practices in the study hospital and evaluated at admission within a week, followed by the same assessments 4 weeks after completing the initial evaluations as a routine process. For appropriate rehabilitation, the patients underwent assessments for cognitive, affective, and language abilities, including MMSE (32), Wechsler Adult Intelligence Scale-IV (WAIS-IV) (33), forward and backward digit spans (34), mood evaluation using the Geriatric Depression Scale (GDS) (35), language evaluation with aphasia quotient (AQ) by Western Aphasia Battery (WAB) (36). Aphasia diagnosis and classification were made by a standardized evaluation criteria varied depending on gender, age, educational level (37). And unilateral visual neglect evaluated by both line bisection test (38) and Albert test (39) which have been used globally as screening tools. The total MMSE score and its subscore for each domain, orientation, registration, recall, attention/concentration, and language (32, 40, 41), were used for retrospective analysis, which have been utilized to measure cognition in patients with stroke (42, 43). Intelligence quotient (IQ) was measured with WAIS-IV, digit span score was evaluated with numbers, and AQ percentile was measured with WAB. All assessments were conducted using nationality appropriate and authorized versions by a clinical psychologist and two speech therapists who were expert professionals. The functional independence measure (FIM) (44) was used to evaluate performance ability in ADL. The FIM cognition scale is composed of five cognitive items assessing the abilities of communication and social cognition with a range of 5–35 points. These assessments were conducted by occupational therapists who were trained and passed the reliability test.

Adverse events were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (45). The side effects were evaluated in all patients who received rTMS, regardless of group designation. Since the treatment was given by a physician, adverse events were directly monitored during the procedure, and the patients were closely monitored during their hospitalization period by the attending staff.

Statistical Analysis

The Statistical Package for the Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analyses. The independent *t*-test was used to compare the demographic data and baseline characteristics between the rTMS and control groups and to compare the outcomes (i.e., score changes from baseline to follow-up) between both groups. A paired *t*-test was used to confirm the changes in scores before and after treatment within the group. Normality was verified based on the results of the Kolmogorov-Smirnov test for the difference

UNDERSTANDING STROKE RECOVERY TO IMPROVE OUTCOMES: FROM ACUTE CARE TO CHRONIC REHABILITATION

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between baseline and follow-up in the measured scores. Statistical significance was set at $P < 0.05$.

RESULTS

Overall Patient Characteristics

Data were collected from 270 patients who underwent initial assessment and follow-up assessments after 4 weeks of rehabilitation. Finally, 49 patients met the inclusion criteria for the rTMS-treated group by receiving rTMS ≥ five times on the ipsilesional DLPFC, and 84 patients were included in the control group (**Figure 1**). The mean age of the rTMS-treated group was 60.4 ± 14.4 years (42.8% female), and that of the control group was 61.3 ± 13.5 years (35.7% female) without differences in demographic characteristics between the groups regarding age, sex, type of stroke, and post-stroke duration. The patients in the rTMS-treated group received 8.7 ± 2.4 times (right hemispheric stroke: 9.1 ± 2.2, left hemispheric stroke: 8.0 ± 2.6) of rTMS.

The baseline characteristics of the rTMS-treated group and control group did not differ in the initial abilities of all evaluated cognitive functions such as MMSE, digit span, FIM cognition score, IQ of WAIS, AQ, and GDS (**Table 1**; **Supplementary Table 1**). Moreover, these clinical characteristics including baseline cognitive abilities and depressive symptoms were not different between the rTMS-treated and control groups at baseline for each hemispheric lesion (**Supplementary Tables 2, 3**). Regarding the existence of depression, 86.8% of the patients showed overt symptoms with a GDS score more than 10 (46) among all the recruited patients with left hemispheric stroke and 75% among all the recruited patients with right hemispheric stroke, without a difference between the two groups for each hemispheric lesion side. Through a medical review, 16 patients with left hemispheric lesion and 30 patients with right hemispheric lesion were reported to have taken antidepressants (sertraline 50 mg or escitalopram 5 mg or 10 mg/day) among total subjects. And all hospitalized patients, regardless of the rTMS treatment, medicated 5 mg of donepezil once a day.

When the initial cognitive functions were compared between the left and right hemispheric lesions, all evaluated scores of cognition and affection, including MMSE, digit span, FIM cognition score, IQ of WAIS, AQ, and GDS, were poorer in the left hemispheric lesion group. Among the rTMS-treated group, the AQ of the left hemispheric lesion was lower than that of the right hemispheric lesion, indicating that the left lesion was more aphasic. In total subjects, 64.9 % of left hemispheric lesion and 23.7 % of right hemispheric patients presented aphasia, and there was no difference in the prevalence between the rTMS-treated and control groups. Among the control group, MMSE total, digit span scores, FIM cognition AQ, and GDS of patients with left hemispheric lesions were lower than those of patients with right hemispheric lesions (**Table 1**). These baseline differences show the typical characteristics of left brain lesions in cognition and speech impairments, as reported in previous reports (47, 48). As for visual neglect, 27.6 % of total right hemispheric lesion patients showed to have neglect, and there was no difference in the prevalence between the rTMS-treated and control groups (**Table 1**).

Total Patient Analyses

Changes in Cognitive Measures and Depression in the rTMS and Control Groups

After 4 weeks, both the rTMS-treated group ($n = 49$) and the control group ($n = 84$) showed significant improvements in most of the assessments. Total MMSE and all of its subscores (orientation, registration, recall, attention/concentration, and language) were elevated ($P < 0.001$). Forward and backward digit span, FIM cognition score, AQ, IQ, and all of its subscores increased in both groups ($P < 0.001$). However, the GDS score showed amelioration of depression only in the rTMS-treated group ($P < 0.001$) and not in the control group (**Table 2**).

Comparison of Outcomes Between the rTMS and Control Groups

In a comparison analysis between the two groups by change of each evaluation score, the rTMS-treated group showed bigger improvements in cognition including total MMSE and all of its subscores ($Ps < 0.05$), especially in the "attention/concentration" domain ($P < 0.001$), forward digit span ($P < 0.001$), and FIM cognition score ($P < 0.001$), compared with the control group. There was no significant difference in the backward digit span, IQ, and AQ. Changes in the GDS score showed a trait of better outcomes in depression in the rTMS-treated group than in the control group ($P = 0.06$) (**Table 2**).

Analyses of Patients With Left Hemispheric Lesions

Changes in Cognitive Measures and Depression in the rTMS and Control Groups

The rTMS-treated group ($n = 22$) and control group ($n = 35$) showed improvements in all measured cognitive tests ($P < 0.05$). However, the GDS score showed amelioration of depression only in the rTMS-treated group ($P = 0.001$) and not in the control group (**Table 3**).

Comparison of Outcomes Between rTMS and Control Groups

In the comparison analysis between the two groups, the rTMS-treated group showed greater improvements compared with the control group in total MMSE, "attention/concentration" subscore of MMSE, and FIM cognition ($P < 0.05$). Improvement in mood assessed using the GDS score indicated amelioration of depression induced by rTMS, with a significant difference between the two groups ($P = 0.002$) (**Table 3**).

Analyses of Patients With Right Hemispheric Lesions

Changes in Cognitive Measures and Depression in the rTMS and Control Groups

The rTMS group ($n = 27$) showed improvements in all measured cognitive scores ($P < 0.05$). In contrast, the control group did not show significant increments in scores of "recall" subscore of MMES ($P = 0.103$) and backward digit span, although it may

TABLE 2 | Comparison of rehabilitation outcomes between rTMS and control groups (total subjects, $N = 133$).

	rTMS group (total $n = 49$)		Control group (total $n = 84$)		P value † (between groups)
	Baseline	Follow-up	Baseline	Follow-up	
MMSE	14.4 ± 7.7	**22.4 ± 5.8***	15.7 ± 7.4	**20.3 ± 7.8***	**0.001**††
Orientation	4.8 ± 2.8	**8.1 ± 2.0***	5.0 ± 2.7	**7.4 ± 2.9***	**0.037**†
Registration	2.1 ± 1.3	**2.7 ± 0.6***	2.4 ± 1.1	**2.6 ± 0.8***	**0.024**†
Recall	1.1 ± 1.4	**2.3 ± 1.6***	0.9 ± 1.3	**1.6 ± 1.5***	**0.014**†
Attention/concentration	1.0 ± 1.3	**2.7 ± 1.7***	1.1 ± 1.4	**1.8 ± 1.7***	**<0.001**††
Language	5.0 ± 2.6	**6.6 ± 1.8***	5.2 ± 2.5	**6.2 ± 2.2***	**0.043***
Digit span					
Forward	4.0 ± 2.1	**5.3 ± 1.7***	4.5 ± 1.9	**5.0 ± 1.7***	**<0.001**††
Backward	2.0 ± 1.2	**2.7 ± 1.2***	2.2 ± 1.5	**2.7 ± 1.4***	0.189
FIM					
Cognition	17.5 ± 8.2	**22.7 ± 10.0***	18.7 ± 7.9	**20.8 ± 8.3***	**<0.001**††
IQ	59.6 ± 16.7	**69.9 ± 18.5***	63.4 ± 15.1	**71.4 ± 15.9***	0.178
VCI	76.5 ± 23.7	**85.1 ± 21.4***	82.3 ± 18.8	**89.5 ± 18.4***	0.527
PRI	62.8 ± 18.9	**71.6 ± 20.9***	64.3 ± 13.4	**72.9 ± 16.5***	0.940
WMI	69.3 ± 77.1	**77.1 ± 20.5***	72.6 ± 17.8	**80.0 ± 18.0***	0.803
PSI	56.5 ± 13.7	**65.2 ± 18.3***	60.5 ± 12.9	**65.9 ± 16.0***	0.141
AQ	63.9 ± 33.1	**75.6 ± 26.5***	71.5 ± 29.9	**79.1 ± 24.8***	0.085
GDS	17.1 ± 9.9	**13.5 ± 8.7***	14.6 ± 7.0	13.5 ± 7.8	0.060

*, *Bold values; $P < 0.05$ significantly higher than baseline within each group comparison.*

P value † compared the changes in each score from baseline to follow-up between two groups by independent t-test. † $P < 0.05$, †† $P < 0.01$.

All values are presented a mean ± standard deviation.

(n) Number of patients evaluated, without remark all patients were evaluated.

MMSE, Mini-Mental State Examination; FIM, Functional Independence Measure; IQ, Intellectual Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; AQ, Aphasia Quotient; GDS, Geriatric Depression Scale.

have marginal significance ($P = 0.058$). The control group also showed improvements in overall cognitive measures ($P < 0.05$). Both groups did not show changes in GDS scores (**Table 4**).

Comparison of Outcomes Between the rTMS and Control Groups

In the comparison analysis between the two groups, the rTMS-treated group showed higher scores in total MMSE and three of its subscores: "registration," "recall," "attention/concentration," both forward and backward digit span, and FIM cognition score ($P < 0.05$) compared with the control group (**Table 4**).

Side Effects

The medical records did not report any serious adverse events related to rTMS. Only three patients discontinued rTMS due to mild headache after their first treatment; thus, they were excluded from this analysis. None of the patients showed deterioration of function.

DISCUSSION

According to the results of the present retrospective study, high-frequency rTMS on the ipsilesional DLPFC might have beneficial effects on cognition in patients with stroke during their subacute phase when the patients are receiving intensive rehabilitation. Although the control group also showed improvement in cognitive function across the board, the rTMS-treated group showed remarkably better outcomes in cognition and mood recovery.

In comparison with the rTMS-treated group and controls without dividing lesions, the rTMS-treated group demonstrated efficacy in total MMSE and all subscores. Since it was invented as a screening tool for dementia, despite of its broad use, it is still controversial whether the MMSE is an appropriate tool for post-stroke patients. However, many previous literatures (49, 50) reported the MMSE to be sufficiently accurate as a screening tool for stroke patients. And it is obvious that MMSE is practically applicable in clinics for post-stroke patients. Among the subscores, greater improvement in the rTMS-treated group was evident in the "attention/concentration" domain.

In another attention representing test, the forward digit span also showed better outcomes in the rTMS-treated group. "Attention" is the most basic ability for further cognitive processes, and working memory is one of the most directly associated functions (51). Furthermore, the rTMS-treated group showed better outcomes in ADL by a higher gain of the FIM cognition score compared with the control group. Therefore, it seems that rTMS treatment exerted a therapeutic effect on attention, which led to better cognitive performance in the daily living of patients with stroke. There was no difference in changes

TABLE 3 | Comparison of rehabilitation outcomes between rTMS and control groups (left hemispheric stroke subjects, $N = 57$).

	rTMS group (total $n = 49$)		Control group (total $n = 84$)		P value† (between groups)
	Baseline	Follow-up	Baseline	Follow-up	
MMSE	12.6 ± 6.8	**21.1 ± 6.1***	13.0 ± 8.5	**17.6 ± 9.2***	**0.004**††
Orientation	4.6 ± 2.7	**8.1 ± 2.0***	4.1 ± 3.2	**6.7 ± 3.7***	0.204
Registration	1.8 ± 1.4	**2.5 ± 0.9***	1.9 ± 1.3	**2.4 ± 1.0***	0.399
Recall	0.8 ± 1.0	**1.5 ± 1.1***	0.5 ± 0.9	**1.0 ± 1.0***	0.484
Attention/concentration	0.6 ± 0.9	**2.3 ± 0.3***	0.8 ± 1.3	**1.5 ± 1.7***	**0.016**†
Language	4.3 ± 2.4	**6.1 ± 2.1***	4.1 ± 2.5	**5.3 ± 2.6***	0.263
Digit span					
Forward	3.9 ± 2.2	**5.0 ± 2.0***	3.8 ± 2.2	**4.6 ± 2.1***	0.306
Backward	1.9 ± 1.3	**2.3 ± 1.2***	1.6 ± 1.5	**2.4 ± 1.7***	0.228
FIM					
Cognition	15.5 ± 5.5	**20.9 ± 5.8***	15.5 ± 7.2	**18.6 ± 8.6***	**0.039**†
IQ	57.3 ± 19.0	**68.0 ± 21.6***	59.2 ± 15.9	**68.1 ± 17.5***	0.485
VCI	69.8 ± 24.8	**79.6 ± 24.2***	69.0 ± 23.0	**77.0 ± 23.3***	0.683
PRI	65.0 ± 22.8	**72.4 ± 24.7***	68.3 ± 15.3	**77.0 ± 17.8***	0.696
WMI	64.9 ± 20.7	**73.1 ± 22.9***	66.7 ± 17.4	**74.1 ± 19.2***	0.720
PSI	55.5 ± 17.2	**64.3 ± 22.4***	60.0 ± 12.6	**64.6 ± 17.6***	0.248
AQ	53.0 ± 23.6	**74.5 ± 23.8***	54.7 ± 23.6	**68.3 ± 28.1***	0.098
GDS	15.4 ± 6.5	**9.8 ± 5.9***	11.4 ± 4.5	11.1 ± 5.6	**0.002**††

*, *Bold values; $P < 0.05$ significantly higher than baseline within each group comparison.*

P value† compared the changes in each score from baseline to follow-up between two groups by independent t-test. † *$P < 0.05$,* †† *$P < 0.01$.*

All values are presented a mean ± standard deviation.

(n) Number of patients evaluated, without remark all patients were evaluated.

MMSE, Mini-Mental State Examination; FIM, Functional Independence Measure; IQ, Intellectual Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; AQ, Aphasia Quotient; GDS, Geriatric Depression Scale.

in IQ between the groups with similarly increased scores during the study period. This may be because the Wechsler scale is not specifically suitable for the assessment of cognitive impairment in patients with stroke, especially to evaluate changes over a month (52). Nevertheless, WAIS-IV was adopted as a cognition scale because there is a lack of other quantitative scales to assess intelligence and sensitively catch cognitive changes in post-stroke patients. For depression, a marginally significant improvement in the rTMS-treated group was observed, which seems to be mostly beneficial for patients with left hemispheric stroke.

The most remarkable finding in this study was the differential responses in cognition and mood recovery by ipsilesional rTMS according to the hemispheric lesion side. In the left DLPFC rTMS-treated group, who had left hemispheric stroke, the significant items that showed beneficial effects of rTMS were total MMSE, only the "attention/concentration" subscore of MMSE, FIM cognition, and GDS. Although the aphasia might have affected other cognitive scales, it seems obvious that attention have attributed the most in cognitive improvement after rTMS. Meanwhile, the right rTMS-treated group, who had right hemispheric stroke, showed better outcomes than the control group in total MMSE, "registration," "recall," and "attention/concentration" subscores of MMSE, both forward and backward digit spans, and finally FIM cognition. According to clinical research, both DLPFC are well-acknowledged regions that implement various cognitive functions and attention control (15, 17, 21, 53). Through a comparison between two group analyses for each hemispheric lesion, ipsilesional DLPFC rTMS treatment in both hemispheres showed common effects on cognitive recovery, especially on attention in post-stroke patients, and the results of our study also support previous studies. The significantly higher increment of FIM cognition score in the rTMS-treated group of each hemispheric lesion seems to be meaningful because cognitive recovery has consequently led to improvement of ADL in the rTMS-treated patients.

In the present study, the most pronounced and specific effect of left DLPFC rTMS was amelioration of depression in patients with left hemispheric stroke. Recent studies have shown that high-frequency rTMS over the left DLPFC has a beneficial effect on refractory major depression and post-stroke depression (54). In this study, we also found a significant reduction in GDS score after rTMS treatment over the left DLPFC, while in the right DLPFC group, there was no effect on depression (55). Our retrospective analysis could provide basis for further prospective studies with new protocol of rTMS treatment depending on the laterality of the lesion in post-stroke patients.

In the right DLPFC rTMS-treated group, having right hemispheric lesions, total MMSE, and the subscores of "registration," "recall," and "attention/concentration" showed significant findings of better outcome. This seems to be a

TABLE 4 | Comparison of rehabilitation outcomes between rTMS and control groups (right hemispheric stroke subjects, $N = 76$).

	rTMS group (total $n = 49$)		Control group (total $n = 84$)		P value † (between groups)
	Baseline	Follow-up	Baseline	Follow-up	
MMSE	15.9 ± 8.2	**23.4 ± 5.5***	17.7 ± 5.8	**22.2 ± 5.9***	**0.003**††
Orientation	5.0 ± 2.9	**8.0 ± 2.1***	5.7 ± 2.9	**8.0 ± 2.1***	0.157
Registration	1.4 ± 0.5	**3.0 ± 0.6***	1.2 ± 0.4	**2.0 ± 0.7***	**0.009**††
Recall	2.3 ± 1.2	**2.8 ± 1.4***	2.7 ± 1.7	2.8 ± 1.6	**0.013**†
Attention/concentration	1.4 ± 0.5	**3.0 ± 1.1***	1.2 ± 0.4	**2.0 ± 1.1***	**0.008**††
Language	5.5 ± 2.6	**7.0 ± 1.5***	6.1 ± 2.2	**6.8 ± 1.7***	0.114
Digit span					
Forward	4.1 ± 1.0	**5.5 ± 1.5***	5.0 ± 1.5	**5.2 ± 1.49***	**0.004**††
Backward	2.1 ± 1.3	**3.0 ± 1.1***	2.7 ± 1.4	2.9 ± 1.26	**0.015**†
FIM					
cognition	19.5 ± 9.9	**23.5 ± 12.8***	21.0 ± 7.6	**22.3 ± 7.8***	**0.002**††
IQ	62.1 ± 14.0	**71.9 ± 14.7***	65.6 ± 14.1	**73.2 ± 14.7***	0.321
VCI	83.6 ± 20.9	**90.8 ± 16.8***	89.0 ± 15.4	**95.6 ± 16.3***	0.753
PRI	60.5 ± 13.8	**70.7 ± 16.6***	61.7 ± 11.6	**70.4 ± 15.2***	0.774
WMI	74.1 ± 17.3	**81.3 ± 17.3***	76.4 ± 17.1	**83.7 ± 16.3***	0.977
PSI	57.6 ± 9.1	**66.2 ± 13.1***	60.8 ± 13.3	**66.8 ± 15.1***	0.357
AQ	73.4 ± 31.0	**76.5 ± 29.2***	82.8 ± 20.8	**86.5 ± 19.5***	0.624
GDS	19.1 ± 9.0	18.0 ± 8.7	16.6 ± 7.2	15.0 ± 7.7	0.975

*, *Bold values; $P < 0.05$ significantly higher than baseline within each group comparison.*

P value † compared the changes in each score from baseline to follow-up between two groups by independent t-test. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$.

All values are presented a mean ± standard deviation.

(n) Number of patients evaluated, without remark all patients were evaluated.

MMSE, Mini-Mental State Examination; FIM, Functional Independence Measure; IQ, Intellectual Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; AQ, Aphasia Quotient; GDS, Geriatric Depression Scale.

meaningful result considering the common tendency of attention deficits in patients with right hemisphere lesions (56). In contrast to the left DLPFC rTMS-treated group who showed improvement only in the forward digit span, the right side rTMS-treated group showed improvement in the backward digit span, which indicates amelioration of working memory. Recovery of cognitive function after stroke, particularly attention and working memory, is directly related to the successful prognosis of cognition (57). Among working memory, verbal memory is measured by typical retention tasks such as forward and backward digit span tests (58). Our results on digit span score improvements in the right DLPFC-treated group are consistent with previous findings that reported activation in the right DLPFC rather than in the left DLPFC in verbal episodic retrieval (59–61). In a more recent study, a neural mechanism involving the DLPFC in proactive and reactive control as a key regulator was suggested with a more specific role of the left DLPFC in proactive control and the implication of the right DLPFC in reactive control related to retrieval of verbal information (59). Our results of increments in MMSE subscores, registration and recall progression only by right DLPFC rTMS treatment are consistent with previous research about the right DLPFC, which is responsible for verbal retrieval and short-term memory such as reactive control.

Since this research was not prospectively conducted, there are several weak points. First of all, our results have inevitable limitations as a retrospective study, which is also prone to selection bias. To reduce the bias as much as possible, control group patients were enrolled without exception who were admitted at the same time and criteria for inclusion and exclusion were the same for each group. Only different points between the groups were treatment of rTMS $\geq$ 5 times over ipsilesional DLPFC or none rTMS. And no significant differences were found in basal demographic characteristics between the groups regarding age, sex, type of stroke, and post-stroke duration. Even though, retrospective analysis cannot be free from the observer effect and unrecognized confounder factors. Second, the number of rTMS treatment therapies varied, and the range of cognitive impairment of the patients was wide. While the baseline functional scores were not different between the rTMS and control groups, it could not assure the homogeneity of the two compared groups. There were differences in cognitive function between the left and right hemispheric lesion patients within each treatment group, and the differences were more prevalent in the control group. This seemed to be caused by the differences in the number of enrolled patients in the groups. Even though significant results appeared during the one-month follow-up, long-term therapeutic effects are needed through follow-up studies, and a randomized controlled prospective study is required. It also seems that visual neglect and aphasia need to be approached by subdividing the group who have the problem for understanding the efficacy mechanism on cognition.

For example, the improvements in right hemispheric lesion group needs to be interpreted through further study especially considering possible link with unilateral neglect which was not fully addressed in this study. The effect of contralesional rTMS on the DLPFC is also needed.

This is the first attempt to determine the effects of rTMS, which can vary depending on the treatment side of the DLPFC. Although further functional and structural studies of rTMS on the right and left DLPFC separately are needed, this study could support the therapeutic potential of rTMS over the ipsilesional DLPFC on cognitive restoration and alleviation of post-stroke depression.

In conclusion, high-frequency rTMS over the ipsilesional DLPFC showed beneficial effects on cognition recovery, and those who received rTMS over the left DLPFC had improved depression in patients with cerebral hemispheric stroke during the subacute phase.

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 Cha University Institutional Review Board (IRB file No: 2017-09-060). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

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HYPOTHESIS AND THEORY
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Pre-stroke Physical Activity and Cerebral Collateral Circulation in Ischemic Stroke: A Potential Therapeutic Relationship?

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Favorable cerebral collateral circulation contributes to hindering penumbral tissue from progressing to infarction and is associated with positive clinical outcomes after stroke. Given its clinical importance, improving cerebral collateral circulation is considered a therapeutic target to reduce burden after stroke. We provide a hypothesis-generating discussion on the potential association between pre-stroke physical activity and cerebral collateral circulation in ischemic stroke. The recruitment of cerebral collaterals in acute ischemic stroke may depend on anatomical variations, capacity of collateral vessels to vasodilate, and individual risk factors. Physical activity is associated with improved cerebral endothelial and vascular function related to vasodilation and angiogenic adaptations, and risk reduction in individual risk factors. More research is needed to understand association between cerebral collateral circulation and physical activity. A presentation of different methodological considerations for measuring cerebral collateral circulation and pre-stroke physical activity in the context of acute ischemic stroke is included. Opportunities for future research into cerebral collateral circulation, physical activity, and stroke recovery is presented.

Keywords: physical activity, exercise, collateral circulation, stroke, recovery, hypothesis

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INTRODUCTION

In ischemic stroke, rapid access to targeted treatment is essential to prevent disability and mortality (1, 2). Prolonged blood flow disruption as a result of vessel occlusions or stenosis can result in permanent brain tissue damage (i.e., ischemic core) (3). Hypoperfused, electrically inactive brain tissue surrounding the ischemic core, known as the ischemic penumbra, can potentially be salvaged or progress to infarction (2, 4). However, the progression of ischemic core growth is highly variable (3). One important factor is the level of perfusion in the penumbra (2). Even when reperfusion is not achieved, the ischemic core does not always grow to the full extent of the vascular territory affected (5). The cerebral collateral circulation system is recognized as an underlying factor that determines the level of perfusion

in the penumbra and associated ischemic core growth in ischemic stroke (6). The level of perfusion offered by the collateral circulation has clinical implications. Leng et al. conducted a systematic review and meta-analysis examining 35 studies on the association between cerebral collateral circulation and the efficacy and safety of endovascular treatments (7). The authors reported that favorable collateral circulation was associated with higher rates of favorable functional outcomes at 3-months post-stroke, reduced risk of symptomatic intracranial hemorrhage during endovascular treatments, and reduced risk of mortality at 3-months (7). Other investigators have further reported that unfavorable collateral circulation is associated with many clinically important stroke outcomes, including faster infarct growth, larger final infarct volumes, proximal occlusions, higher stroke severity on admission, and poorer functional outcomes after stroke (8–12).

Given the established link between favorable collateral circulation and improved stroke outcomes, the cerebral collateral circulation system is regarded as a potential therapeutic target to improve outcomes in acute ischemic stroke (6, 13). Pharmaceutical and non-pharmaceutical strategies to optimize collateral circulation in the acute stroke setting have been proposed, including optimal head position during acute care (14, 15), medications to induce blood volume expansion, vasodilation or hypertension, neural stimulation, partial occlusion of the aorta, and limb compression devices (6, 13). However, the most appropriate strategies remain unclear (6). Increasing physical activity, among other lifestyle factors, may also be a potential strategy to optimize pre-stroke collateral circulation (16). Pre-stroke physical activity has been associated with lower admission stroke severity, reduced infarct volume, lower risk of mortality, and favorable functional outcomes after stroke (17–23). Yet our understanding of the association between pre-stroke physical activity and collateral circulation in acute ischemic stroke is limited.

The purpose of the current article is to provide a hypothetical basis for and discussion of the association between pre-stroke physical activity and collateral circulation. Specifically, we will (1) describe the collateral circulation system and factors influencing collateral circulation recruitment, (2) describe physical activity and the potential association between pre-stroke physical activity and collateral circulation, (3) discuss how collateral circulation and pre-stroke physical activity can be measured and (4) discuss future directions for the potential utility of collateral circulation and physical activity assessment in secondary prevention and recovery after stroke.

SEARCH STRATEGY

For this hypothesis and theory review, we searched the PubMed electronic database and Google Scholars for peer-reviewed journal article. The search was conducted using appropriate Boolean connectors where applicable, including individual or combined keywords and concepts associated with physical activity, exercise, collateral circulation, and ischemic stroke. Reference lists of relevant studies were hand searched. Relevant human and animal studies were included. No date restrictions were applied.

THE CEREBRAL COLLATERAL CIRCULATION SYSTEM

The cerebral collateral circulation system refers to complex networks of supplementary blood vessels that are recruited to provide alternative routes to maintain adequate cerebral blood flow when primary blood vessels are obstructed (24). These supplementary blood vessels are particularly important in ischemic stroke, where inadequate arterial blood flow results from vessel narrowing (i.e., stenosis) or embolism (i.e., occlusion). The anatomical structures of the cerebral collateral circulation system are complex, and can be subdivided into primary and secondary collateral systems, illustrated in **Figure 1** (24). Primary collaterals refer to arteries of the Circle of Willis that connect the anterior and posterior circulation of the brain (24). Specifically, the Circle of Willis is a ring-like structure that connects the left and right anterior cerebral arteries (ACA) *via* the anterior communicating artery, and the middle cerebral arteries (MCA) and posterior cerebral arteries (PCA) *via* the posterior communicating arteries (**Figure 1A**) (25). The secondary collaterals refer to the leptomeningeal arteries, which form anastomosis between the distal segments of ACA and MCA, and between the PCA and MCA (**Figure 1B**) (6).

Pathophysiology of Cerebral Collateral Recruitment

The pathophysiology of cerebral collateral recruitment in ischemic stroke is not well understood in humans, and has primarily been described in animal models (26). Investigators propose that the extent and timing of cerebral collateral circulation recruitment are crucial factors, and may be broadly dependent on the following factors: the anatomical variations in collateral vessels, the capacity of blood vessels to vasodilate in response to ischemia, and individual risk factors (13, 24).

The Anatomical Variations in Collateral Vessels

The recruitment of primary and secondary collaterals depends on natural anatomical variations, size, number, and distribution of vessels. In response to a large vessel occlusion, the primary collateral circulation system provides immediate diversion of blood flow to the ischemic region primarily through the anterior and posterior communicating arteries within the Circle of Willis (24). The involvement of these primary collaterals depends on the natural, anatomical variations in the Circle of Willis. Using magnetic resonance angiography (MRA) in 874 men and 990 women, Hindenes et al. found 47 unique variations in the Circle of Willis, where the absence of the posterior communicating arteries is the most common variation (27). This is clinically relevant, as acute MCA occlusions in patients with a present ipsilateral posterior communicating artery are more likely to have favorable functional outcomes (i.e., modified Rankin score < 2) after successful endovascular mechanical thrombectomy, compared to those without an

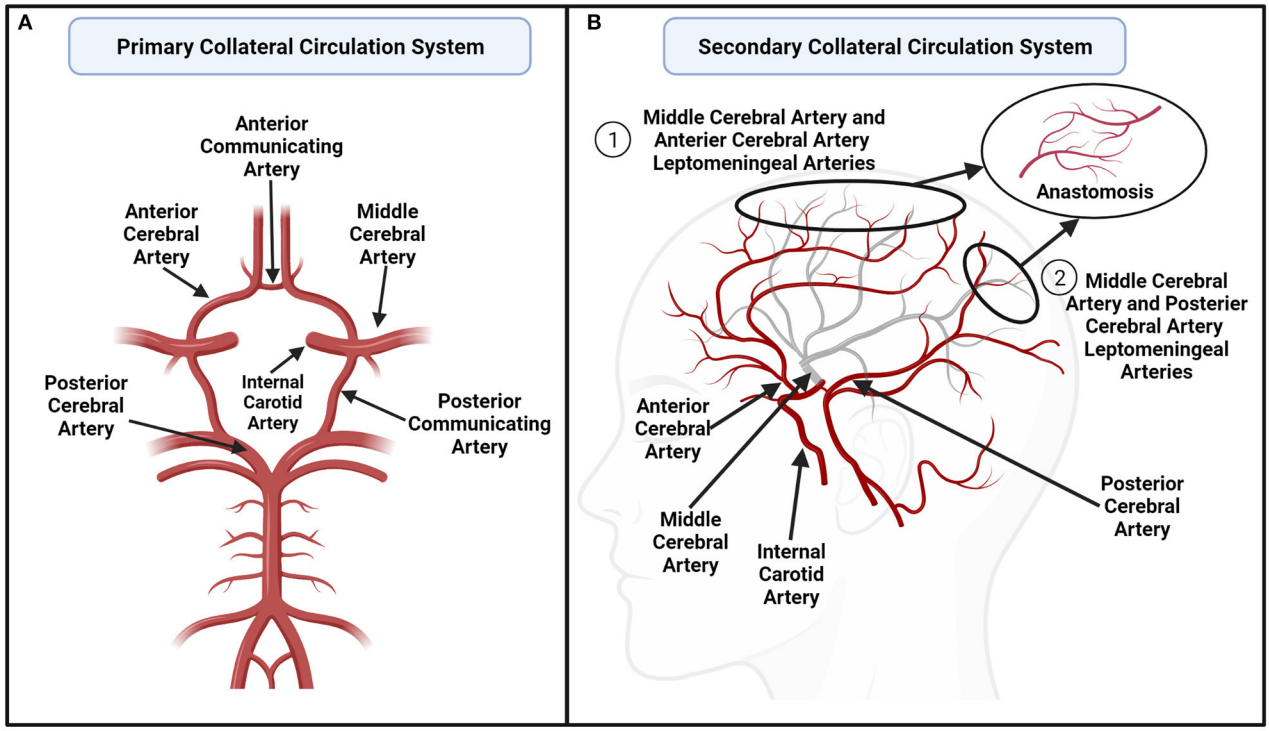

FIGURE 1 | (A) An illustration of the primary collateral circulation system, including the individual arteries of the Circle of Willis. The left and right anterior cerebral arteries (ACA) are connected by the anterior communicating artery, while the middle cerebral arteries (MCA) and posterior cerebral arteries (PCA) are connected by the posterior communicating arteries (25). **(B)** A sagittal, transparent view of selected right cerebral arteries to illustrate an example of the secondary collateral circulation system, where the MCA (gray arteries) forms leptomeningeal arterial anastomoses with the (1) ACA and (2) PCA. Created with BioRender.com.

ipsilateral posterior communicating artery (28). The recruitment of leptomeningeal collaterals is hypothesized to occur when the primary collaterals have failed to provide adequate blood flow to the ischemic regions (24), since leptomeningeal arteries are primarily observable in the later phases of ischemia (29). Anatomical variations in the presence of leptomeningeal collaterals have also been investigated by numerous authors using evidence ranging from human cadaver brain dissections to advanced brain imaging, with high inter-individual variability in the number and size of the leptomeningeal arteries (29).

The Capacity of Collateral Vessels to Vasodilate

The recruitment of collaterals may also depend on the capacity of the cerebral vasculature to vasodilate in response to ischemic stress through endothelial and metabolic mechanisms (26, 30). Animal studies have demonstrated the importance of endothelial function (i.e., the ability of endothelial cells to produce vasodilatory factors, such as nitric oxide) for collateral recruitment (26). Investigators have inhibited the production of endothelial-derived nitric oxide in rats, which has been shown to reduce cerebral collateral recruitment during ischemia and lead to subsequent larger infarct sizes (31). Additionally, inhalation of nitric oxide during ischemia, a known cerebrovascular vasodilator, can promote cerebral collateral recruitment and reduce infarct size in rats (32). In humans, assessing the association between endothelial function and collateral recruitment in response to an acute ischemic stroke is complex due to the priority for establishing rapid revascularization via administration of hyperacute therapies. Inferences can be made from assessing collateral recruitment of acute stroke patients with chronic small vessel disease, a patient group where poor endothelial function is well-established (33). Lin et al. examined the association between collateral recruitment and small vessel disease in 100 acute ischemic stroke patients who received mechanical thrombectomy (30). Participants who were categorized as having small vessel disease (i.e., presence of severe white matter hyperintensities, lacunar strokes, microbleeds, or enlarged perivascular space) were twice as likely to have poor cerebral collateral circulation (30). The authors postulated that increased stiffness of arterioles, including leptomeningeal arteries, associated with small vessels disease may lead to impaired endothelial function of leptomeningeal collaterals (30). In support of this finding, Giurgiutiu et al. studied 73 ischemic stroke survivors and found that greater white matter hyperintensity volumes were independently associated with poor collateral circulation (34). Mark et al. reported similar findings when examining 178 stroke survivors who received mechanical thrombectomy, where more extensive white matter hyperintensities were independently associated with poor collateral circulation (35).

Given that the vasodilatory responses in cerebral circulation occurs from large arteries to the microcirculation, inferences can also made about collateral vessel recruitment by examining the evidence of the endothelial function of the larger arteries, such as the MCA, or arteries in the Circle of Willis (36). For instance, the recruitment of primary collaterals may depend on their vasodilatory capacity (37). Kim et al. used transcranial Doppler ultrasonography (TCD) to measure flow diversion in the ipsilateral ACA and PCA within 24 h of clinical angiography in 51 patients with acute M1 MCA stenosis or occlusion, and found that 47% of patient had adequate flow diversion (i.e., >30% greater flow velocity compared to contralesionally side) and were associated with recruitment of leptomeningeal collaterals (38). Impaired endothelial function assessed at the MCA or basilar artery is more commonly observed in stroke survivors when compared to healthy age-matched controls, likely due to combined effects of pre-stroke vascular risk (i.e., chronic hypertension) and stroke-related tissue injury (39). Therefore, endothelial function of the MCA post-stroke may be a surrogate measure of collateral circulation recruitment in ischemic stroke. However, the evidence relating endothelial function of the MCA in subacute or chronic phases of stroke and collateral circulation recruitment in response to ischemia are conflicting (40–43). For instance, Hofmeijer et al. investigated the association between collateral circulation and endothelial function using TCD at the MCA in 70 patients with symptomatic carotid artery stenosis (40). The authors found that poor endothelial function at the MCA was associated with the recruitment of collateral circulation via the ophthalmic (TCD) or leptomeningeal arteries (angiography) on the symptomatic hemisphere (40), which may be counter-intuitive. To explain this observation, investigators have postulated that the presence of angiogenic adaptations *via* the development of collateral arteries may be a response to post-stroke ischemic injury and chronic hypoperfusion (24). Therefore, these studies may not sufficiently reflect the association between endothelial function and collateral recruitment in the setting of an acute ischemic stroke, and further investigation is needed.

Individual Risk Factors for Poor Collateral Recruitment

Older age and modifiable risk factors have been identified as potential individual risk factors for poor collateral circulation (13, 24, 29, 44). In animals, aging is associated with a reduction in the size, number, and diameter of leptomeningeal collateral arteries (45), a process that is also thought to occur in humans (13, 24). Bullitt et al. assessed cerebrovascular structures using MRA in 100 healthy human adults, and found an age-related decline in the number of small vessels (<1 mm diameter) and an abnormal increase in the level of curvature in vessels (46). How these finding may applied to leptomeningeal arteries, however, was not specified. In addition to older age, Menon et al. examined the collateral circulation status of 206 consecutive stroke patients with MCA occlusions, and found that poor collateral circulation status was independently associated with metabolic syndrome (i.e., having three or more of the following: high triglycerides, low high-density lipoprotein cholesterol, high plasma glucose, high blood pressure or medication to control blood pressure, or obesity) (16). Fujita et al. examined the association between chronic hypertension (defined as pre-stroke hypertension diagnosis or use of antihypertensive medications) and collateral circulation in 100 acute ischemic stroke patients, and found that chronic hypertension was associated with poorer collateral recruitment (47). A meta-analysis by Malhotra et al. including nine studies investigated the association between pre-stroke statin treatment, collateral circulation, and infarct size, and found that pre-stroke statin treatment was associated with smaller infarct size, and inconclusive association with collateral circulation status (48). Overall, these studies identified potential individual, modifiable risk factors associated with poor collateral circulation.

PHYSICAL ACTIVITY AND ITS POTENTIAL ASSOCIATION WITH CEREBRAL COLLATERAL RECRUITMENT

Physical activity is defined as "any bodily movement produced by skeletal muscle that results in energy expenditure," and can be sub-typed as leisure-time, household, work, and transportation (49). Exercise is a specific subtype of leisure-time physical activity, which involves planned, structured, and repetitive bodily movements with the purpose of improving or maintaining one of more components of physical fitness, such as cardiorespiratory fitness or muscle strength (49). Exercise can also be further sub-categorized as aerobic or resistance exercise. Aerobic exercise is defined as exercise that involves large muscle groups that can be maintained continuously in a rhythmic nature (50). Resistance exercise is defined as exercise involving periodic bodily movements where external weights provide progressive overload to increase skeletal muscles strength and mass (51). The following section will discuss various cerebrovascular responses to physical activity, primarily aerobic exercise, that may influence collateral circulation. In **Table 1** and **Figure 2**, we summarized the factors influencing cerebral collateral circulation and proposed benefits of physical activity that may improve cerebral collateral circulation.

Cardiovascular Response to Physical Activity

The cardiovascular response to physical activity is highly complex and has been extensively described (58, 60, 61). Briefly, the onset of physical activity causes heart rate and stroke volume to increase, resulting in increased cardiac output to meet the increased metabolic demands of contracting skeletal muscles (60). Systolic blood pressure increases with increasing intensity of physical activity, while diastolic blood pressure remains stable or may even decrease (62). Specifically to cerebral circulation, physical activity acutely increases cerebral blood flow with greater increases with higher intensity physical activity (63). This increase in blood pressure and blood flow results in two broad types of interactions at arterial walls to further increase in blood flow through vasodilation: circumference strain and sheer

stress (58). Circumference stress occurs when increases in blood pressure stretch and strain the circumference of arterial walls. Increased exposure to circumferential strain on endothelial cells triggers the production and upregulation of endothelial factors, such as nitric oxide. Furthermore, this circumferential strain also stretches the vascular smooth muscles, and subsequently, induces contraction of the smooth muscles to further increase cerebral blood flow. The second type of interaction is called shear stress, where increased blood flow results in parallel forces applied by the blood along the vessel endothelium, which also stimulates the production of endothelial factors, such as nitric oxide. Among numerous factors, this production and upregulation of nitric oxide from these two interactions relaxes vascular smooth muscles, resulting in acute vasodilation and increased blood flow. In addition to nitric oxide, this circumferential strain and shear stress also induces the production of vascular endothelial growth factors, responsible for arteriole and capillary growth (i.e., angiogenesis), with the purpose of providing more blood flow to the required tissues (58, 64).

TABLE 1 | Potential association between physical activity and cerebral collateral circulation recruitment.

Factors influencing cerebral collateral circulation	Proposed benefits of physical activity
Collateral vessel anatomical variations, size, number, and distribution (27, 29)	Promoting growth of new arteriole blood vessels *via* vascular endothelial growth factors (52, 53)
Capacity to vasodilate (30) • Endothelial function and nitric oxide bioavailability (26)	Cerebrovascular adaptations • Increase nitric oxide bioavailability (54, 55) • Increased cerebral blood flow and reactivity (56)
Individual risk factors • Older age (13, 29) • Metabolic syndrome (16) • Hypertension (47) • Pre-stroke statin treatment (48)	Reduce individual risk factors (57) • Hypertension • Type 2 diabetes • Cardiovascular disease • Obesity

Cerebrovascular Adaptations to Physical Activity

Aging is associated with endothelial dysfunction, arterial stiffening, impaired angiogenesis, and risk of cardiovascular disease (65–67). While mechanisms behind these processes are complex and not fully understood, the reduction in bioavailability (i.e., production and release) of nitric oxide with age in humans may be a key link (66, 67). Various measures of cerebral endothelial and vascular function also decline with age, including reduction in global and regional cerebral blood flow

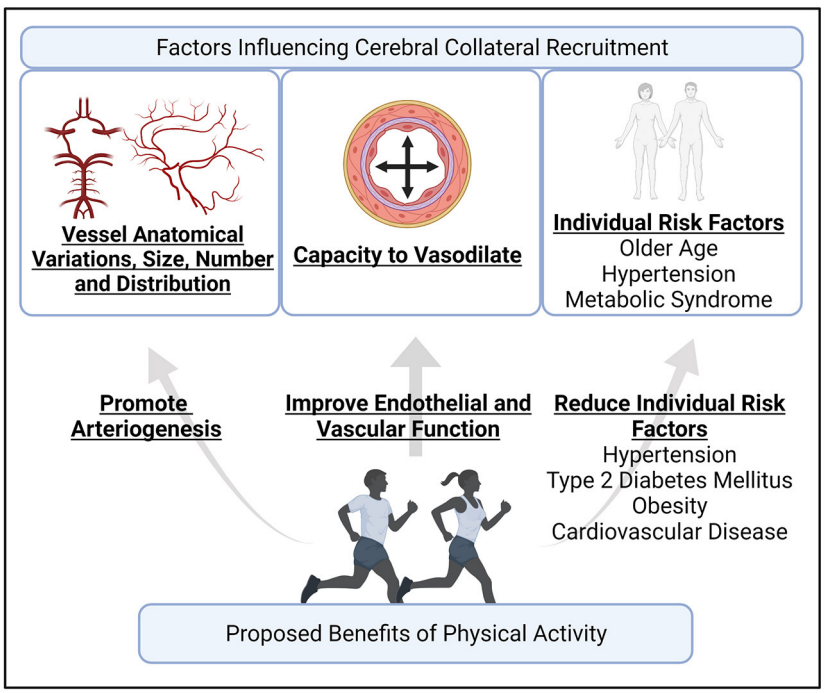

FIGURE 2 | An illustration of the proposed factors influence cerebral collateral recruitment, and how the benefits of physical activity may contribute to favorable collateral circulation recruitment. Cerebral collateral circulation recruitment depends on individual anatomical variations, number, size, and distribution of blood vessel, the capacity of blood vessels to vasodilate, and individual risk factors, such as age (13, 24). Physical activity can potentially contribute to arteriogenesis, including leptomeningeal arteries (52, 58), can improve cerebral endothelial and vascular function (56), and is well-documented in reducing the risk of hypertension, type 2 diabetes mellitus, obesity, and cardiovascular disease (59). Created with BioRender.com.

and cerebrovascular reactivity (i.e., capacity of blood vessels to response to physiological stress) (68). Wu et al. cross-sectionally assessed global cerebral blood flow using MRI and transcranial 4D flow imaging in 82 people ranging between 7.2 months and 60.7 years old, and found that cerebral blood flow declines with age, starting at 18 years old (69). Similarly, Miller et al. cross-sectionally assessed cerebrovascular reactivity in 39 participants between the age 21-67 years old using MRI and transcranial 4D flow imaging, and found that older participants had lower cerebrovascular reactivity compared with younger participants in global and individual vessel blood flow in the MCA, intracranial artery and basilar artery (70). This age-related decline in blood flow and cerebrovascular reactivity may be associated with poor collateral recruitment observed in older ischemic stroke patients previously discussed.

Life-long physical activity in humans may prevent age-related decreases in nitric oxide bioavailability. Nyberg et al. assessed bioavailability of nitric oxide in 32 people of various age and physical activity levels, and found that older, sedentary participants had reduced nitric oxide bioavailability compared with active, older participants (71). Based on these findings, physical activity is regarded as a potential strategy to increase nitric oxide bioavailability (54, 55). A recent review conducted by Facioli et al. included 16 studies and found that various exercise types (aerobic, resistance, Pilates, Tai Chi), intensities and durations of exercise interventions were associated with increased production of nitric oxide in people with hypertension (72). The effects of physical activity may also translate to improvements in multiple measures of cerebrovascular function. Smith et al. (56) conducted a systematic review and meta-analysis including 34 studies and examined the association between cardiorespiratory fitness (i.e., objectively measured peak oxygen [VO_{2peak}] consumption during a graded exercises test) and cerebrovascular function, and the effect of exercise training on cerebrovascular function in healthy and clinical populations. In this review, cerebrovascular function was quantified as cerebral blood flow, reactivity (i.e., change in MCA blood flow given a change in hypercapnic conditions), and resistance (i.e., ratio of mean arterial pressure to cerebral blood flow). The authors found that higher cardiorespiratory fitness was associated with improved cerebrovascular resistance and reactivity compared to lower fitness. However, only participants who were categorized as extreme levels of high cardiorespiratory fitness were associated with higher cerebral blood flow compared with lower fitness levels. In two studies, improvements in cerebrovascular reactivity were associated with corresponding increases in cardiorespiratory fitness after taking part in an aerobic exercise interventions (73, 74). One study reported improvements in cerebrovascular reactivity in healthy older adults using a combined aerobic and resistance training exercise program (75). However, these results were inconsistent in three other studies including stroke, breast cancer, and chronic kidney disease survivors using aerobic exercise training (73, 76, 77). While meta-analysis results suggested that exercise interventions were not associated with changes in global cerebral blood flow, improvements in cerebral blood flow to specific regions (hippocampus and anterior cingulate cortex) were reported by some authors (78–80), but there results were inconsistent (81, 82). The authors highlight the results may have been influenced by heterogenous exercise intervention designs, including intervention lengths (2-12 months), exercise types, and lack of reporting on attendance and adherence to intervention training (56). Taken together, the authors concluded that their findings suggested that higher cardiorespiratory fitness with life-long exercise is associated with improved cerebrovascular function, and enhances our understanding of exercise as a potential approach to decrease age-related changes in cerebrovascular function (56). Higher quality, randomized controlled trials are needed to conclusively determine the benefits of physical activity intervention on cerebrovascular function, as well as determining exact duration, intensity, type and timing of interventions (56). Overall, this evidence highlights the potential effect of physical activity on improved capacity for vasodilation associated with collaterals recruitment.

Physical activity can potentially influence the growth of new arteriole blood vessels (i.e., arteriogenesis) through the production and upregulation of vascular endothelial growth factors (52, 58). Vital et al. conducted a systematic review examining the effect of exercise interventions on peripheral concentrations of vascular endothelial growth factors in humans (83). Of the 10 studies included, four studies (two randomized controlled and two non-randomized controlled trials) reported an increase in vascular endothelial growth factors in various elderly populations after the interventions, primarily involving aerobic exercise (83). While the six remaining studies (four randomized controlled, one non-randomized controlled, and one randomized uncontrolled trial) found no change in vascular endothelial growth factor concentrations, the heterogeneity in type of physical activity, duration and length included across interventions made it difficult to effectively determine optimal dose of exercise (83). Boyne et al. examined 16 chronic stroke survivors and found an the acute increase in circulating vascular endothelial growth factors after a single bout of high intensity interval treadmill training (84). However, visible changes in vasculature in cerebral collateral circulation as a result of physical activity has primarily been demonstrated in animal models (52). One known human, cross-sectional study conducted by Bullitt et al. examined the association between self-reported physical activity and cerebral vascular structure (i.e., vessel number, average vessel radius, and vessel shape) of the MCA, ACA, and PCA assessed using MRA in 14 healthy older adults (53). The authors found that participants categorized as "high activity" (i.e., engaged in regular aerobic activities for at least 180 min per week for the past 10 years) trended toward having greater number of small vessels (<1 mm diameter), but not larger diameter vessels, and smoother vessel curvature compared to inactive participants (53). While not mentioned by the authors, these greater number of small vessels associated with higher physical activity levels may also include leptomeningeal arteries. The authors were unable to detect arteries smaller than 0.5 diameter due to limitations in voxel size in MRA techniques, potentially excluding the leptomeningeal arteries (53). Overall, this provides promising evidence that physical activity may help prevent age-related attrition in collateral arteries in humans.

Physical Activity Guidelines and Individual Risk Factors

The wide range of physical and mental health benefits of physical activity are well-documented and evidenced by numerous systematic reviews and meta-analyses (59, 85–89). In particular, Warburton et al. conducted a comprehensive systematic review that included 254 articles, primarily observational studies, highlighting consistent evidence for the independent association between physical activity and reduced risk of all-cause mortality and prevalence for a variety of chronic diseases, such as cardiovascular disease, hypertension, stroke, obesity, and type II diabetes mellitus (57). Numerous additional meta-analyses of randomized controlled trials have also reported that physical activity interventions are effective in the prevention and treatment of hypertension (54 trials, 2,419 participants) (90), type 2 diabetes mellitus (11 trials, 846 participants) (91), and favorable modification of numerous cardiometabolic biomarkers (160 trials, 7,487 participants), including lipid profiles, fasting insulin, and glycosylated hemoglobin A1c (92). As such, the American Heart Foundation and American College of Sports Medicine recommend older adults to engage in at least 30-min of moderate-to-vigorous physical activity per day to prevent and manage chronic diseases (93). The American Heart Association Stroke Council have similar recommendations for stroke survivors to improve physical function and reduce risk factors for stroke for secondary prevention (94). Given these benefits, physical activity may help reduce individual risk factors associated with poor collateral circulation.

STUDIES DIRECTLY ASSESSING THE ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND CEREBRAL COLLATERAL CIRCULATION

The effect of physical activity on cerebral collateral circulation has been studied primarily in animals. Rzechorzek et al. showed that voluntary wheel-running in mice (i.e., equivalent to incidental physical activity in humans) reduced age-related decrease cerebral collateral artery diameter, length, and number, and infarct size after middle cerebral artery occlusion, compared to sedentary mice (95). Furthermore, these adaptions were associated with upregulation of endothelial nitric oxide (95). No identified studies have evaluated the association between pre-stroke physical activity and cerebral collateral circulation in human acute ischemic stroke. Although the association between nitric oxide and cerebral collateral circulation in human ischemic stroke remains unclear, one of the mechanisms underlying the potential effects of pre-stroke statin treatment on collateral circulation in humans includes the upregulation of endothelial nitric oxide (48). However, the effect of physical activity interventions on coronary collateral circulation in people with coronary artery disease has been examined (96). Nickolay et al. summarized the evidence from seven studies that examined the effect of aerobic exercise interventions to increase coronary collateral flow in humans, and revealed consistent evidence that aerobic exercise is beneficial in promoting coronary collateral circulation, using angiography or the Collateral Flow Index (i.e., considered the "gold standard" for assessing coronary collateral flow) (96). In particular, Möbius-Winkler et al. randomized 60 patients with severe coronary artery disease to high intensity or moderate intensity aerobic exercise training, and showed increased coronary collateral circulation compared with usual care patients using Collateral Flow Index and angiographic evidence (97). Stoller et al. examined muscle tissue in 110 patients undergoing diagnostic coronary angiography, and found that patients with greater self-reported leisure-time physical activity levels had greater femoral artery collateral circulation (98). While no studies have been conducted in humans, these studies provide evidence in mammalian models to motivate further investigation in the associations between cerebral collateral circulation and physical activity in human acute ischemic stroke.

MEASURING CEREBRAL COLLATERAL CIRCULATION

Measurement considerations for cerebral collateral circulation are summarized in **Table 2**. The conventional method of evaluating the collateral circulation status in acute ischemic stroke involves using visual grading systems, often assessing the presence, extent and/or timing of collateral vessels (namely leptomeningeal arteries) relative to the ischemic region (99). Different collateral recruitment grading systems have been developed using brain imaging to visual collateral vessels (99). The most commonly used grading systems (106) are those developed by the American Society of Interventional and therapeutic Neuroradiology and Society of Interventional Radiology (ASITN/SIR) (107), Alberta Stroke Program Early CT (ASPECT) Score for collaterals (108), Christoforidis et al. (109, 110), and Miteff et al. (111). Seker et al. compared these four grading systems using dynamic CTA, and found that ASITN/SIR and the ASPECT score to be superior to Christoforidis and Miteff systems in predicting infarct volumes in 30 acute stroke patients with M1 or terminal carotid artery occlusions (106). Furthermore, ASITN/SIR grading system has been used by multiple investigators to predict stroke outcomes in acute ischemic stroke patients, where favorable collateral grading has been associated with smaller infarct core volume and favorable functional outcomes (8, 112, 113).

The "gold standard" imaging modality to visualize cerebral collateral circulation in ischemic stroke is digital subtraction angiography (13, 114). However, digital subtraction angiography is invasive and costly, so other methods may be preferred (13, 114, 115). Furthermore, in current clinical practice, the imperative for rapid revascularisation means that a full set of angiographic images, with injection of multiple arteries, is not obtained prior to treatment. This limits the assessment of collateral flow largely to MCA occlusion. The anterior cerebral, but not posterior cerebral, collateral pathways can be assessed based on an internal carotid artery injection. However, non-invasive multi-modal brain imaging techniques performed as part of standard clinical care for acute stroke provide numerous opportunities for cerebral collateral circulation assessment,

TABLE 2 | Measurement considerations for cerebral collateral circulation and pre-stroke physical activity.

Outcome	Methodology	Strengths	Limitations
Cerebral collateral circulation	Visual grading scales using angiography (DSA, MRI, CTA, CTP) (99)	"Gold Standard" (namely DSA) (13)	Requires expert input (100)
	Hypoperfusion intensity ratio (101)	Automated; requires minimal expert input (100)	Indirect measure (101)
	Transcranial Doppler (99)	Can be completed post-stroke (40–43)	Unclear clinical relevance to acute ischemic stroke (13)
Pre-stroke physical activity	Self-report questionnaires	• Suitable of retrospective and case-control studies (17) • Inexpensive and easy to administer (102)	Risk of recall bias (102, 103)
	Objective measurements (accelerometers and pedometers)	• Suitable for prospective cohort studies • Reduced risk of bias and improve accuracy (104)	Expensive and time consuming (13, 105)

CTA, computed tomography angiography; CTP, computed tomography perfusion; DSA, digital subtraction angiography; MRI, magnetic resonance imaging.

including MRI, MRA, computed tomography angiography (CTA) and perfusion (CTP) (13, 99, 100, 116). For MRI, fluid-attenuated inversion-recovery sequences can be used to visualize "vascular hyperintensities" as an indirect method of assessing collateral circulation in acute ischemic stroke (117). Single- and multi-phase CTA and/or MRA are often used to identify the presence of large vessel occlusion, and can also be used to assess collateral vessels (13, 100). In addition to providing invaluable information for the selection of patients for thrombolytic and endovascular therapy (118–122), CTP offers multiple opportunities for collateral circulation assessment (100). With post-processing software, source images from CTP (maximum intensity projections) can be used to reconstruct four dimensional CTA to assess collateral circulation (123). Time-to-maximum (Tmax) is a perfusion parameter derived from deconvolution with an arterial input function, indicates the severity of blood flow delay which, in the context of arterial occlusion, reflects collateral blood flow quality (124). Regions of brain with perfusion delay defined as Tmax $>$ 6 s provides an estimate of the tissue at risk (ischemic core and penumbra) (101, 125). The hypoperfusion intensity ratio (HIR), defined as the volumetric ratio of tissue with Tmax $>$ 10 s to Tmax $>$6 s, can serve as an indirect estimate of collateral circulation status (101, 125). The HIR has been well correlated with collateral grading in acute ischemic stroke patients as assessed by digital subtraction angiography by multiple investigators (8, 112, 126). Other CTP parameters have been correlated with collateral circulation, including cerebral blood volume (CBV) and cerebral blood flow (CBF) (105, 127). Specifically, higher relative CBV (rCBV), defined as the ratio of mean CBV values within the Tmax $>$ 6 s regions to mean CBV values within the Tmax $\leq$ 4 s regions (normal brain tissue), has been correlated with favorable collateral grading in acute ischemic stroke patients (105). Using CBF $<$ 30% to estimate the ischemic core volume, slower baseline ischemic core-growth rate, defined as the ischemic core volume divided by the time between stroke onset and CTP imaging, has been correlated with favorable collateral grading in acute ischemic stroke patients (127). Finally, while not routinely assessed, TCD can be used to measure flow velocities and collateral circulation (41, 128). Specifically, TCD has been used to measure flow diversion in the ipsilateral anterior and posterior communicating arteries (i.e., $>$30% higher than contralateral flow velocity) within 24 h of clinical angiography in acute M1 MCA stenosis or occlusion, and has been associated with recruitment of leptomeningeal collaterals as seen on digital subtraction angiography (38). TCD can also be used to measure collateral flow at the ophthalmic arteries (40, 41).

MEASURING PRE-STROKE PHYSICAL ACTIVITY LEVELS

Measurement considerations for pre-stroke physical activity are summarized in **Table 2**. Measuring pre-stroke physical activity is challenging with inherent limitations based on study design (103, 129). Based on a recent systematic review we conducted, along with other studies measuring pre-stroke physical activity (23, 130–132), most studies were retrospective and case-control designs and relied on self-reported physical activity questionnaires to recall pre-stroke activities (17, 18). Questionnaires are relatively inexpensive, low resource burden, convenient to administer, and ideal for clinical settings (102). However, they are prone to risk of recall and social desirability bias, leading to questionable accuracy, especially for incidental, unstructured physical activity (102). Assessing pre-stroke physical activity soon after stroke incidence (i.e., during their acute hospital stay) may reduce potential recall bias associated with memory. However, additional challenges may present in acute stroke patients including impaired cognition and memory, aphasia, and additional social desirability factors associated with self-image after stroke (103). Prospective cohort studies have the capacity to include objective measurements of physical activity, including accelerometers and pedometers, to reduce risk of bias and improve accuracy of physical activity

measurement (104). However, prospective cohort designs are often expensive and time-consuming due to the long follow-up and large samples required for disease incidence (103, 133). As such, few prospective cohort studies have been conducted, including the Physician's Health Study (132) and Women's Health Initiative cohorts (23), but neither studies included objective measures of physical activity. Nevertheless, self-reported questionnaires remains a feasible, cost-effective and pragmatic method to measure pre-stroke physical activity in acute or subacute settings, as demonstrated by many investigators (17, 18).

Specific to acute clinical settings, assessing pre-stroke physical activity can be challenging. The selection of measurement tools need to consider the balance between burden of administering the questionnaire (i.e., time and attentional resources of patients and healthcare providers) and the level of detail on type and dose (i.e., intensity, frequency, and time) of pre-stroke physical activity (102). A variety of pre-stroke physical activity questionnaires have been used in the literature (17, 18). Authors have used measures that are relatively less time consuming, such as single-questionnaire measures to assess if they meet minimum duration and frequency of leisure-time physical activity (134–137) or standardized questionnaires [i.e., Saltin-Grimby Physical Activity Level Scales (138)]. However, the brief nature of these questionnaires may provide limited detail on physical activity type and dose and may preclude further discussion on how to modify physical activity after stroke. Authors have also used relatively longer and more detailed physical activity quesitonnaires (130, 139, 140), such as the International Physical Activity Questionnaire (141) and the Physical Activity Scale for the Elderly (142). These standardized questionnaires provide more information of physical activity type and dose, and may also be useful in continued assessment and physical activity counseling post-stroke. Furthermore, the selection of questionnaires needs to be age-appropriate, where the types of physical activities assessed should be those commonly engaged by older adults (17).

DISCUSSION

Potential Barriers and Solutions to Measuring Collateral Circulation

Given the well-documented benefits of physical activity and potential positive influence on cerebral vascular function discussed above, we hypothesize that greater pre-stroke physical activity is associated with better collateral circulation in ischemic stroke. Assessing pre-stroke, and post-stroke, physical activity in acute and subacute clinical settings is feasible, and the advent of advanced brain imaging integrated into routine clinical care offers a cost-effective opportunity to assess of collateral circulation in acute ischemic stroke. However, collateral circulation grading using advanced imaging modalities often requires expert input from experienced neurologists and radiologists, and potential post-processing techniques by imaging scientists (100). This may be a barrier for collateral circulation grading where such expertise is limited within clinical and research settings. The HIR and rCBV may be solutions to this barrier, as perfusion maps that include Tmax and CBV parameters and associated HIR and rCBV values can be generated by multiple automated software, such as the RApid Processing of Perfusion and Diffusion (RAPID) software, without extensive and ongoing expert input (100, 101, 105). Clinically relevant HIR threshold values have been established to reflect favorable or unfavorable collateral status. Olivot et al. examined 99 acute ischemic stroke patients, and reported that an HIR $\geq$ 0.4 was associated with greater infarct growth and final infarct volume, greater admission stroke severity, and unfavorable functional outcomes after stroke (8). Similar thresholds have been reported by other authors, where favorable HIR has been associated with less infarct growth, favorable functional outcomes, and even potentially eligibility for thrombectomy (112, 143–145). Arenillas et al. examined 158 acute ischemic stroke patients, and reported that higher rCBV was associated with favorable collateral circulation and slower infarct growth at 27-h follow-up (105), and favorable functional outcome in patients after acute ischemic stroke (105). Furthermore, Cortijo et al. invested 100 acute ischemic stroke patietns, and reported that lower rCBV was associated with poor colleateral circulation, and poor functional outcome in the absence of recanalisation (146). Overall, both HIR and rCBV serve as accessible opportunities for a wider group of health professions (i.e., physiotherapists and exercise physiologists) and research communities to indirectly assess collateral circulation status with relatively minimal on-going expert input. However, in the absence of acute ischemic stroke and clinical imaging, in the case of potential clinical trials, follow-up assessments to evaluate the change in collateral circulation will require expert input, as HIR and rCBV has not been assessed outside of the hyperacute phases of stroke. Advanced MRA may potentially be used to visualize collateral vessels (13), and TCD measurements at the MCA, ACA, or PCA in response to forced-dilatory responses (i.e., hypercapnic breathing maneuvers) may be used as surrogate measure of collateral recruitment (40–43). However, further investigation is required regarding the clinical relevance of cerebrovascular function assessments conducted post-hyperacute stroke phase (13).

Physical Activity, Collateral Circulation, and Post-stroke Recovery

Physical activity is a widely accepted and important strategy for the prevention and management of stroke. Notably, physical activity is currently recommended to improve physical function and manage vascular risk factors for secondary prevention in people who have had a stroke (94). However, to improve our understanding on the role of physical activity on key stroke recovery outcomes, generating new information on the possible link between physical activity and collateral circulation is a worthwhile endeavor. The Stroke Recovery and Rehabilitation Roundtable regard clinically acquired CT imaging, including perfusion, in the hyperacute phase of stroke as a potential biomarker for stroke recovery and a developmental priority for future research (147). Exercise and physical activity interventions are effective and recommended for reducing disability, and

improving mobility and physical function in stroke survivors (148, 149). If physical activity and collateral circulation are associated, collateral circulation status may emerge as a biomarker to stratify or identify patients for clinical trials, such that we can target patients with poor collateral status and suspected poor functional outcomes who would most benefit from enrolling in physical activity interventions. These physical activity interventions can potentially reduce the risk of poor clinical outcomes in the event of first-ever strokes for high-risk populations or recurrent strokes for stroke survivors through improvements in cerebral collateral circulation. Furthermore, physical activity interventions have the potential to improve functional recovery after stroke. Limaye et al. conducted a systematic review examining the effect of aerobic exercise interventions on serum biomarkers of neuroplasticity in human stroke survivors (150). The authors included nine studies, and found that aerobic interventions can increase brain-derived neurotrophic factors, insulin-like growth factor 1, and VEGF. However, further investigation is needed to discern how these serum biomarkers of neuroplasticity are associated with collateral circulation, the optimal exercise type and dose, most appropriate timing to commence physical activity interventions after stroke (i.e., how early), and the effect on functional recovery across different phases (i.e., acute, subacute and chronic) post-stroke in humans (148, 150).

The association between cerebral collateral circulation and cardiorespiratory fitness has also not been examined. While physical activity is closely associated with cardiorespiratory fitness (151), cardiorespiratory fitness is a direct physiological measurement associated with endothelial function, and potentially provides more accurate prediction cardiovascular disease risk compared with physical activity alone (152). However, assessment of cardiorespiratory fitness is relatively more burdensome for patients and requires specialized equipment and trained personal to conduct (153). While cardiorespiratory fitness is related to cerebrovascular function (56), further investigation is needed to explore the association between cardiorespiratory fitness and cerebral collateral circulation.

CONCLUSION

Cerebral collateral circulation has physiological and clinical prognostic value and may be an important therapeutic target for acute ischemic stroke survivors. While the effect of physical activity on cerebrovascular function has been investigated, the association between physical activity and cerebral collateral circulation is unknown. Future studies can take advantage of routinely acquired medical imaging in primary stroke centers to assess collateral circulation status, its association with physical activity, and potential utility as a biomarker to identify patients who would benefit from physical activity and stroke recovery interventions.

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

SH led the manuscript and designed, conceptualized, and drafted the manuscript. SK, EW, BC, and AB played major roles in designing, conceptualizing, and revising the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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STUDY PROTOCOL
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Effects of Repetitive Peripheral Sensory Stimulation in the Subacute and Chronic Phases After Stroke: Study Protocol for a Pilot Randomized Trial

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Background: Repetitive peripheral nerve sensory stimulation (RPSS) is a potential add-on intervention to motor training for rehabilitation of upper limb paresis after stroke. Benefits of RPSS were reported in subjects in the chronic phase after stroke, but there is limited information about the effects of this intervention within the 1st weeks or months. The primary goal of this study is to compare, in a head-to-head proof-of-principle study, the impact of a single session of suprasensory vs. subsensory RPSS on the upper limb motor performance and learning in subjects at different phases after stroke subacute and chronic phases and mild upper limb motor impairments after stroke. In addition, we examine the effects of RPSS on brain perfusion, functional imaging activation, and γ-aminobutyric acid (GABA) levels. Subjects with mild upper limb motor impairments will be tested with MRI and clinical assessment either at an early (7 days to 3 months post-stroke) or at a chronic (>6 months) stage after stroke.

Methods: In this multicenter, randomized, parallel-group, proof-of-principle clinical trial with blinded assessment of outcomes, we compare the effects of one session of suprasensory or subsensory RPSS in patients with ischemic or hemorrhagic stroke and upper limb paresis. Clinical assessment and MRI will be performed only once in each subject (either at an early or at a chronic stage). The primary outcome is the change in performance in the Jebsen–Taylor test. Secondary outcomes: hand strength, cerebral blood flow assessed with arterial spin labeling, changes in the blood oxygenation level-dependent (BOLD) effect in ipsilesional and contralesional primary motor cortex (M1) on the left and the right hemispheres assessed with functional MRI (fMRI) during a finger-tapping task performed with the paretic hand, and changes in GABA levels in ipsilesional and contralesional M1 evaluated with spectroscopy. The changes in outcomes will be compared in four groups: suprasensory, early; subsensory, early; suprasensory, chronic; and subsensory, chronic.

Discussion: The results of this study are relevant to inform future clinical trials to tailor RPSS to patients more likely to benefit from this intervention.

Trial Registration: NCT03956407.

Keywords: sensory stimulation, stroke, rehabilitation, upper limb, nerve stimulation

INTRODUCTION

Upper limb paresis is very common after stroke, a leading cause of disability worldwide (1, 2). Interventions based on intensive, repetitive tasks training can improve motor performance (3). Over the past two decades, neuromodulation interventions, such as repetitive transcranial magnetic stimulation (TMS) (4), transcranial direct current stimulation (5), and repetitive peripheral sensory stimulation (RPSS) (6), have been investigated as potential add-on therapies to boost the effects of training in subjects with stroke.

Repetitive peripheral sensory stimulation, in particular, is a straightforward intervention designed to enhance somatosensory input. In RPSS, trains of electric pulses are delivered to peripheral nerves by surface electrodes with parameters of stimulation aimed to predominantly activate proprioceptive and large cutaneous sensory fibers (6). The intensity of stimulation is set to elicit paresthesia but minimal or absent motor responses. RPSS targets a brain sensorimotor network known to be physiologically relevant for motor performance and learning (7). Sensory information is relayed from peripheral nerves to the spinal cord, then, *via* the dorsal medial lemniscus in the brainstem, reaches the thalamus and finally, the sensorimotor cortex. Increased excitability, activity, or use-dependent plasticity of the motor cortex have been reported in healthy subjects (8–10) or subjects with stroke (11–13) after 2 h of RPSS. The connections between neurons that represent the motor area of the stimulated body segment may be strengthened, leading to enhancement of motor performance or learning (9, 14–16). Disinhibition of silent synapses by alterations in glutamatergic receptors or reduction of GABAergic inhibition, as well-activation of silent synapses and modulation of neuronal interactions (17) may mediate these effects. The presence of functional and structural connections between areas that are responsible for motor control (16) and its relationship with somatosensory afferents underlies the rationale for the use of RPSS in individuals with motor impairment, such as stroke (18).

In subjects in the chronic phase after stroke, the effect size of RPSS to improve upper limb motor function is similar to or greater than the effect sizes of other neuromodulation interventions (6). On the other hand, information about the effects of RPSS in the subacute phase after stroke is limited. While all studies in chronic subjects with mild-to-moderate upper limb motor impairments showed benefits of this intervention, only two addressed effects in the subacute stage: one reported an increase in thumb strength after one session of RPSS compared to stimulation to the level of perception (19), whereas another described more significant improvement after *subsensory* RPSS compared to *suprasensory* RPSS (20). In patients in the chronic phase after stroke, suprasensory stimulation led to greater improvements than subsensory stimulation, and the latter was used as a control intervention in patients in the chronic phase after stroke (21, 22). Therefore, the finding of greater effects of subsensory stimulation, compared to suprasensory stimulation in patients in the subacute phase (20), was surprising and raised the hypothesis that optimal intensities/doses of stimulation may be different early, compared to at a later stage after stroke. Until now, patients in the subacute and chronic stages have not been included in a single study, in order to perform head-to-head comparisons between the effects of subsensory and suprasensory stimulation at these two phases after stroke.

Neuronal excitability, activity, or connectivity undergo changes over time after stroke. For instance, motor and sensory representations near the lesion may be remapped after cortical infarcts (23). Connectivity between primary sensorimotor and secondary motor areas changes over several weeks (24). Intracortical inhibition assessed with TMS may decrease in the contralateral motor cortex early after a cerebellar stroke and increase in the chronic phase, more than 6 months later (25).

Since excitability changes over time after lesion onset, and effects of neuromodulation interventions are known to be state-dependent (19), it is expected that results of these interventions vary at different stages after stroke. It is possible that, early after lesion onset, the variability in activity or excitability during the dynamic process of spontaneous recovery contributes to a less consistent effect of neuromodulation interventions. A systematic review and meta-analysis indicated that the potential benefits of transcranial direct current stimulation might be greater in patients in the chronic than in the subacute stage after stroke (26, 27). Furthermore, constraint-induced movement therapy (CIMT), a rehabilitation intervention that increases afferent input and provides training to decrease learned non-use of the upper limb, seems to be more beneficial in the chronic than in the subacute phase after stroke considering that the EXCITE trial (28) showed significant benefits of CIMT in patients treated between 3 and 9 months post-stroke, whereas the VECTORS (29) study showed no differences in effects of this intervention, compared to usual care, on average within the first 10 days after stroke.

Data from TMS studies suggest that RPSS enhances cortical excitability in animals (30), healthy subjects (31, 32), and patients in the chronic phase after stroke affecting the corticospinal tract (24). RPSS, compared to no stimulation (sham), leads to an increase in signal intensity and in the number of voxels activated in the primary motor cortex (M1) during thumb movements, in a paradigm of functional MRI (fMRI) based on the blood oxygen level-dependent (BOLD) effect. Perfusion in M1 assessed with arterial spin labeling at rest in healthy subjects increases

after RPSS (7). This finding may be explained by increased blood flow driven by enhanced neuronal activity in M1. Whether RPSS can increase BOLD activation or global/regional cerebral blood flow (CBF) in subjects with stroke at different stages remains to be determined.

Likewise, the effects of RPSS on synaptic activity or concentration of neurotransmitters are unknown. γ-Aminobutyric acid in the sensorimotor cortex has been implicated in the processing of afferent input. For instance, in healthy subjects, GABA concentrations evaluated with magnetic resonance spectroscopy predict changes in perceptual outcome after afferent, tactile stimulation of fingertips (33). In rats, GABAergic inhibition modulates responsiveness to afferent stimulation of the forepaw (34). The GABA concentration or activity in M1 may influence responsiveness to RPSS. Furthermore, RPSS may also increase or decrease GABA levels in the cortex. Until now, these hypotheses have not yet been tested.

The primary goal of this study is to compare the effects of a single session of RPSS on motor performance and motor learning in subjects with stroke in the subacute (EARLYgroup) and chronic (CHRONICgroup) phases with mild upper limb motor impairments. We hypothesize that enhancement of motor performance and motor learning by RPSS will be significantly greater in subjects in the CHRONICgroup than in subjects in the EARLYgroup, when exposed to the same experimental paradigm. In addition, we compare the effects of a single session of RPSS on cerebral perfusion, changes in the BOLD effect, and on GABA levels changes in ipsilesional and contralesional M1. Our hypothesis is that changes in these outcomes will be significantly greater after RPSS in subjects in the chronic, than in the early stage.

METHODS AND ANALYSIS

Study Design

This is a multicenter, randomized, parallel-group, proof-of-principle clinical trial with blinded assessment of outcomes. **Figure 1** summarizes the study protocol.

Location and Setting

This ongoing study is conducted in three hospitals in Brazil: Hospital Israelita Albert Einstein (HIAE, coordinating center), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) both in São Paulo, and Hospital São Rafael (HSR) in Salvador. Initially, the study would involve two centers (HIAE and HSR). HCFMUSP was included as an additional center due to difficulties in patient recruitment. The coordinating center (HIAE) was responsible for the design of the protocol, submission of the project to the HIAE Ethics Committee and to the funding agency (Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP), creation of the research forms, and management of the project. It is also responsible for the submission of amendments, for providing and assessing the training of researchers involved in the protocol, and for communication with all centers. Weekly meetings were performed between researchers from the three centers.

The first patient was included in December 2019. The study was interrupted in March 2020 due to the COVID-19 pandemic. Recruitment was restarted in São Paulo in May 2021 and in Salvador in July 2021.

The protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) statement (**Supplementary Materials**).

Participants

The inclusion and exclusion criteria are shown in **Table 1**. Subjects able to perform at least four of the tasks of the Jebsen–Taylor test (JTT) are included. The JTT scores the time (in seconds) required to perform activities often used in daily living: copying a sentence; turning over cards; picking up small common objects such as coins, bottle-cap, and paper clips; simulated feeding using a spoon; stacking checkers; and moving large light and heavy objects (32, 35).

Recruitment

Subjects are recruited in the community through advertisements on websites or social media, and from admissions to HSR, HIAE, and HCFMUSP. In the three hospitals, preliminary eligibility is assessed according to information from medical records. Information about the protocol is also sent to physicians or therapists from these three institutions and from other hospitals or clinics, to be disseminated to patients who may be interested in participating in the study.

Subjects' Characteristics

The following characteristics are evaluated at baseline in the first experimental session (**Figure 1**): age, gender, ethnicity, years of education, time from stroke, type of stroke (ischemic/hemorrhagic), medications, lesion side/location, etiology of ischemic strokes according to the Causative Classification System (36) and scores in the following scales: the Modified Rankin Scale, National Institutes of Health Stroke Scale (NIHSS) (37), Modified Ashworth Scale (MAS—elbow, wrist, and finger joints) (38), Oldfield Inventory (prior to stroke) (39), Fugl-Meyer Assessment of Sensorimotor recovery (upper limb—FMA) (40), Mini-Mental State Examination (37), Patient Health Questionnaire-9 (PHQ-9) (41), and Edinburgh Handedness Inventory (39). Assessments are performed by researchers (therapists or medical students). Prior to the onset of patient recruitment, all researchers had to be certified in performance of the NIHSS (https://www.nihstrokescale.org/). After availability of a certification of the Portuguese version of the MRS (https://docs.google.com/forms/d/e/1FAIpQLSfJIzi6G9SH8VaPxqe7txcK55ApfFRVvReWV37FRaARG6PbYQ/viewform), all researchers involved in the MRS assessment were certified. A video with demonstrations of how to administer and rate each item of the FMA was produced, watched, and discussed in meetings with all researchers, prior to realistic simulations in which the researchers played roles of assessors and "patients." Data collection only started in each center after the local principal investigator considered that characteristics of the patients and outcomes had been consistently evaluated in the realistic simulations. After the beginning of the COVID-19

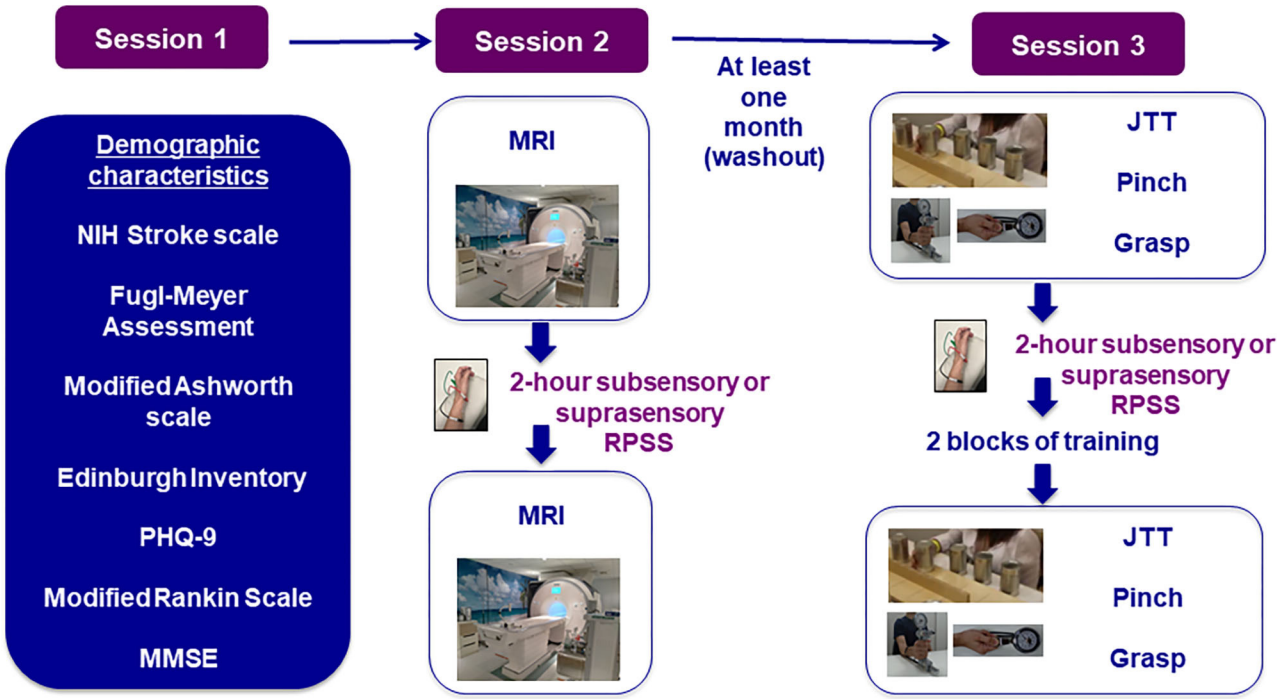

FIGURE 1 | Experimental paradigm. NIH, national institutes of health; PHQ-9, patient health questionnaire-9; MMSE, mini-mental state exam; MRI, magnetic resonance imaging; RPSS, repetitive peripheral nerve sensory stimulation; JTT, jebsen–taylor test.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Ischemic or hemorrhagic stroke confirmed by computed tomography or magnetic resonance imaging, between 7 days and 3 months before enrollment (subacute phase), and at least 6 months (chronic phase) • Ability to perform at least 4 of 7 tasks performed in daily life that is part of the Jebsen–Taylor test; • Upper limb paresis contralateral to the lesion	• Inability to provide consent • Anesthesia of the paretic hand • Severe spasticity at the paretic elbow, fist or fingers, defined with a score larger than 3 on the Modified Ashworth Scale • Shoulder pain or join deformity in the paretic limb • Lesions affecting cerebellum, or cerebellar pathways in the brainstem • Uncontrolled psychiatric disease • Neurological diseases such as Parkinson disease or chronic uncontrolled chronic disease such as cancer or cardiac insufficiency • Aphasia or severe cognitive deficit

pandemic, data were not collected for several months. All researchers involved in the assessment of characteristics of patients or outcomes were trained again before data collection was restarted.

An experienced radiologist defines lesion locations by the evaluation of MRI (FLAIR, T2, and T1-weighted images—see "Imaging protocol") as: right/left; frontal/temporal/occipital/parietal/insular; corticosubcortical, cortical, or subcortical; involving or not the precentral gyrus, postcentral gyrus, centrum semiovale, corpus callosum, posterior limb of the internal capsule, thalamus, basal ganglia, mesencephalon, pons, or medulla.

At HIAE, the presence of motor-evoked potentials (MEPs) to TMS is assessed by the principal investigator, who has been trained and performed the procedure for the past 20 years, in the absence of contraindications (42). A safety screening questionnaire is filled before the procedure (43). TMS is delivered to the affected hemisphere through a figure-of-eight-shaped coil (MC B-70, outer diameter 100 mm, max dB/dt31 kT/s near the coil surface) held by an investigator, connected to a biphasic MagPro X100 (Alpine Biomed). Electromyography (EMG) activity is recorded at rest from the surface electrodes placed over the *abductor pollicis brevis* muscle in the paretic hand. EMG responses are amplified (× 1,000), filtered (2 Hz−2 kHz) and sampled at 5 kHz with a computerized data acquisition system built with the LabVIEW graphical programming language (44). The intervals between TMS pulses are randomized between 5 and 7 s. If no MEPs are registered at 100% of the stimulator's output, they are considered "absent."

Randomization, Allocation Concealment, and Blinding

Patients are randomized to one of four groups: suprasensory or subsensory in the EARLYgroup, suprasensory or subsensory in the CHRONICgroup. The randomization sequence was created by a statistician in an Excel spreadsheet in 12 blocks of 4 patients at HIAE or HCFMUSP and in 6 blocks of 4 patients

at HSR, weighted 1:1 toward the suprasensory treatment group. Randomization was stratified by phase after stroke (subacute or chronic), gender, age (18–50, 51–79, ≥80 years), side of upper limb paresis and baseline upper limb FMA scores (≤47/66 or >47/66). Randomization tables are kept in locked cabinets accessed only by the principal investigator and the researcher responsible for RPSS in each center, and password-protected files.

Researchers responsible for the evaluation of outcomes are blinded to treatment allocation. All researchers received training before the onset of data collection. Videos with instructions for administration of the JTT were produced, and realistic simulations were performed. Patients are not informed about the type of stimulation they receive (suprasensory or subsensory) and are naive to the experimental hypothesis. They are instructed not to share their perceptions about the experimental sessions with other participants and researchers.

Interventions

Suprasensory or subsensory RPSS was initially administered in the second experimental session (**Figure 1**) at HSR and at HIAE, and also in the third experimental session at HIAE. After approval of an amendment in August 2021, RPSS started to be administered in the first visit, after the assessment of the patient characteristics. This protocol corresponds to version 5 of the project and includes all the amendments approved until August 2021.

Subjects are comfortably seated during RPSS. Trains of electrical pulses (1 ms of duration for each) at a frequency of 10 Hz are delivered at 1 Hz (500 ms on and 500 ms off) to the median nerve on the wrist by one pair of surface electrodes (Kendall; cathode, proximal) connected to a customized stimulator (Alfamedic Ltda, São Paulo, Brazil; maximum output, 130 V). The median nerve is stimulated between the tendons of the flexor carpi radialis and palmaris longus with the cathode positioned 2–3 cm proximal to the wrist. Three measurements of the minimum stimulation intensity required to elicit paresthesia (sensory threshold) are performed.

For suprasensory stimulation, intensities are set at the highest intensity able to induce paresthesia without overt muscle contraction or pain and adjusted if required (21, 39, 45). In subsensory, the intensity of stimulation is below sensory threshold, not sufficient to elicit paresthesia (20).

Every 5 min, participants are asked about the sensations elicited by stimulation in order to avoid fluctuations in wakefulness and in attention to the stimulated body part (46). The intensity of stimulation is increased if paresthesia becomes weaker, and lowered if they become uncomfortable or during the 2-h period. Usually, it is necessary to adjust the intensity of stimulation due to changes in the intensity of paresthesia during the 2-h period. There may be changes in skin impedance and subjects in the RPSS group may report increase or decrease in paresthesia. The intensity of stimulation is then adjusted to elicit strong paresthesia in the absence of pain or movement. In the subsensory group, the initial intensity defined so that no sensations are elicited may lead to paresthesia during the 2-h period. When this occurs, the intensity of stimulation is lowered below the sensory threshold. During RPSS, subjects watch videos of their choice.

A single session of RPSS has been shown to improve motor performance in the absence of training (19–22, 47) and to enhance effects of training (11, 16, 18, 22). In session 3 (**Figure 1**), patients are initially familiarized with the JTT by performing each task once in two blocks of practice. Then, baseline assessments are performed. After suprasensory RPSS or subsensory for 2 h, the JTT scores and strength are reassessed. Then, the subjects undergo two blocks of training of tasks of the JTT under the supervision of a rehabilitation professional blinded to the type of stimulation received (22). During motor training, subjects are instructed to perform the JTT tasks that they can complete as fast as possible. Two blocks of training are administered. In each block, each task is performed once. JTT performance is reassessed after training.

Adverse events are monitored during and immediately after the stimulation. Studies included in a systematic review did not report any serious adverse events (6). Two studies described contact dermatitis on the skin under the electrode. If hyperemia is identified after stimulation, this will be reported as an adverse event. If it resolves spontaneously in 30 min, no further action is taken. If there is itching or persistent hyperemia, a topical corticoid cream may be used. In all three centers, the visits and experiments take place inside hospitals with medical resources. A specific insurance policy for clinical trials was taken for financial protection of the sponsor and researchers.

The visual analog scale (VAS) assessed before and after stimulation and after training, to grade sleepiness, fatigue, and anxiety (42).

Outcome Measures

Primary Outcome: Change in Motor Performance After Stimulation

The primary outcome is change in the JTT performance after stimulation, compared to baseline (**Figure 1**): (JTT pre-stimulation – JTT post-stimulation/JTT pre stimulation) × 100. The task of copying a sentence is not performed. Previous studies showed that RPSS can enhance JTT performance and motor learning in subjects in the chronic phase after stroke (20, 29).

Secondary Outcomes

Change in motor performance after training JTT is also assessed after two blocks of training (**Figure 1**). Changes in JTT after stimulation + training are calculated as: [(JTT post-stimulation + training – JTT pre-stimulation)/(JTT pre-stimulation)] × 100.

Hand Strength

Lateral pinch and grasp strength are measured with a dynamometer (Saehan grip) according to a protocol with established validity (44). In Session 3 (**Figure 1**), patients are initially familiarized by performing lateral pinch and grisp strength once, using the dynamometer. Then, for outcome assessments, five trials of pinch and handgrip are performed before and after stimulation (**Figure 1**). During each trial, the patient is instructed to perform the movement for 5 s. The average of five trials is calculated. Improvement in pinch strength

after RPSS was previously described in separate studies that included patients in the subacute (8) and chronic (39) post-stroke phases (44).

Imaging Outcomes

Before and after RPSS, GABA+ (GABA plus coedited macromolecules) levels, CBF assessed with arterial spin labeling, and task-related BOLD fMRI activation are assessed at HIAE. MRI is performed before and after suprasensory RPSS or subsensory on a 3T Magnetom PRISMA scanner (Siemens Medical Solutions, Erlangen, Germany) using a 64-channel 1H receive-only head coil, without contraindications.

A standard questionnaire is used to assess potential exclusion criteria for MRI (**Supplementary Materials**). The following sequences are acquired: MEGA-PRESS (48), BOLD fMRI (TR: 2,000 ms, TE: 25 ms, matrix 84 × 84, FOV 210 mm, number of slices: 42, slice thickness: 2.5 mm, voxel: 2.5 mm) and perfusion (3D GRASE Pseudo-Continuous Arterial Spin Labeling, pCASL; TR: 4,300 ms, TE: 36.76 ms, bandwidth: 2,604 Hz/Px, label time 1,500 ms, post-labeling delay: 2,000 ms). In addition, before RPSS a high resolution T1 volumetric (voxel size: 0.5 × 0.5 × 1 mm^3, matrix size: 256 × 256, field of view: 256 × 256 mm^2, TR: 2,500 ms, TE: 3.47 ms, TI: 1,100 ms, flip angle: 7 degrees) and after, DWI (voxel size: 2 mm, isotropic; TR:10,200 ms; TE:103 ms) and GRE (voxel size: 0.9 mm × 0.9 mm × 5 mm, matrix size: 256 × 192, field of view: 240 mm, TR: 250 ms, TE:15 ms) are acquired.

The GABA spectroscopy data are collected with MEGA-PRESS (30 × 30 × 30 mm^3 voxel, TR 2,000 ms, TE 68 ms; water suppression band set to 4.7 ppm, and an editing band alternated between 1.9 ppm and 7.5 ppm in even and odd acquisitions; 192 averages-−96 "edit off" and 96 "edit on") and a water reference scan using the MEGA-PRESS sequence without MEGA water suppression. Data are collected first from the right and then from the left cerebral hemispheres. Therefore, the ipsilesional and contralesional hemispheres are assessed. In each hemisphere, the region of interest is centered on the "hand knob" in the primary motor cortex (49). Patients are instructed to keep their eyes closed during imaging acquisition.

During fMRI scans, six blocks of finger tapping followed by rest are performed. Before being scanned, subjects practice a self-paced rhythmic finger tapping task consisting of 6 epochs of 30 s of finger tapping alternated with epochs of 30 s rest. Patients are instructed to keep their eyes open. Performance of finger tapping is not one of the inclusion criteria but because patients must be able to perform the JTT in order to be included, only patients with mild upper limb impairments participate in the study. All patients are encouraged to try to perform the task as accurately as possible. It is possible that some patients, despite mild motor impairments, are not able to accurately perform finger tapping. In order to check task performance, finger tapping during fMRI is videotaped. Two researchers review all the videos. Data from patients unable to perform finger tapping are excluded from the analysis.

Sleepiness can potentially influence task performance and GABA levels. Subjects are instructed not to drink alcohol 48 h before the tests, sleep the night before, drink the usual amount of coffee, and do not perform vigorous physical activity on the day of the test. Before MRI (**Figure 1**), the Epworth Sleepiness Scale is evaluated (50). VAS scores for sleepiness, fatigue, and anxiety (51), blood pressure, and heart rate are assessed before and after MRI.

Imaging Data Analysis

GABA Spectroscopy

Data processing for the GABA quantification is carried out using Gannet v. 3.1.5, an open-source software coded with MatLab (52). Ratios of GABA levels between the affected and unaffected hemispheres, before and after suprasensory or subsensory RPSS, will be compared (53) in the EARLY and the CHRONIC groups. The pipeline for analysis is shown in **Supplementary Materials**.

pCASL Data

Post-processing of pCASL data is performed offline using a Java-based software package called CereFlow (Translational MRI, LLC, Los Angeles, CA, USA). First, label and control paired ASL images are corrected for motion and physiological noise using principal component analysis (54). Subsequently, pairwise subtraction between label and control images is performed, averaging to generate the mean difference dataset. CBF is then calculated using the standard pCASL model recommended by ASL white paper (55). The computed CBF maps are then normalized into a canonical space of the Montreal Neurological Institute template. Once normalized, an additional template of cerebral vascular territories is applied to extract the average CBF values in the following regions: leptomeningeal and perforating anterior cerebral artery, leptomeningeal and perforating middle cerebral artery, posterior cerebral artery, anterior choroidal artery, and posterior communicating artery on both (56). Furthermore, the Alberta Stroke Program Early CT Score system is applied to extract average CBF and arterial transit time (ATT) values in M1—M6 perfusion territories, the caudate nucleus, the lentiform nucleus, and the internal capsule (57, 58).

FMRI Pre-processing

The FMRI data processing is performed using FMRI Expert Analysis Tool (FEAT) Version 6.00 in FSL[1] High-resolution registration to the MNI152 standard space image is carried out using FLIRT (59, 60). To properly register patient's brain images into standard space, we use spatial normalization using cost function masking (61), first registering functional images into patients' T1 images, and then to MNI 152 standard space using a lesion mask to down-weight affected tissue during the registration process. Lesion masks will be hand-drawn by a researcher who received extensive training in how to perform this procedure. The following pre-statistics processing is applied: motion correction using MCFLIRT (60), slice-timing correction using Fourier-space time-series phase-shifting, non-brain tissue removal using BET (62), spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high-pass temporal filtering (Gaussian-weighted least-squares

[1] FMRIB's Software Library, https://www.fmrib.ox.ac.uk/fsl

straight line fitting, with sigma = 120 s). Time-series statistical analysis is carried out using FILM with local autocorrelation correction (62).

Sample Size

Considering the SD of the data from Conforto et al. (22), it was estimated that to assess the primary outcome with a power of 80%, 68 patients should be included in the protocol. Considering an expected 5% dropout rate, the sample size was increased to 72. Half of the patients will have <6 months post-stroke and half, at least 6 months. Forty-eight patients will be included at HIAE or HCFMUSP and 24 at HSR.

Data Monitoring

The assessments of behavioral outcomes are videotaped. Since May 2021, all the data have been entered in electronic case report forms built in the REDCap platform (redcap.einstein.br). The data registered in paper forms before the onset of the COVID-19 pandemic were also entered in the platform. The forms detail all the procedures and definitions used in the protocol. The principal investigator oversees the conduct of the study, has meetings with the researchers at least once a week, and reviews the data at least once a month. All data are stored in secure servers in the research centers, with password and computer access restricted to researchers involved in the project.

Quality of imaging data is checked after each MRI by the author BH. Quality of ASL data is also checked by the author DJJW before analysis.

All the procedures in the protocol must follow Good Clinical Practice guidelines. Every 6 months, an independent Research Integrity Committee audits all the documents from the protocol, including consent forms, case report forms, standard operating procedures, and reports submitted to the Ethics Committee.

The local principal investigators from the three centers are given access to the data sets available on the password-protected REDCap platform. To ensure confidentiality, data shared with all the project team members are blinded from any identifying participant information.

Statistical Analysis

Mean (±SD) or median (ranges) is presented according to the data distribution. Normality is tested with the Shapiro–Wilk test. Changes in JTT scores, strength, GABA levels, and CBF are compared between the four groups with general linear models or generalized estimating equation models with factors INTERVENTION (suprasensory/subsensory) and GROUP (subacute/chronic) according to the distribution of the data. The *p*-values below 0.05 are considered statistically significant.

For perfusion analyses, ratios between CBF in the affected/unaffected hemisphere and ratios between CBF in each region of interest in the affected/unaffected hemisphere are assessed. Due to the exploratory nature of these analyses, corrections for multiple comparisons are not performed.

For fMRI, a statistical analysis is implemented using a general linear model approach. Activity in ipsilesional and contralesional M1 during finger tapping is modeled by 30 s boxcar convolved with a double gamma function regressor. We also include a regressor with the first temporal derivative of the main regressor and nuisance regressors derived from the extended motion parameters. Two first-level analyses per participant are run, one pre-stimulation and one post-stimulation. Second level of analysis is carried to estimate the within-subject contrast between pre- and post-stimulation using a fixed-effects model, by forcing the random effects to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (63–65). At the third level of analysis, we estimate contrasts for each group of participants using one-sample *t*-tests to verify if there were effects of stimulation and independent *t*-tests to see changes between groups using a mixed effects model in FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (63–65). Z (Gaussianized T/F) statistic images are thresholded using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $p = 0.05$ (66). If there is a significant difference in change in motor performance (JTT or strength) between suprasensory and subsensory groups in either the chronic or subacute stage after stroke, bivariate analyses are performed (regressions or chi-square tests) to assess the relationship between each of these variables at baseline, and the magnitude of the improvement in behavior: baseline JTT or strength, age, sex, the intensity of RPSS (relative to sensory threshold), extent of BOLD activation (number of voxels and signal intensity) in M1, CBF (global and regional), or GABA concentration in M1 at baseline. Multiple regression is performed to assess the effects of variables if *p*-values are below 0.1 in bivariate analyses 0.05 (66).

DISCUSSION

Effective telerehabilitation options are deeply needed due to the constraints that the COVID-19 pandemic have imposed on face-to-face treatment. RPSS is a strong candidate as an add-on therapy to the upper limb motor training in this context because it provides neuromodulation utilizing a portable device. Operation of the device is straightforward. If future clinical trials can confirm the benefits of this intervention to subjects with stroke, and if RPSS can be safely administered by patients, relatives, or caregivers, in line with the results from Dos Santos-Fontes et al. (67), a novel tool for home-based neurorehabilitation may emerge for clinical practice. The results of this proof-of-principle study in which a single session of stimulation is delivered are relevant to plan clinical trials in which several sessions of stimulation are administered, as performed in other studies that assessed effects of RPSS in outpatient facilities (20, 68–71).

The first studies about interventions' effects on motor rehabilitation in stroke were published more than two decades ago. Yet, the evidence of clinical benefit for these interventions is scarce, and doubts have been shed about their future as therapeutic strategies (72). Major reasons for the gap between studies performed in neuromodulation laboratories and evidence-based rehabilitation practice are insufficient comprehension of mechanisms underlying different interventions, and the inclusion of patients with heterogeneous characteristics in proof-of-principle studies and clinical

trials. Stroke is a heterogeneous condition and a "one-size-fits-all" approach is unlikely to significantly impact motor rehabilitation (73–75).

Examples of success of therapeutic approaches that target particular types of patients can be found in studies that led to novel reperfusion treatments in the hyperacute phase after stroke. For instance, after several trials that failed to prove benefit of mechanical thrombectomy (76), studies that included novel devices and narrowed eligibility criteria according to specific neurobiological hypotheses according to clinical and imaging characteristics showed that, for patients more likely to benefit, mechanical thrombectomy is a game-changing strategy (77).

This study aims to compare the effects of a single session of RPSS on learning and motor performance of patients after stroke in two different stages—chronic and subacute. The results of this study will be critical to help close one of the gaps about effects of RPSS on the performance and motor learning in subjects with stroke. They will be relevant to inform future clinical trials based on mechanisms to tailor RPSS to patients more likely to benefit from this intervention. This goal is achieved by comparing behavioral effects according to time after stroke (primary outcome) and by providing preliminary evidence of mechanisms underlying these effects (secondary outcomes). If there is a relation between time after stroke, GABA levels, BOLD activation or CBF measured with ASL, and responsiveness to RPSS as an add-on treatment to motor training, these factors should be considered to select patients for clinical trials.

One limitation of this study is that only patients with mild-to-moderate upper limb impairments are included. This strategy was adopted because this is a proof-of-principle study and eligibility criteria were narrowed to test a specific hypothesis. More work will be necessary to test whether the effects of RPSS differ according to the time after stroke, in patients with moderate-to-severe upper limb motor impairments.

Another potential limitation of this study is the choice of the control stimulation. There is no consensus about the best control or sham condition for RPSS. According to a standard definition, "sham is an arm type in which a group of participants receives a procedure or device that appears to be the same as the actual procedure or device being studied but does not contain active processes or components"[2] We opted for subsensory stimulation—the stimulator is on, but subjects do not have paresthesia. Other possible controls are no stimulation (with or without placement of electrodes on the skin) or leg stimulation (11, 12, 14). A disadvantage of no stimulation is that subjects may conclude that they are not receiving active treatment, to the lack of paresthesia at any point during the experiment. A limitation of subsensory stimulation is that, in the 1st weeks after stroke (44), this intervention may have similar effects to stimulation above sensory threshold in the chronic phase. A caveat of stimulation of lower limb nerves is that subjects may deduct that this consists of a control/sham intervention if the upper limb performance is tested, or if the upper limb training is provided as part of the experimental protocol. Further studies are necessary to compare patients' perceptions about different types of controls for RPSS.

In summary, the results of the protocol "Comparison between the mechanisms underlying the effects of peripheral repetitive stimulation on upper limb motor performance in the subacute and chronic phases after stroke" will be relevant to inform future clinical trials in order to tailor RPSS to patients more likely to benefit from this intervention, in early or chronic stages. In addition, this study will provide preliminary data about mechanisms underlying effects of this intervention on GABA levels in the primary motor cortex, BOLD activation, and CBF perfusion in different stages after stroke.

[2]Glossary of Common Site Terms, https://clinicaltrials.gov/ct2/about-studies/glossary.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa, Hospital Israelita Albert Einstein. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC, BH, EA, GS, and IS contributed to conception and design of the study. AC wrote the first draft of the manuscript. DW, FZ, GR, JK, MO, and RA wrote sections of the manuscript. All authors contributed to manuscript revision, read, 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.2022.779128/full#supplementary-material

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Clinical Imaging-Derived Metrics of Corticospinal Tract Structural Integrity Are Associated With Post-stroke Motor Outcomes: A Retrospective Study

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Objective: The primary objective of this study was to retrospectively investigate associations between clinical magnetic resonance imaging-based (MRI) metrics of corticospinal tract (CST) status and paretic upper extremity (PUE) motor recovery in patients that completed acute inpatient rehabilitation (AR) post-stroke.

Methods: We conducted a longitudinal chart review of patients post-stroke who received care in the Emory University Hospital system during acute hospitalization, AR, and outpatient therapy. We extracted demographic information, stroke characteristics, and longitudinal documentation of post-stroke motor function from institutional electronic medical records. Serial assessments of paretic shoulder abduction and finger extension were estimated (E-SAFE) and an estimated Action Research Arm Test (E-ARAT) score was used to quantify 3-month PUE motor function outcome. Clinically-diagnostic MRI were used to create lesion masks that were spatially normalized and overlaid onto a white matter tract atlas delineating CST contributions emanating from six cortical seed regions to obtain the percentage of CST lesion overlap. Metric associations were investigated with correlation and cluster analyses, Kruskal-Wallis tests, classification and regression tree analysis.

Results: Thirty-four patients met study eligibility criteria. All CST overlap percentages were correlated with E-ARAT however, ventral premotor tract (PMv) overlap was the only tract that remained significantly correlated after multiple comparisons adjustment. Lesion overlap percentage in CST contributions from all seed regions was significantly different between outcome categories. Using MRI metrics alone, dorsal premotor (PMd) and PMv tracts classified recovery outcome category with 79.4% accuracy. When clinical and MRI metrics were combined, AR E-SAFE, patient age, and overall CST lesion overlap classified patients with 88.2% accuracy.

Conclusions: Study findings revealed clinical MRI-derived CST lesion overlap was associated with PUE motor outcome post-stroke and that cortical projections within the CST, particularly those emanating from non-M1 cortical areas, prominently ventral premotor (PMv) and dorsal premotor (PMd) cortices, distinguished between PUE outcome groups. Exploratory predictive models using clinical MRI metrics, either alone or in combination with clinical measures, were able to accurately identify recovery outcome category for the study cohort during both the acute and early subacute phases of post-stroke recovery. Prospective studies are recommended to determine the predictive utility of including clinical imaging-based biomarkers of white matter tract structural integrity in predictive models of post-stroke recovery.

Keywords: stroke, clinical MRI, motor recovery, outcome prediction, premotor and motor cortex, corticospinal tract (CST)

INTRODUCTION

Stroke is a leading cause of long-term adult disability in the United States (US) (1). Early, accurate prediction of recovery of motor function post-stroke would enable precision-based rehabilitation strategies to improve outcomes and reduce disability (2, 3). However, current clinical practice lacks validated objective tools necessary to accurately predict motor recovery and deliver optimally-targeted interventions (1, 2, 4, 5).

The majority of motor recovery occurs early after stroke, typically plateauing around 3-months post-injury, and is thought to be primarily regulated by molecular mechanisms underlying structural and functional reorganization of the motor system within both lesioned and non-lesioned hemispheres (6–9). The corticospinal tract (CST) is the canonical descending motor output pathway responsible for generating voluntary movements and is particularly important for fine motor control of dexterous distal movements in both animals and humans (6, 9, 10). Approximately 40% of the CST originates directly from the primary motor cortex (M1), while an additional ∼30% of the CST is comprised of tracts originating from non-M1 motor areas such as premotor cortex (PM), supplementary motor cortex (SMA), and cingulate motor areas (11–14). Pyramidal cells within M1 generate signals for execution of movements in context (15). PM and cingulate regions are known to be involved in control of both the cognitive aspects of motor planning (including spatial attention) and the execution of movement itself, while the SMA is thought to contribute to temporal specificity of muscle activation, particularly during reaching movements (11, 16–20). The CST also encompasses projections from the primary somatosensory cortex (S1) to the SC suppling sensory information that informs movement output, enabling precision and refinement of motor control (21). Stroke-induced disruption of the CST often results in functional impairment of the hand and upper limb and is known to particularly affect the recovery of fine motor control (7, 22, 23). Prior studies have shown associations between paretic upper extremity (PUE) motor recovery and disruptions of M1 contributions to the CST post-stroke (22–25). More recently, other studies have evaluated differential contributors to CST structural integrity with inconclusive results (16, 25–29). Thus, less is currently known about the relevance of non-M1 projections within the CST to specific elements of PUE motor recovery.

Models to predict PUE motor recovery outcome have been developed and implemented in other healthcare systems (30–35). The Predict Recovery Potential (PREP2) prediction tool, developed and internally validated in New Zealand, predicts PUE motor outcomes using a combination of clinical assessments and objective neurological biomarkers (30). PREP2 employs transcranial magnetic stimulation (TMS) of M1 to measure CST functional integrity and the National Institutes of Health Stroke Scale (NIHSS) score to differentiate functional prognosis in the subset of individuals with initially low PUE strength (30, 36). TMS assessment is not currently standard-of-care in US hospitals however, clinical neuroimaging is routinely used to diagnose stroke in the US and can be used to quantify structural integrity of the CST.

Using magnetic resonance imaging (MRI), the structural integrity of the descending sensorimotor system can be quantified by measuring both the location and extent of stroke lesion overlap with the CST and has been used to identify how damage to anatomic structures relates to post-stroke motor outcomes (25–27, 32, 37–39). Several studies have shown that poorer motor outcomes are correlated with a greater extent of lesion encroachment within the CST (22–25, 39). Interestingly, structural MRI may outperform the use of clinical bedside measures of PUE strength or functional impairment (3, 23, 32, 40), but most of these studies employed research-grade MRI with higher resolution compared to standard-of-care clinical MRI (27). In the absence of both TMS and research-grade MRI, routine acute clinical MRI may offer alternative estimates of lesion overlap and anatomical integrity that are already available. In fact, studies using clinical MRI have emerged providing high quality evidence for imaging-derived prediction of motor return post-stroke, but have yet to combine those standard-of-care, diagnostic MRI metrics with clinical measures to predict functional outcome (3, 22, 26, 27, 41).

Previously, we observed that estimated shoulder abduction and finger extension (E-SAFE) PUE strength from assessments

at admission to acute inpatient rehabilitation (AR) could distinguish PUE motor recovery outcomes with 70% accuracy but that clinical metrics alone were unable to distinguish between *Limited* and *Poor* recovery outcome groups (42). Further, most previous work has not evaluated MRI prognostic utility for hemorrhagic stroke (22, 27, 41). Accordingly, there is a need to investigate possible markers of CST integrity that differentiate outcomes for both ischemic and intracerebral hemorrhagic strokes and is of particular importance for those patients with initially-lower levels of volitional control who exhibit the most difficult to predict recovery patterns (27, 30, 43, 44).

The primary objective of this study was to retrospectively investigate associations between clinical MRI-based metrics of CST status and PUE motor recovery in patients that completed AR post-stroke. We predicted that clinical MRI-based measures of lesion disruption to M1 and non-M1 contributions to the CST would be associated with PUE function outcome at ∼90 days post-stroke. Our exploratory prediction was that metrics of lesion-based CST disruption would improve the predictive accuracy of PUE motor recovery outcome over use of clinical metrics alone, particularly for those with initially lower levels of PUE strength.

MATERIALS AND METHODS

Study Population and Selection Criteria

We conducted a longitudinal retrospective chart review of all patients admitted with a primary diagnosis of stroke to Emory University Hospital (EUH), a representative, urban, academic, comprehensive stroke care center in the US, between September 1, 2016 and August 31, 2018. Using previously established inclusion and exclusion criteria, we identified eligible patients (30). Major inclusion criteria included the following: first ever or recurrent, ischemic or intracerebral hemorrhagic stroke; new upper extremity weakness beginning at or after current stroke onset; over the age of 18 years (30). In addition, individuals were required to have remained within the EUH system for acute hospitalization, acute inpatient rehabilitation at Emory Rehabilitation Hospital, and Emory outpatient therapy through at least 90 days post-stroke to permit longitudinal assessment of PUE recovery outcomes and reduce the heterogeneity of post-stroke care for the study cohort across the continuum of recovery. Lastly, patients were required to have received clinically-diagnostic MRI during their acute stroke workup at EUH. This study received Emory University Institutional Review Board approval and patient consent was waived.

Data Extraction and Analysis

Clinical Variables

As previously described, clinical metrics including demographic information, stroke characteristics, care continuum metrics, and provider documentation of post-stoke motor function were extracted from Cerner Powerchart, the institutional electronic medical record system of the Emory Healthcare system (42).

Provider documentation of PUE strength and post-stroke disability included manual muscle test scores, sensation, coordination, language impairments, and measures of mobility. These metrics were recorded serially by different providers within the care continuum including physicians, physical therapists, occupational therapists, and speech language pathologists [data extraction methodology detailed in (42)]. Shoulder abduction (SA) and finger extension (FE) manual muscle tests were used to calculate a SAFE score (/10) for each patient (30, 32, 45). If an objective SAFE score was not available in clinical documentation, an E-SAFE score was calculated using available assessments of PUE strength with preference given to strength of muscles with similar spinal cord segmental innervation (46, 47). If the E-SAFE score was documented more than once during acute hospitalization, the assessment performed closest to inpatient day-3 was used; in the AR setting, the E-SAFE score performed closest to admission was used, in accordance with previous work (30, 32, 38, 42).

The Action Research Arm Test (ARAT) was used as the primary dependent variable to quantify PUE functional outcome for each patient. The ARAT is a validated, sensitive, and reliable test, commonly used in stroke-related research to measure level of upper extremity function (48). Due to the retrospective nature of the study design, ARAT scores were estimated from therapy documentation at ∼90 days post-stroke in accordance with the grading criteria for each test. Estimated ARAT (E-ARAT) scoring was conducted by two licensed, clinical neurologic therapists who were otherwise blinded to study findings. Rehabilitation provider notes were evaluated in detail to extract the following measures for each patient: clinical assessments of PUE muscle and grip strength, coordination, active and passive range of motion, observational movement analysis, therapeutic activity, exercises performed, rehabilitation goals, Nine-Hole Peg Test and Box and Block Test scores as compared to matched, normative values (49–52). Each clinician independently reviewed the electronic medical record and determined maximal and minimal scores for each ARAT test item, creating a score range for every patient. E-ARAT for every patient was calculated by taking the median score from both clinicians and averaging the two values.

Previously reported three-cluster cluster analysis produced distinct outcome groups with centers at least 12 points apart (the minimal clinically important difference) on the E-ARAT and were defined as *Good*, *Limited*, and *Poor* PUE outcome groups, corresponding to diminishing levels of PUE function (42).

Image Processing and Lesion Mapping

Standard-of-care clinical MRI were obtained from the Department of Radiology at EUH. Stroke topography was determined using diagnostic, clinically-obtained T2-weighted images. Diffusion weighted images were utilized for ischemic strokes and gradient echo images were used for hemorrhagic strokes in order to maximize visual contrast and improve the specificity of lesion identification. Scans performed closest to the date of admission were used when multiple MRI sequences were acquired during the acute inpatient stay. Lesion masks were created in ITK-SNAP version 3.8.0 (53) by a member of the research staff who was otherwise blinded to participant outcomes. Lesions were traced in a slice-by-slice manner in the axial plane using a semi-automated segmentation process. In this

process, a scalar "speed" image was created to delineate between structures of interest (53, 54). Active contour segmentation was then guided by both the speed image and manually-placed initialization seeds (54). Traces were manually adjusted as necessary in the sagittal and coronal planes to ensure accuracy of the three-dimensional segmentation. Once drawn, lesion mask location and extent were independently verified visually and with neuroradiology documentation. A board-certified vascular neurologist (S.B.) provided additional consultation to ensure accuracy of lesion masks. Lesion volume was automatically calculated by ITK-SNAP software (53).

T1-weighted images (anatomical scans), T2-weighted images (pathological scans), and lesion masks (lesion map) were used as inputs for spatial normalization into standard Montreal Neurological Institute (MNI) space using Statistical Parametric Mapping software (SPM12) (55, 56). SPM's combined normalization-segmentation process was employed via the associated clinical toolbox using the 2 mm T1-weighted MNI152 template, a standard template bounding box [−90 −126 −72; 90 90 108], and 2 mm^3 voxel size (55–57). Validation of normalization in standard stereotaxic space was then visually confirmed to ensure proper alignment of cortical boundaries, subcortical anatomical landmarks, and drawn lesions.

CST Lesion Overlap Calculation

The spatially normalized lesion mask for each participant was processed through custom MNI ROI overlap software to obtain CST lesion overlap using the sensorimotor area tract template (SMATT) atlas (58, 59). The SMATT atlas delineates contributions to the CST emanating from six cortical seed regions: M1; ventral and dorsal premotor areas (PMv and PMd); supplementary and pre-supplementary motor areas (SMA and preSMA); and primary somatosensory cortex (S1) (58). SMATT was created using a slice-by-slice thresholding technique in both right and left hemispheres to minimize tract overlap while conserving tract volume (58). Data analysis output included voxel sizes for each tract, the number of voxels disrupted by the lesion, and percent tract lesion overlap. The lesion load output was individuated by seed region (M1, PMv, PMd, SMA, preSMA, and S1), therefore a whole CST lesion overlap percentage (CST overlap) was calculated by summing the number of voxels in each tract, the number of voxels overlapped by the region and dividing the two metrics. This calculation was conducted using tract voxel numbers for the affected hemisphere, as there are slight differences in CST size between right and left hemispheres (58). A non-M1 CST lesion overlap percentage was calculated using similar methodology, but omitting overlap data from the M1 CST only. CST lesion overlap percentage was also calculated using the Johns Hopkins University white matter tractography atlas (JHU) (60). The JHU atlas has been employed more often in tractography studies, so it was used to comparatively assess SMATT atlas utility (27, 60).

Statistical Methodology

Descriptive analysis was performed to summarize the distribution of variables of interest for the entire cohort. Non-parametric correlation analyses (Spearman's rho, r_S) were performed to evaluate the relationship between CST lesion overlap metrics, lesion volume, and level of paretic upper extremity motor function at 3-months post-stroke (E-ARAT scores). Parametric correlation analyses (Pearson's correlation coefficient, r) were performed to evaluate the relationship between continuous MRI variables. Independent-samples means comparisons were then conducted using Kruskal-Wallis tests to identify differences in MRI metrics between outcome groups and to evaluate the effects of stroke type on PUE motor function outcome. To explore which MRI-derived factor(s) may predict outcome cluster group, a classification and regression tree (CART) analysis was conducted. Gini was used to maximize homogeneity of child nodes with respect to the value of the target variable. Clinical and MRI metrics including all tract overlap percentages from both SMATT and JHU atlases, lesion volume, stroke characteristics, patient age, patient comorbidities, E-SAFE scores, sensation, coordination, language impairments, and measures of mobility were available as inputs using a maximum tree depth of 2, a minimum terminal node size of 3, and automated pruning to avoid over-fitting. Positive (PPV) and negative (NPV) predictive values, sensitivity, and specificity of the resulting decision tree were also calculated. The interrater reliability of the E-ARAT scores conducted by the two clinician raters was assessed with an intraclass correlation coefficient (ICC), calculated using a two-way mixed effects model, considering people effects to be random and item effects to be fixed (48, 61).

Tests were two-tailed with significance set to $p < 0.05$. Significance values were adjusted for multiple comparisons using Bonferroni correction with a two-tailed significance level of $p = 0.0083$ for correlation analyses (0.05/6 comparisons and $p = 0.02$ for t-tests) (0.05/3 comparisons). All statistical analyses were conducted using IBM® Statistical Package for the Social Sciences (SPSS).

RESULTS

Of the 599 patients admitted to EUH with a primary diagnosis of stroke during fiscal years 2016–2018, 34 patients [median age: 64 (36–84) years, female: 14] met full study eligibility criteria. Twenty-five patients were diagnosed with ischemic stroke (70.6%), 8 with hemorrhagic stroke (23.5%), and 2 with ischemic stroke with hemorrhagic conversion (5.9%). Twelve strokes (35.3%) were localized in the right hemisphere, 17 (50.0%) in the left hemisphere, and 5 (14.7%) had bilateral involvement. Twenty-nine (85.3% of strokes) had subcortical involvement; 4 (11.8%) were localized to the brainstem. Seven patients (20.6%) had previous clinical stroke while 24 (70.6%) had some degree of white matter disease. A lesion heat map for all 34 participants is depicted in **Figure 1**. The median time to Acute E-SAFE assessment was 3.0 days (range = 0–12 days) and required estimation for 91% of patients. The median time to AR SAFE evaluation was 7 days (range = 2–27 days) and required estimation in 97% of patients. The median time to MRI was 1 day (range = 0–6 days). The median time to E-ARAT assessment was 90.5 days (range = 69–428 days) (**Table 1**).

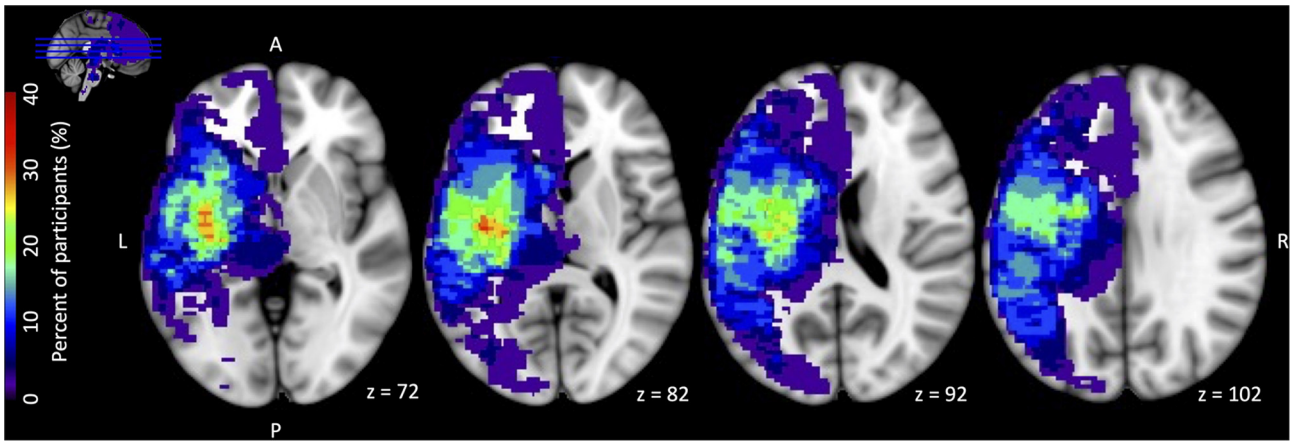

FIGURE 1 | Stroke lesion overlap heat map for all 34 participants. All lesions were flipped onto the left hemisphere for display. For the 5 participants with stroke involvement in bilateral hemispheres, the hemisphere contralateral to the affected paretic upper extremity was used for stroke location purposes. Color bar on the left has a maximum value 40% = 13 participants (maximal overlap voxel = red).

TABLE 1 | PUE outcome cluster group data.

PUE recovery outcome group	Good Median (range)	Limited Median (range)	Poor Median (range)
Number of individuals (% total)	18 (52.9%)	12 (35.3%)	4 (11.8%)
E-ARAT[a] score* (/57)	42.3 (35–50.8)	28.13 (18.5–33.5)	11.5 (1.5–14.8)
Acute E-SAFE[b] score** (/10)	6 (1–8)	3 (0–8)	0 (0–0)
AR[c] E-SAFE[b] score*** (/10)	8 (4–10)	3.5 (0–8)	0.5 (0–2)
Acute LOS[d] (EUH), days	7 (2–25)	6.5 (2–27)	6 (1–23)
AR[c] LOS[d] (ERH), days	19 (6–35)	20 (7–35)	19.5 (17–25)
Outpatient therapy duration, days	99.5 (44–314)	82 (37–271)	71 (29–157)
Number of outpatient visits	20.5 (12–50)	23.5 (11–54)	18 (7–22)
Lesion volume (mm^3)	6,182 (450–169,300)	28,645 (180–153,300)	77,495 (4,705–163,000)
Total CST[e] load (%) (SMATT)[f]	3.9 (0.0–22.5)	11.5 (6.0–35.1)	31.7 (13.0–61.8)
Number of SMATT[f] CST[e] tracts affected	5 (0–6)	6 (3–6)	6 (6–6)

[a]*E-ARAT, estimated ARAT.*
[b]*E-SAFE, estimated SAFE.*
[c]*AR, acute inpatient rehabilitation.*
[d]*LOS, length of stay.*
[e]*CST, corticospinal tract.*
[f]*SMATT, Sensorimotor area tract template.*
**34/34 scores estimated; **31/34 (91%) scores estimated; ***33/34 (97%) scores estimated.*

Interrater agreement for E-ARAT scores was high (ICC = 0.846, 95% CI: 0.69–0.92, $p < 0.0005$). Additional patient characteristics have been summarized previously (42).

Correlation Analyses

Spearman's correlation analyses revealed the SMATT CST overlap to be moderately negatively correlated with E-ARAT [SMATT CST r_s (32) = −0.443, $p = 0.0087$] (**Figure 2A**). The JHU CST overlap was also significantly correlated with E-ARAT, though less strongly [JHU CST r_s (32) = −0.361, $p = 0.036$] (**Figure 2B**). JHU CST and SMATT CST overlap were highly and significantly correlated [r (32) = 0.919, $p < 0.0001$]. Lesion volume was not associated with E-ARAT scores [lesion volume r_s (32) = −0.071, $p = 0.69$].

Further correlation analyses were conducted to evaluate which regions within the SMATT atlas were most highly correlated with the E-ARAT. PMv overlap percentage was the only tract that remained significantly correlated after adjusting for multiple comparisons [r_s (32) = −0.457, $p = 0.0066$] (see **Table 2**).

Kruskal-Wallis Results

The Kruskal-Wallis tests showed significant differences between outcome groups for all SMATT tract lesion overlap percentages. *Post-hoc* pairwise comparisons revealed that almost all significant differences were between *Good* and *Poor* outcome groups.

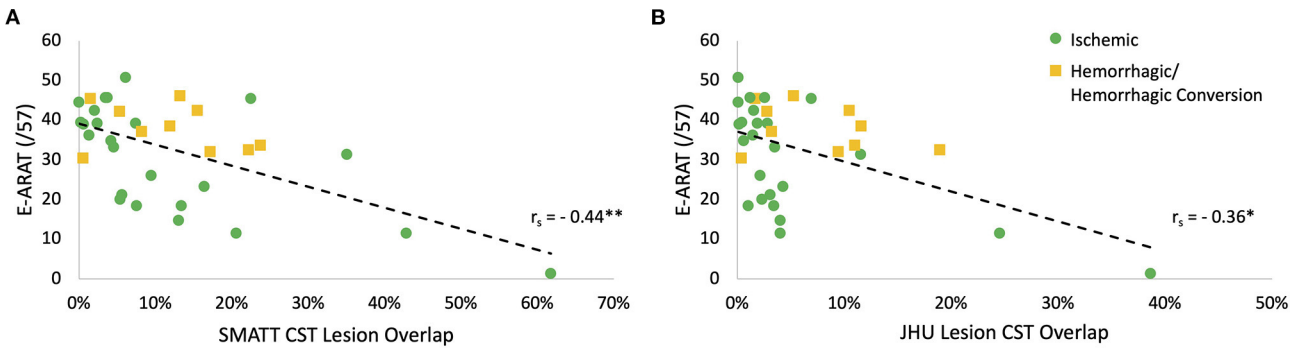

FIGURE 2 | Corticospinal tract (CST) lesion overlap is correlated with paretic upper extremity (PUE) motor outcome. **(A)** Sensorimotor area tract template (SMATT) CST lesion overlap is moderately correlated with estimated Action Research Arm Test (E-ARAT) score; ($r_s = -0.44$, $n = 34$, $^{**}p = 0.0087$). **(B)** Johns Hopkins University (JHU) atlas CST lesion overlap is weakly correlated with E-ARAT score; ($r_s = -0.36$, $n = 34$, $^{*}p = 0.036$). *Correlation is significant to the 0.05 level (two-tailed); **Correlation is significant to the 0.01 level (two-tailed).

TABLE 2 | SMATT tracts correlate with E-ARAT scores and distinguish between PUE outcome groups ($n = 34$).

Tract name	Spearman correlations	Kruskal-Wallis tests	Pairwise comparisons (median difference in % overlap, p^a)
SMATT CST	r_s (32) = −0.443, $p = 0.0087^*$	H (2) = 11.41, $p = 0.003^*$	*Good-Poor*: 20.25, $p^a = 0.007^{**}$ *Good-Limited*: 7.55, $p^a = 0.072^{\dagger}$
M1	r_s (32) = −0.344, $p = 0.046^*$	H (2) = 7.84, $p = 0.02^*$	*Good-Poor*: 25.25, $p^a = 0.024^{**}$
PMd	r_s (32) = −0.413, $p = 0.015^*$	H (2) = 12.15, $p = 0.002^{**}$	*Good-Poor*: 32.10, $p^a = 0.002^{**}$ *Limited-Poor*: 23.76, $p^a = 0.073^{\dagger}$
PMv	r_s (32) = −0.457, $p = 0.0066^{**}$	H (2) = 13.66, $p = 0.001^{**}$	*Good-Poor*: 53.28, $p^a = 0.005^{**}$ *Good-Limited*: 10.36, $p^a = 0.018^{**}$
preSMA	r_s (32) = −0.414, $p = 0.015^*$	H (2) = 10.65, $p = 0.005^{**}$	*Good-Poor*: 29.08, $p^a = 0.004^{**}$ *Limited-Poor*: 22.79, $p^a = 0.084^{\dagger}$
SMA	r_s (32) = −0.375, $p = 0.029^*$	H (2) = 11.54, $p = 0.003^{**}$	*Good-Poor*: 28.88, $p^a = 0.004^{**}$
S1	r_s (32) = −0.381, $p = 0.026^*$	H (2) = 7.02, $p = 0.03^*$	*Good-Poor*: 18.79, $p^a = 0.057^{\dagger}$

*Correlation is significant.
**Correlation remained significant after Bonferroni correction. All p-values reported for pairwise comparisons (last column) represent adjusted significance (p^a).
†Approaching significance after Bonferroni correction.

Only PMv lesion overlap revealed a significant difference between *Good* and *Limited* outcome groups (*Good-Limited* median difference = 10.36%, $p = 0.018$) (**Figure 3A**), though SMATT CST lesion overlap showed a non-significant trend for a difference between *Good* and *Limited* outcome groups after Bonferroni correction (SMATT CST *Good-Limited* median difference = 7.55%, $p = 0.072$). See **Table 2**, pairwise comparisons. No MRI variable significantly differentiated the *Limited* from *Poor* outcome groups, though overlap percentages from 2 non-M1 CST contributors, PMd and preSMA, were both approaching significance after Bonferroni correction (PMd *Limited-Poor* $p = 0.073$, preSMA *Limited-Poor* $p = 0.084$) (**Figures 3B,C**). Lesion volume was not significantly associated with PUE outcome category [H (2) = 2.06, $p = 0.36$]. PUE outcome (E-ARAT) was not significantly different for those with ischemic vs. hemorrhagic stroke [H (1) = 1.46, $p = 0.23$]. Lengths of stay in both acute and rehabilitation hospitals were not significantly different between groups, nor was the duration of outpatient therapy or number of outpatient visits different (**Table 1**).

Figure 4 depicts representative lesions overlaid on the SMATT atlas template for 2 individuals from different outcome groups. Participant A (**Figure 4,** top right, middle, left) achieved a PUE outcome in the *Good* category. Participant B (**Figure 4,** bottom right, middle, left) achieved a PUE outcome in the *Limited* category. Right, Middle, and Left slices depict the axial, coronal, and sagittal slices, respectively. Stroke lesions are depicted in light red with dark red outline. Individual contributions to the CST are color coded (see figure key). Both individuals had similar whole CST lesion overlap (participant A = 9.51%, participant B = 11.97%) but participant A had higher relative contribution of M1 CST lesion overlap (Participant A M1 overlap = 18.87%, non-M1 overlap = 9.28%; Participant B M1 overlap = 1.94%, non-M1 overlap = 12.46%).

Exploratory CART Analysis

When only MRI-derived metrics were made available for an exploratory CART analysis, it yielded a decision tree selecting SMATT PMd tract overlap <15% and SMATT PMv tract overlap ≤15% to classify patients. The resulting decision tree was 79.4% accurate when decision tree predictions were tested against the outcome cluster classification (correct classification for 27 of 34 patients) (**Figure 5A**). SMATT PMd tract overlap <15% distinguished those in the *Poor* outcome group from *Limited* or *Good* outcome groups with 80% accuracy (4 of the 5 *Poor* PUE outcome predictions were true). The largest error was introduced when distinguishing *Limited* from *Good* outcome groups where PMv overlap ≤ 15% only did so accurately for half those in the *Limited* outcome group. Most inaccurate predictions were higher than the achieved outcome (i.e., 5 individuals predicted to be in the *Good* outcome group achieved an E-ARAT within the *Limited* outcome score range). However, 1 individual predicted

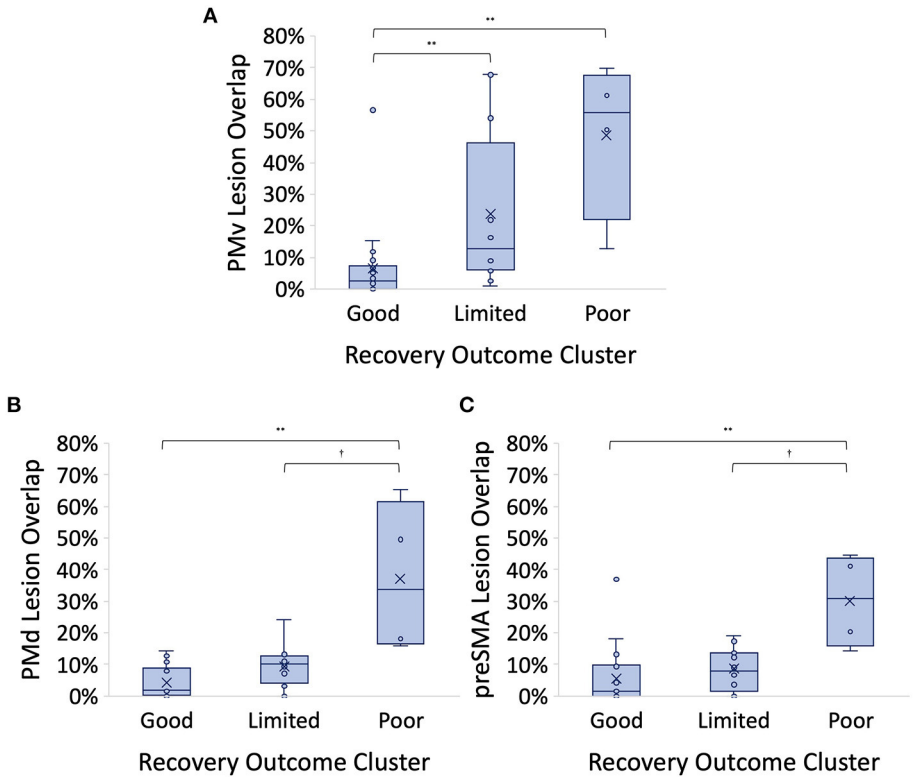

FIGURE 3 | (A) Ventral premotor (PMv) corticospinal tract (CST) lesion overlap % is higher for those in the *Good* outcome group over those in both the *Limited and Poor* outcome groups. *Good-Limited* $p = 0.018$, *Good-Poor* $p = 0.005$. **(B)** Dorsal premotor (PMd) CST lesion overlap % is higher for those in the *Good* outcome group over those in the *Poor* outcome group and showed a non-significant trend for a difference between *Limited* and *Poor* outcome groups. *Good-Poor* $p = 0.002$, *Limited-Poor* $p = 0.073$. **(C)** Pre-supplementary motor (preSMA) CST lesion overlap % is higher for those in the *Good* outcome group over those in the *Poor* outcome group and showed a non-significant trend for a difference between *Limited* and *Poor* outcome groups. *Good-Poor* $p = 0.004$, *Limited-Poor* $p = 0.084$. All p values reported represent adjusted significance; Cluster centers denoted with "x" in the figure; horizontal bars represent medians $^*p < 0.05$ level, $^{**}p < 0.01$ level; †Approaching significance after Bonferroni correction.

to be in the *Poor* outcome group achieved an E-ARAT within the *Limited* outcome score range and 1 individual predicted to be in the *Limited* outcome group achieved an E-ARAT within the *Good* outcome score range. The resulting decision tree was 75% accurate in outcome group prediction for those with ischemic stroke (18 of 24 patients with ischemic strokes were correctly classified) and 90% accurate in outcome group prediction for those with hemorrhagic stroke (9 of 10 patients with any hemorrhagic involvement were correctly classified). See **Figure 5A** for further statistics on predictive values, sensitivity, and specificity.

When all clinical and MRI metrics were made available to the CART analysis as potential predictors of PUE outcome, it yielded a decision tree selecting AR E-SAFE, patient age, and SMATT CST overlap to classify patients with 88.2% accuracy (correct classification for 30 of 34 patients) (**Figure 5B**). For those with AR E-SAFE < 4, all of whom had ischemic strokes, SMATT CST lesion overlap > 18% delineated *Poor* from *Limited* outcome groups with 90.0% accuracy (correct classification for 9 of 10 patients). However, similar error as in (A) was introduced for those with higher strength at admission to AR (AR E-SAFE > 4) where patient age > 75 years was selected to differentiate *Good* from *Limited* outcome groups but only did so accurately for half those in the *Limited* outcome group. All inaccurate predictions were higher than the achieved outcome (i.e., 3 individuals predicted to be in the *Good* outcome group achieved an E-ARAT within the *Limited* outcome score range; 1 individual predicted to be in the *Limited* outcome group achieved an E-ARAT within the *Poor* outcome score range). The resulting decision tree was 91% accurate in outcome group prediction for those with ischemic stroke (22 of 24 patients with ischemic strokes were correctly classified) and 80% accurate in outcome group prediction for those with hemorrhagic stroke (8 of 10 patients with any hemorrhagic involvement were correctly classified). See **Figure 5B** for further statistics on predictive values, sensitivity, and specificity.

DISCUSSION

Current study findings revealed that clinical MRI-derived CST lesion overlap was associated with PUE motor outcome post-stroke and that cortical projections within the CST, beyond those emanating from M1, were able to distinguish between PUE motor outcome groups. Further, results suggest that exploratory

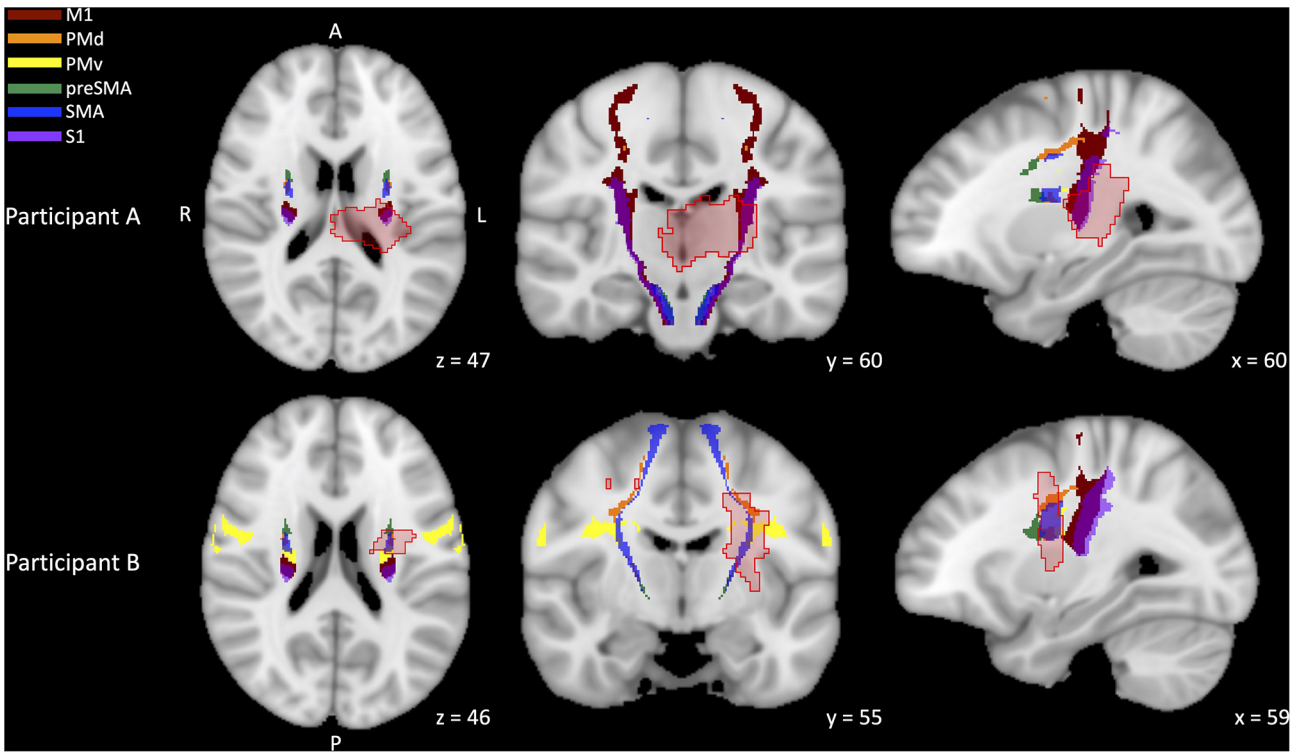

FIGURE 4 | Representative stroke lesions and sensorimotor area tract template (SMATT) corticospinal tract (CST) templates. CST templates have been differentiated by contributing region: primary motor cortex (M1, dark red), dorsal premotor cortex (PMd, orange), ventral premotor cortex (PMv, yellow), pre-supplementary motor cortex (preSMA, green), supplementary motor cortex (SMA, blue), primary somatosensory cortex (S1, purple). Stroke lesions are depicted in light red with dark red outline. Participant A [top (right, middle, left)] achieved a PUE outcome in the *Good* category. Participant B bottom (right, middle, left) achieved a PUE outcome in the *Limited* category. Right, Middle, and Left slices depict the axial, coronal, and sagittal slices, respectively. Both individuals had similar whole CST lesion overlap (A = 9.51%, B = 11.97%) but participant A had higher relative contribution of M1 CST lesion overlap (A M1 overlap = 18.87%, participant B M1 overlap = 1.94%).

predictive models using clinical MRI metrics, either alone or in combination with clinical measures, can accurately identify recovery outcome category for patients during both the acute and early subacute phases of post-stroke recovery that underwent AR post-stroke.

Clinically-Derived Lesion Overlap of CST Were Associated With Recovery of PUE Motor Function

Clinically-derived lesion overlap percentages for both the entire CST and specifically for the PMv CST contribution emerged as metrics with significant associations to PUE outcome at 90 days post-stroke. This observation is in agreement with previous studies employing higher-resolution MRI that showed functional PUE outcome was correlated with extent of injury to both M1 (26) and non-M1 tracts (16, 25, 26, 39, 62). However, our retrospective study provides evidence that lower-resolution, routinely available clinical scans may provide imaging-based information with prognostic utility for PUE motor outcome post-stroke. Our results indicate there may be advantages to evaluating the structural status of tracts outside of M1 CST and are in agreement with those from a prior study where CST integrity of the tract projecting to PMd was positively correlated with grip strength post stroke (39), and a recent study wherein connectivity between M1, premotor, supplementary motor and parietal areas was necessary for more robust PUE recovery post-stroke and was particularly important for those with greater motor impairment (29). Also in keeping with findings from previous studies (25, 26), lesion volume was not significantly associated with PUE outcome suggesting lesion location may be a more important factor contributing to PUE motor function than total lesion volume.

Current findings suggest that PUE functional outcome level is likely to be higher when there is a smaller extent of CST injury, in particular when PMv descending CST injury is minimal. This novel finding aligns with the role of PMv in upper limb planning and control. The PMv has been implicated in proper anticipatory shaping of the hand for grasping actions in both non-human primates and humans and several subtests of the ARAT require grasping an object to complete the task (19, 63, 64). Further, studies in non-human primates have shown that CST projections from PMv differentially terminate in upper cervical segments to potentially provide a unique contribution to control of the head, neck, and/or shoulder musculature necessary for reaching tasks (11, 19). Additionally, intracortical stimulation of the area within PMv with the densest direct connectivity to upper cervical segments elicited movement in the thumb and fingers (11, 19). Thus, stroke-related disruption of these direct

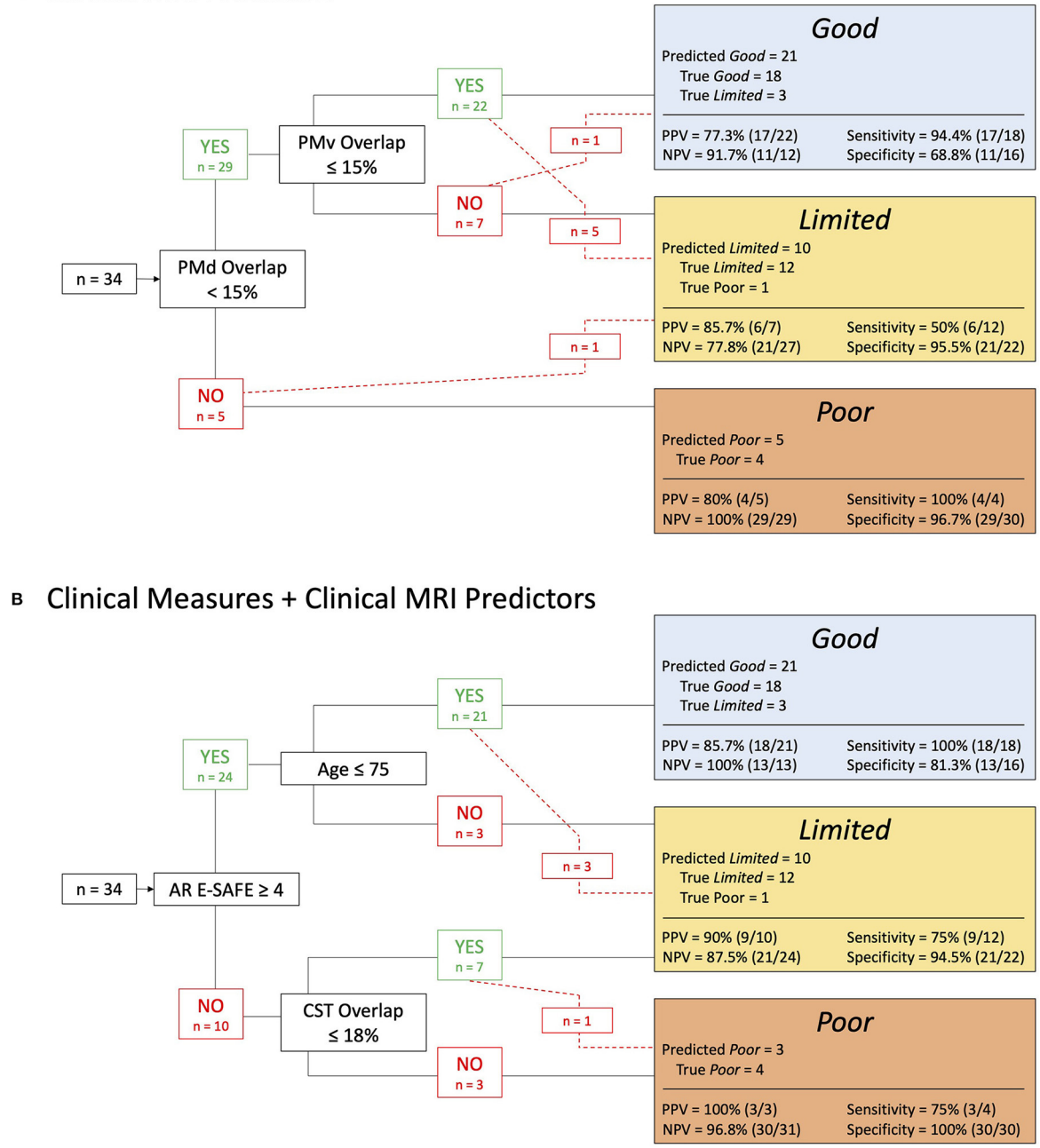

FIGURE 5 | (A) Dorsal (PMd) and ventral (PMv) premotor tract overlap predicts paretic upper extremity (PUE) outcome category with 79% accuracy. **(B)** Estimated shoulder abduction finger extension manual muscle test score assessed at admission to acute inpatient rehabilitation (AR E-SAFE), patient age, and corticospinal tract (CST) lesion overlap % predicts PUE outcome category with 88% accuracy. PPV, positive predictive value; NPV, negative predictive value.

PMv CST projections may underlie specific deficits resulting in poorer execution of functional reaching and grasping tasks that affect PUE recovery outcome level.

Our results underscore the relevance of contributions to the CST from cortical motor areas beyond M1, though most differences elucidated by individual contributing tracts in our study were between the highest- and lowest-functioning outcome groups. However, closer inspection of group differences in CST lesion overlap revealed that with the exception of one patient, individuals with greater than 20% disruption to PMd had a *Poor* outcome. These findings are in concert with another recent study wherein PMd lesion load was found to be the most robust neuroimaging predictor of 6-month PUE motor impairment (16). Authors from that study posited that the significant influence of PMd projections on motor recovery post-stroke may be due to the similar relative size of CST projections from M1

and PMd and their similar activation during complex motor tasks (16). Our results are further corroborated by a prior study that associated PMd lesion load with reduced grip strength post stroke (39).

PMd is commonly thought to be a motor planning center because of its known contributions to cognitive aspects such as spatial attention and working memory and its many projections to M1 (19, 20). PMd receives inputs from supplementary motor areas as well as parietal and prefrontal cortices, likely illustrating some role in integration and planning prior to motor execution (19). However, PMd also acts to control the execution of movement and contributes to descending motor signals both indirectly *via* its connections with M1 and directly through its CST projections (19, 20). Though the termination site of these direct projections are less clear in humans, animal literature has shown that direct projections from PMd to the spinal cord terminate on interneurons, descending subcortical motor networks, and in the region of motoneurons which may imply a more complex modulatory role in motor execution, one that has a major impact on motor performance (12, 19).

In a previous study (32), a single participant achieved minimal actual recovery of PUE motor function though the predicted outcome by an earlier iteration of PREP was expected to be notable (equivalent of a Good outcome in later studies). This individual displayed acute weakness (SAFE < 5) but was MEP+ during TMS assessment of M1 CST functional integrity (32). The authors speculated that part of the rationale for the overestimation of PUE outcome was due to "isolated and complete" damage to the premotor cortex which would not have been detectible using M1 CST based lesion analysis nor TMS assessment targeting M1 (32). Our findings support the notion that disruption to non-M1 motor areas may influence post-stroke recovery, particularly in patients with more profound PUE impairment, and highlight the potential utility of further investigating projections within the CST beyond those from M1.

Clinical MRI-Based Metrics of Acute Post-stroke CST Status Identified Recovery Outcome Category in Patients Undergoing AR

Clinical MRI-derived CST lesion overlap may offer an earlier indication of PUE outcome (as early as 24 h post-stroke) than previously established clinical measures of PUE strength (42). Despite previous work using clinical MRI showing that M1 CST bore the strongest association with PUE outcomes (27), here we demonstrated that lesion overlap in non-M1 CST contributors (PMd and PMv tracts) were able to distinguish PUE outcome groups and did so with similar predictive accuracy for both ischemic and hemorrhagic stroke. When considering the clinical utility of outcome predictors, accurate assessments available during acute hospitalization may be preferable for early clinical decision making to optimize resource management. In the timeframe of acute hospitalization, our findings indicated that non-M1 projections within the CST offered the strongest predictor of PUE outcome suggesting that prospective evaluation of clinical MRI-based CST metrics is warranted to determine if lesion involvement in M1 and/or non-M1 cortical projections is predictive of PUE recovery.

CST lesion overlap improved predictions using clinical metrics alone. In our cohort, PUE outcome predictions made using a combination of clinical measures and MRI biomarkers (AR E-SAFE, patient age, CST lesion load) showed improved PUE outcome prediction accuracy over use of either clinical metrics or MRI metrics alone. Our findings are in close agreement with a recent study that found that the combination of initial PUE impairment, patient age, and PMd CST structural integrity was a strong predictor of 6-month PUE impairment (16). The current findings are in line with previous finding showing: (1) PUE strength is a gross measure of baseline impairment that provides a general indication of the capacity to generate force required for functional task performance; (2) both initial impairment and patient age are predictors of functional motor outcome (3, 65–68); and (3) CST structural integrity provides insight into the underlying neural resources available for spontaneous biological recovery and experience-dependent plasticity in addition to more specific information regarding resources for sensorimotor control, motor planning, sequencing, and execution (66, 68). Quantifying CST structural integrity post-stroke may be particularly important for those with initially-lower levels of volitional control as the resolution of early strength deficits is likely to be significantly influenced by CST tract status (2, 32, 43, 44). Lesions localized within the CST are frequently associated with more severe, persistent loss of PUE motor function than lesions in other sites suggesting that certain areas of the brain and/or neuronal cell constituents may be more amenable to spontaneous biological recovery and/or plastic reorganization after stroke (7, 22–25, 27). Disruption of CST from non-M1 cortical contributors may cause a loss of unique modulatory function carried out by those descending fibers rather than a total loss of premotor cortical function, as these areas also project directly to M1. However, there is not yet a functional parcellation distinguishing contributions of descending vs. M1 projections of the PM to motor control. Therefore, structural biomarkers that quantify disruption to M1 and non-M1 CST projections may offer the specificity necessary to differentiate PUE functional recovery outcome categories however, they do not yet allow us the specificity to predict loss of specific domains of motor planning, execution or refinement. Additional studies are needed to further characterize potential tract-based biomarkers of domain-specific motor recovery.

Limitations

Our retrospective study design has strengths and limitations. An advantage of the retrospective study design is that it allowed for critical appraisal of current standards of clinical care and recovery outcomes within the study cohort, thus our dataset may more accurately represent the true recovery experience for patients post-stroke. However, the retrospective design also required estimation of measurements including E-ARAT performance, the primary outcome measure in our study. Although estimation may introduce some measurement error to current findings, we previously showed good inter-rater reliability for the estimation approach suggesting results were not

subjected to systematic bias. It was also not possible to control for differences in the content of therapy provided at each stage of post-stroke care which may limit generalizability in comparison with previous studies. However, individuals received therapy in the same rehabilitation setting and should have received a similar dosage and type of therapeutic intervention. Further, the therapy duration across the continuum of care was found to be similar across outcome groups.

The use of lower-resolution clinical MRI data processing may have introduced error during the normalization process as co-registration to a high-resolution standard template may result in imprecise alignment with neuroanatomic structures and diminished accuracy of lesion boundary localization. The template image and tract atlas (27) used for normalization in our study was derived from scans of 152 young, healthy individuals (mean age = 25 years) which may be less analogous to our cohort of individuals (mean age = 62 years) than an age-matched template due to known age-related changes (69, 70)." Lower resolution (larger voxel sizes) may lead to artificially larger lesion load values. The consequences could include overrepresenting lesion load in specific tracts. Relying on clinical scans, therefore, could result in missing subtle differences in lesion load compared to higher resolution images with small voxel sizes. Despite these limitations, we still observed tract-specific associations with clinical imaging routinely collected with standard-of-care management post-stroke highlighting the possible translational significance of the current findings (71).

We adopted a conservative threshold for statistical significance, which may have increased the likelihood of type 2 error given the size of the study cohort. Therefore, we also chose to report non-significant trends in the results. In seeking a clear MRI metric that differentiates between *Limited* and *Poor* outcomes, further prospective research with a larger cohort size may be warranted. Further, a few patients with high CST lesion overlap may have influenced the correlation between lesion load and PUE outcomes (**Figure 2**), however, these data points are consistent with our a priori hypotheses and corroborate previous results (16).

Lastly, although our exploratory CART analysis yielded decision trees that accurately predicted outcome for between 79 and 88% of individuals, the small sample size and category distribution may have led to overfitting of the model. Automated pruning was utilized to avoid overfitting of CART results, but predictive accuracy of decision trees created by the CART analysis were not tested using an independent testing data set, which could limit generalization of findings to other patient populations. Thus, definitive conclusions on the predictive merit of these decision trees should be viewed as a preliminary guide to future larger-scale prospective studies. CART results and predictions based upon retrospective chart review enable clinicians to make decisions that are historically consistent but may not be optimal for care planning and management. Further investigation and validation of predictive models using larger datasets will be necessary to confirm these preliminary study findings.

CONCLUSIONS

The current findings indicate that biomarkers of CST integrity derived from routinely-available clinical MRI are associated with level of recovery of PUE function and may provide additional information to inform predictive models of functional outcome. Prospective studies are recommended to determine the utility of including clinical imaging-based biomarkers of white matter tract structural integrity in predictive models of post-stroke recovery. In an era of precision medicine, biologically-informed algorithms that accurately predict recovery outcome hold promise for improving care plan development, patient management, and optimized allocation of rehabilitation resources.

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 Emory University Internal Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS and MB: project conception, research design, and data interpretation. MS: data acquisition, analysis, and manuscript preparation. MS, MB, NB, and SB: manuscript consultation, review, and approval. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Case Report: True Motor Recovery of Upper Limb Beyond 5 Years Post-stroke

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Most of motor recovery usually occurs within the first 3 months after stroke. Herein is reported a remarkable late recovery of the right upper-limb motor function after a left middle cerebral artery stroke. This recovery happened progressively, from two to 12 years post-stroke onset, and along a proximo-distal gradient, including dissociated finger movements after 5 years. Standardized clinical assessment and quantified analysis of the reach-to-grasp movement were repeated over time to characterize the recovery. Twelve years after stroke onset, diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS) analyses of the corticospinal tracts were carried out to investigate the plasticity mechanisms and efferent pathways underlying motor control of the paretic hand. Clinical evaluations and quantified movement analysis argue for a true neurological recovery rather than a compensation mechanism. DTI showed a significant decrease of fractional anisotropy, associated with a severe atrophy, only in the upper part of the left corticospinal tract (CST), suggesting an alteration of the CST at the level of the infarction that is not propagated downstream. The finger opposition movement of the right paretic hand was associated with fMRI activations of a broad network including predominantly the contralateral sensorimotor areas. Motor evoked potentials were normal and the selective stimulation of the right hemisphere did not elicit any response of the ipsilateral upper limb. These findings support the idea that the motor control of the paretic hand is mediated mainly by the contralateral sensorimotor cortex and the corresponding CST, but also by a plasticity of motor-related areas in both hemispheres. To our knowledge, this is the first report of a high quality upper-limb recovery occurring more than 2 years after stroke with a genuine insight of brain plasticity mechanisms.

Keywords: stroke, motor, recovery, upper-limb, dexterity, motion analysis, corticospinal tract, fMRI

INTRODUCTION

Motor recovery usually occurs within the first 3 months after stroke and is more limited for upper limbs than lower limbs (1–6). Similarly, recent modeling showed that the probability to recover upper limb motor function is extremely limited after the first 12 weeks post-stroke onset (7), which can be explained by the damage sustained by the contralateral corticospinal tract (CST) and the limited vicarious capacities of the motor system to compensate for this complex and lateralized function, especially for the individual finger movement and manual dexterity (8). A patient with a complete motor deficit of the right upper limb after stroke was followed for 12 years. He presented a remarkable late recovery of the upper-limb motility, in terms of strength, individual finger movement, and manual dexterity, 5 years after stroke onset.

The aim of the present study was to assess objectively the upper-limb recovery of this patient over a long-time period and to explore the potential mechanisms underlying this unusually delayed recovery. For this purpose, 3D kinematic analysis were carried out as well as a neuro-anatomo-functional study of the CST, using diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS) techniques.

CASE DESCRIPTION

The patient was a 53-year-old male, right-handed according to the Edinburgh laterality questionnaire. He underwent a stroke of cardio-embolic origin in the territory of the left superficial middle cerebral artery. He had an initial complete right hemiplegia and a severe mixed aphasia. He experienced intravascular thrombolysis 6 h after the onset of symptoms. His affected inferior limb recovered quite fast, and he was able to walk without limitation 3 months after the stroke, while he was unable to initiate movement in the right upper limb. He never had somato-sensory impairment nor spasticity. After 3 months of inpatient rehabilitation, he was discharged home and kept up with a standard physiotherapy of 30 min, 3 times a week. A home self-training program was monitored by the physiotherapist, including finger tapping exercises as soon as it was possible. The aphasia progressed, and he recovered oral comprehension, but a moderate expressive aphasia persisted. In the affected upper limb, the recovery was delayed and happened very gradually, along a proximal-distal gradient. Slight proximal movements, at the shoulder and elbow, re-appeared 6 months after the stroke onset. Slight global movements of the fingers were observed in the second year. A thumb-index finger grip was possible 4 years after the stroke, and gross prehension the following year. Six years after stroke onset, the movements were dissociated on the whole upper limb comprising the fingers. Nine years after the stroke, all kinds of prehension, gross, and fine, were functional. A brain MRI, performed 10 years after stroke onset, showed a single large infarction in the left superficial middle cerebral artery territory, sparing the cranial part of the precentral gyrus.

Patient Perspective

The patient was well-informed about the prognosis of his stroke. He spontaneously reported at a follow-up consultation that he was able to move his fingers, conscious that it was unexpected at such a delay. When proposed to participate in a clinical study to characterize and better understand this recovery, he showed great interest. He has always been very active and involved in his rehabilitation. He resumed driving, tinkers and gardens regularly using both hands.

MATERIALS AND METHODS

Grip strength, manual dexterity, and function of the upper limb were assessed 3 months, and 5, 9, and 12 years after stroke using standardized tests. Grip strength was measured using a Jamar dynamometer (9). The strength considered was the mean of 6 trials. Manual dexterity was measured using Box and Blocks test (10) and Purdue Pegboard right hand subtest (11). The results are expressed as a percentage of the normal value for the corresponding age group. Motor function was measured using Fugl-Meyer Upper Extremity Scale (FMA-UE) (12).

Kinematic Analysis of Reach-to-Grasp Movement

Repeated kinematic analyses of reach-to-grasp movement were performed at 5, 9, and 12 years after stroke onset. Results were compared to those of 6 right-handed control subjects (mean ± standard deviation (SD) age = 58.2 ± 5.5 years). Each participant sat facing a table. In rest position, the right hand laid on the table close to the trunk, in mid-pronation, thumb, and index finger in contact on the median line. A glass, 60 mm in diameter, was placed at 40 cm from the rest position, 20° to the right side of the median line.

Each participant was asked to take the glass with the right hand as naturally as possible and to lift it slightly. An alert-signal (red diode) flashed for 2 s to indicate the beginning of each trial. Then, a go-signal (green arrow) lit up, triggering the data acquisition. The beginning and end of each movement was determined by sensors placed under the rest position and under the glass. The glass was presented 11 times to each participant. We used a 3D motion capture system (Vicon 370®, Oxford, UK) with 5 infrared cameras to record the movement of 3 retro-reflective passive markers, placed on the thumb, index, and the internal radial styloid, at a frequency of 50 Hz. After recording and 3D reconstruction, the position of each marker was filtered with a Butterworth low-band pass filter, with a cut-off frequency of 6 Hz. Then, from the spatial position of the markers, movement parameters were computed using a homemade Handimain software. Relevant parameters related to the reach [movement time (MT), velocity peak (VP), time to velocity peak (TVP)], and grasp [maximal grip aperture

Abbreviations: CST, corticospinal tract; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; FA, fractional anisotropy; FMA-UE, Fugl-Meyer Upper Extremity Scale; PMC, premotor cortex; PLIC, posterior limb of the internal capsule; ROI, region of interest; SMA, supplementary motor area; TMS, transcranial magnetic stimulation.

(MGA) and time to maximal grip aperture (TMGA)] phases (13) were studied.

The Movement Time (MT) is the time between the initiation of the movement and the closure of the grip on the glass. The Velocity Peak (VP) is the maximal value of the wrist marker velocity during the movement. The Maximal Grip Aperture (MGA) measures the maximal distance between the thumb and index fingers during the grasp phase. These parameters were determined in a semi-automatic procedure with trial-by-trial validation by one expert experimenter. The trials for which the values were more or less than 2 standard deviations were removed.

MRI and Transcranial Magnetic Stimulation (TMS)

Twelve years after stroke onset, the patient was examined by MRI and TMS.

Conventional anatomic MRI, DTI and fMRI were performed at the MRI department of CERMEP-Imagerie du vivant (Lyon, France) on a 1.5T Siemens Sonata MRI system (Siemens Medical Solutions, Erlangen, Germany). Ten healthy control subjects [mean ± SD (range) age = 47.7 ± 11.8 (30–66) years] were included in the fMRI study. All control subjects were right-handed, had a normal or corrected-to-normal vision, and had no history of neurological nor psychiatric disorders. The study was approved by the local ethics committee (CPP Sud-Est IV) and all participants gave their written informed consent.

Conventional 3D T1-weighted (T1w) images [repetition time (TR) = 2,120 ms, echo time (TE) = 3.9 s] of the brain were acquired using the following parameters: voxel size = 1 × 1 × 1 mm^3, field of view (FOV) = 320 × 224 mm^2, 384 axial slices.

DTI was performed to evaluate the integrity of corticospinal tracts (CST) using a 2D spin-echo echo-planar imaging diffusion sequence repeated twice (TR = 6,500 ms; TE = 86 ms; 24 diffusion-gradient orientations with b = 1,000 $s.mm^{-2}$, 56 axial slices, FOV = 240 × 240 mm, voxel size = 2.5 × 2.5 × 2.5 mm^3). The fractional anisotropy (FA) asymmetry index (FA-AI) was calculated from the left and right posterior limbs of the internal capsule (PLIC) and CST.

fMRI was performed using a finger opposition task of the thumb and the 4 other fingers. Statistical activation maps were created, first to contrast movement and rest in the patient as well as in each control subject, then to contrast movement and rest in the control group.

TMS was used to test the functional integrity of the ipsi-lesional corticomotor pathway following a methodology consistent with the International Federation of Clinical Neurophysiology guidelines (14).

The anatomic MRI, DTI, fMRI, and TMS methods are detailed in **Appendix A** (**Supplementary Material** online).

RESULTS

Grip strength, manual dexterity, and function of the paretic upper limb improved between the 5th and the 12th year post-stroke. Grip strength, manual dexterity and proximal motility of the paretic upper limb remained lower than normal at the 12th year, whereas distal motility reached the maximum score (**Table 1**). FMA-UE showed that proximal motility improved between 3 months and 5 years and then remained stable, whereas hand motility improved until the 12th year, indicating a proximo-distal gradient in recovery.

Kinematic Analysis of Reach-to-Grasp Movement

Data collected at 5, 9, and 12 years post-stroke onset are presented in **Table 2**, **Figure 1**.

Regarding the reach component, mean MT of the patient was 279% of the control value at the 5th year assessment. It decreased by 44% between the 5th and the 9th year and then increased by 11% between the 9th and the 12th year. It was 157% of the control value at the 9th year and 173% of the control value at the 12th year assessment. VP remained lower in the patient than in controls by 53–57% at all time points. Regarding the grasp component, mean MGA was 92% of the control value at the 5th year assessment. It increased by 26% between the 5th and the 9th year and then decreased again by 9% between the 9th and the 12th year. It is 104% of the control value at the 12th year. Moreover, the shape of the grip aperture curve of the patient became smoother and more similar to that of the control subjects from the 5th to the 12th year.

DTI

As illustrated in **Figure 2**, the FA analysis, performed along the CST profile, differentiated two parts. In the upper part, where the CST goes between the lesion and the lateral ventricle, the FA was significantly lower in the left tract compared to the right. This argues for an alteration of structural integrity of the CST limited to the infarcted area. In the lower part, the FA was not significantly different between the right and left tracts, indicating that this alteration was not extended downstream of the infarction. The patient FA asymmetry index (FA-AI) measured at the level of the PLIC was equal to 0.423.

fMRI

The patient performed the task correctly with both hands. While he performed finger movements with the right impaired hand, fingers from his left hand displayed slight involuntary movements during most of the run, consistent with mirror movements. Significant brain activations during the finger opposition task in the patient are reported in **Figure 3**.

The finger movement of both hands was associated with widespread activations in the contralateral sensorimotor areas. The finger movement of the right impaired hand additionally elicited a small activation of the ipsilateral sensorimotor areas. While the activation of the right motor area elicited by the left hand movement covered a large part of the precentral gyrus, the activation of the left motor area elicited by the right affected hand movement was limited to the upper part of the precentral gyrus, the lower part being infarcted. A wide activation was observed in the ipsilateral cerebellum during the finger movement of the

TABLE 1 | Standardized clinical evaluation of the paretic hand of the patient, at 3 months, and 5, 9, and 12 years post-stroke.

Delay from stroke onset	3 mths	5 yrs	9 yrs	12 yrs
Fugl-Meyer Upper Extremity Scale (/66)	0	46	54	56
Proximal motility (/36)	0	26	26	26
Wrist motility (/10)	0	9	10	10
Hand motility/prehension (/14)	0	8	12	14
Coordination and speed (/6)	0	3	6	6
Grip strength (kg)	NM	NM	25 (40.8; 61%)	33 (41.4; 80%)
Manual dexterity				
Box and blocks test	NM	26 (75.2; 35%)	32 (71.3; 45%)	42 (68.4; 61%)
Purdue pegboard right hand subtest	NM	NM	5.5 (13.6; 42%)	6.5 (13.6; 49%)

mths, months; yrs, years; NM, non-measurable. For Fugl-Meyer Upper Extremity Scale, brackets indicate the maximum score. For grip strengh and manual dexterity, brackets indicate the normal value for the age group and the percentage of the normal value.

TABLE 2 | Kinematic parameters of the reach-to-grasp movement for the paretic upper limb of the patient and for the right upper limb of 6 control subjects.

	Patient			Controls
	Y5	**Y9**	**Y12**	
	Mean *(SD)*			
Transport phase				
MT (msec)	2,805.7 *(724.2)*	1,572.5 *(149.2)*	1,740.9 *(156.5)*	1,004.7 *(84.6)*
VP (mm/sec)	513.0 *(39.5)*	474.9 *(29.0)*	481.4 *(25.3)*	1,098.4 *(96.0)*
TVP/MT (%)	15.8 *(7.4)*	35.4 *(3.2)*	32.0 *(2.7)*	39.5 *(2.6)*
Grasp phase				
MGA (mm)	108.8 *(7.5)*	136.3 *(5.0)*	123.9 *(7.4)*	118.6 *(4.7)*
TMGA/MT (%)	51.6 *(22.8)*	57.8 *(6.0)*	42.5 *(3.9)*	69.7 *(5.6)*

Y5, Y9, Y12 correspond to 5, 9, and 12 years after stroke onset. MT, movement time; VP, velocity peak; TVP, time to velocity peak; MGA, maximum grip aperture; TMGA, time to maximum grip aperture. The italic values correspond to standard deviations of each parameter.

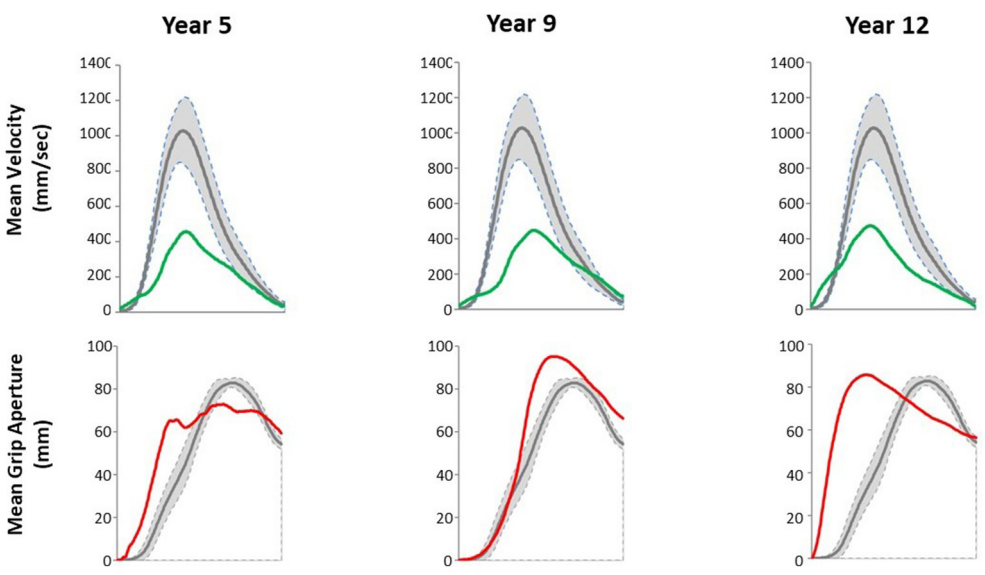

FIGURE 1 | Mean velocity and mean grip aperture profiles relative to a standardized prehensile movement time for a glass located on the right side for the patient (green and red) and in a group of six healthy controls (gray). In the control group mean ± SD is plotted.

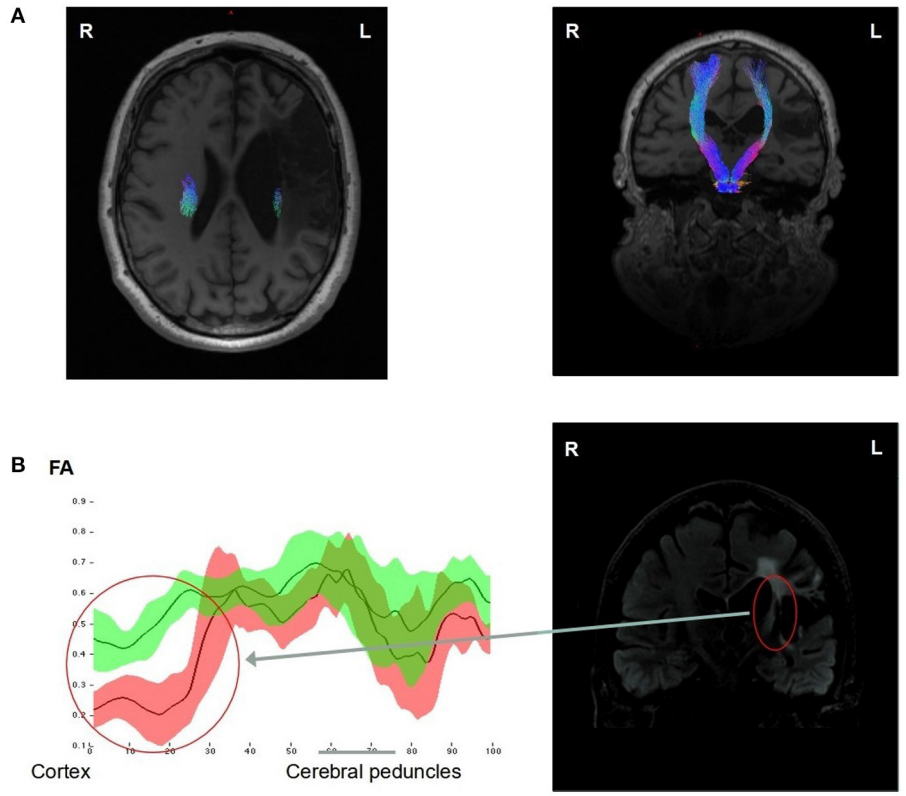

FIGURE 2 | DTI analysis of the corticospinal tracts (CST) of the patient 12 years after stroke onset. The CSTs of both hemispheres were reconstructed and represented in the axial and coronal T1w MRIs showing a reduction of the fiber numbers in the left CST compared to the right, particularly in its upper part, going between the ischemic lesion and the lateral ventricle **(A)**. FA measures (mean ± 1 SD) along both CST profiles, going from the up cortex to the down cerebral peduncles regions, showed a significant decrease (>2 SD) in the left (red) CST compared to the right (green) CST, in the upper part of the left CST (Red circle) **(B)**.

left hand, but not during the finger movement of the right affected hand.

For comparison, brain activations during the finger opposition task observed in the control group are reported in **Supplementary Table** (**Supplementary Material** online).

TMS

Motor evoked potentials were normal at both upper limbs, without any asymmetry regarding central conduction time and amplitude of responses to transcranial magnetic stimulation. When stimulating selectively one hemisphere with the butterfly coil under neuro-navigation, the cortical excitability threshold was estimated at 57% in the left hemisphere and 70% in the right hemisphere. With a stimulation at 120% of motor threshold, no response of the upper limb ipsilateral to the stimulation was elicited, neither at rest nor facilitated by voluntary contraction of the target muscle.

DISCUSSION

Although affected by a complete motor deficit of the right upper limb immediately after stroke, which is known to be a prognostic factor of poor recovery (15), our patient presented a remarkable recovery of upper-limb motility including strength, individual finger movement, and manual dexterity 5 years after stroke onset. This recovery took place much later than usually reported in the literature (8).

As recommended by Kwakkel et al. (16), standard clinical measures were associated with quantified movement analysis herein to better discriminate between neurological recovery and behavioral compensation. The evolution of FMA-UE between the 3rd month and the 12th year showed a motor recovery according to a proximo-distal gradient corresponding to the most frequent recovery profile after a supratentorial stroke (12, 17). Grip strength was measurable only after 5 years, which argues against a regression of non-use (18) or a motor neglect (19). Likewise, fine prehension movements required for Purdue Pegboard test became possible only after 5 years.

Kinematic analysis findings showed that the movement parameters of the paretic hand improved over time. MT representative of the reach phase decreased between the 5th and the 9th year, consistently with the FMA-UE that showed an improvement of proximal motility during the first 5 years after stroke. MGA, representative of the grasp phase, was lower

A

Cerebral area		left hand					right hand				
		Cluster size	Z	Activation peak coordinates (mm)			Cluster size	Z	Activation peak coordinates (mm)		
				x	y	z			x	y	z
Inferior frontal	R	100	7.57	44	33	10	118	7.36	62	16	3
Supplementary motor	R + L	1139	inf	0	-3	69	620	inf	-3	-4	64
Precentral	L						3321*	inf	-40	-21	66
Precentral	R	5338*	inf	33	-19	75	442*	inf	34	-18	78
Precentral	R	1155	7.63	54	9	48					
Postcentral	R	1261*	inf	62	-10	22	455	inf	64	-6	22
Supramarginal	R						100	7.19	57	-27	18
Superior parietal	R	240	inf	27	-51	72					
Cerebellum	L	3334	inf	-26	-49	-18					

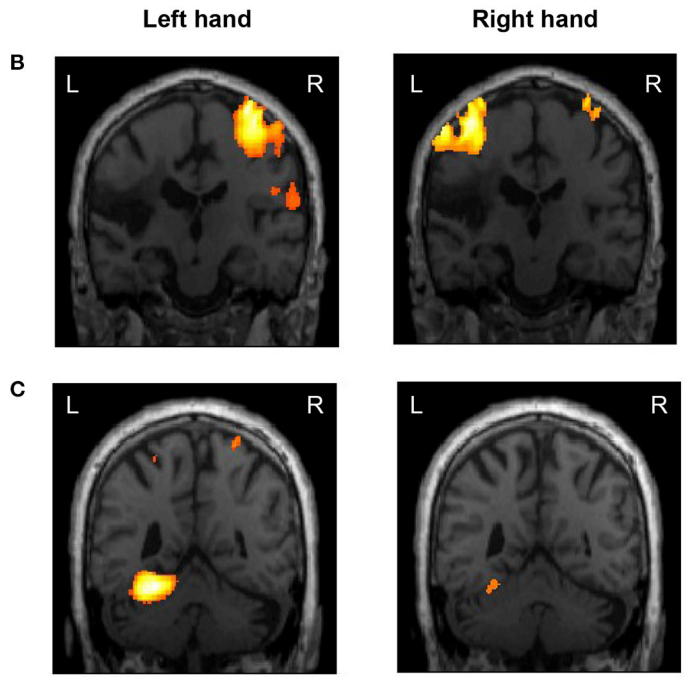

FIGURE 3 | fMRI activations during a finger opposition movement in the patient 12 years after stroke. Brain areas activated by the movement of the left unaffected hand and the right affected hand of the patient compared to rest. The coordinates of the local maximum and the *Z* score were displayed for each significantly activated cluster of more than 100 voxels ($p < 0.001$, FWE corrected). The origin of the coordinates is at the anterior commissure in the Talairach space. R, right; L, left; inf, infinite. *Clusters including both pre- and post-central gyri **(A)**. Activation maps were represented in the coronal plane corresponding to the activation peak of the cluster ($p < 0.001$, FWE corrected at the voxel level) of the contralateral primary motor cortex **(B)** and the cerebellum **(C)** during the left and right hand exercise (L, left; R, right).

than in controls at the 5th year, as observed in patients with a severe distal impairment. It became larger than in controls at the 9th year, as observed in patients with mild to moderate distal impairment (20). It finally decreased to approach the control value at the 12th year, arguing for an improvement of distal motility over the 12 year period (13). The improvement in motor scores and movement characteristics is more in favor of a true motor recovery than a compensation process taking advantage of the preserved proximal motility (21). The recovery of dissociated finger movements could be explained by the re-establishment and/or reorganization of anatomo-functional brain areas involved in motor control of the right hand and fingers and a left functional CST (8, 22).

DTI and TMS findings supported this hypothesis. As shown by the FA measurement, an alteration of the integrity of the left CST was found in the upper portion of the

tractus. DTI tractography showed that the left CST was thinner than the right CST, but some of the fibers were preserved all along the left CST, from the primary motor cortex to the cerebral peduncle. The left CST displayed signs of injury but presumably regained some functionality, as demonstrated by the motor evoked potentials. This finding is in line with the literature showing that recovery of selective finger movements is dependent on CST integrity (23, 24).

The fMRI study showed that the network activated during the finger movement of the right affected hand comprised motor and non-motor brain regions of both hemispheres. Among these regions, a large activation was located in contralateral sensorimotor areas, which is known to be associated with a good motor recovery (25). This network is broader than the network activated by the same movement performed with the non-affected hand. This is in line with previous imaging studies and suggests the recruitment of additional areas to compensate for the partial lesion of the motor cortex and the CST (26–31). The activation of sensori-motor regions of the ipsilateral hemisphere during the movement of the right affected hand could also be related to mirror movements of the left upper limb during the task (32, 33). The ipsilateral cerebellum was activated during the finger movement of the left unaffected hand in the patient, but not during the finger movement of the right affected hand. This observation can be interpreted as a persistent crossed cerebellar diaschisis (34). Due to the small number of control subjects compared to a single patient, the comparison between patient and controls has limited value and will not be discussed here.

In summary, these findings add to emerging evidence that, in some patients, motor recovery of the upper limb may not be restricted to the first 3 to 6 months after stroke onset. From a sample of 219 individuals with mild-to-moderate upper limb hemiparesis, an extension of this critical time window for recovery has already been demonstrated up to 18 months post-stroke (35). In the SALGOT study, a few patients showed improvement in FMA-UE or Action Research Arm Test between 3 and 12 months post-stroke (36). Bach-y-Rita had already reported a significant motor recovery over a 5-year period after a brainstem infarct in a 65 year old patient. Common points with our patient were an extensive home rehabilitation program, a strong motivation and a very active life (37). Sörös et al. described some recovery of the upper limb motricity 23 years after stroke in a young man, but they did not give information about fine motricity of the fingers (38). Stinear et al. (39) have reported that CST integrity is a predictor of functional potential in chronic stroke patients. Indeed, in patients with motor evoked responses to TMS in the affected upper limb, an intensive rehabilitation program can lead to meaningful gains 3 years after stroke. Although some cases of unusually late recovery have already been reported, it is the first time such a good quality recovery from a complete paralysis is described in this time frame and it is so precisely studied. This remarkable recovery could be explained by the combined restoration of nerve conduction in the affected CST (40) together with a cortical brain reorganization rather than the involvement of the opposite CST (41, 42). This might be explained by the removal of a central conduction block analogous to neuropraxia in the peripheral nervous system (43).

This remarkable late motor recovery of upper limb invites experts and physicians to temper their statements regarding the time course of recovery after stroke. It also highlights the interest of combining different techniques such as quantified movement analysis, structural and functional imaging, and electrophysiology for an extensive understanding of exceptional cases.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP Sud-Est IV. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC: data analysis and writing. JL and GR: conception of the study, monitoring, proofreading, and technical advice. NA-O: TMS, data analysis and technical advice, and proofreading. PRe: quantified movement analysis, data analysis and technical advice, and proofreading. FC: technical advice about MRI. JR: technical advice about fMRI data analysis. GK, SH, and CS: DTI, data analysis and technical advice. SB: fMRI control subjects and data analysis. PRi: quantified movement analysis. DS-M: technical advice, monitoring, and proofreading. 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.2022.804528/full#supplementary-material

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Leveraging Factors of Self-Efficacy and Motivation to Optimize Stroke Recovery

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The International Classification of Functioning, Disability and Health framework recognizes that an individual's functioning post-stroke reflects an interaction between their health condition and contextual factors encompassing personal and environmental factors. Personal factors significantly impact rehabilitation outcomes as they determine how an individual evaluates their situation and copes with their condition in daily life. A key personal factor is self-efficacy—an individual's belief in their capacity to achieve certain outcomes. Self-efficacy influences an individual's motivational state to execute behaviors necessary for achieving desired rehabilitation outcomes. Stroke rehabilitation practice and research now acknowledge self-efficacy and motivation as critical elements in post-stroke recovery, and increasing evidence highlights their contributions to motor (re)learning. Given the informative value of neuroimaging-based biomarkers in stroke, elucidating the neurological underpinnings of self-efficacy and motivation may optimize post-stroke recovery. In this review, we examine the role of self-efficacy and motivation in stroke rehabilitation and recovery, identify potential neural substrates underlying these factors from current neuroimaging literature, and discuss how leveraging these factors and their associated neural substrates has the potential to advance the field of stroke rehabilitation.

Keywords: stroke, self-efficacy, motivation, neurorehabilitation, neuroimaging, biomarker

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INTRODUCTION

Stroke is a heterogeneous condition resulting in profound and wide-ranging effects on physical, psychological, and social aspects of an individual's life (1, 2). Neurorehabilitation is an important component in an individual's recovery post-stroke (3). The World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) model is a universally recognized framework for health and disability (4) that delineates various levels of disability in stroke, including impairments, activity limitations, and participation restrictions (5). Rehabilitation therapists and clinicians utilize this framework to guide evaluation, treatment strategies, and goal-setting post-stroke (6).

Early stroke rehabilitation practice primarily focuses on recovery of impairments in the body structure and function domain of the ICF to optimize physical functioning. Such an approach is frequently based on motor learning principles of providing intensive, progressive, and task-specific interventions to improve physical function and capacity (i.e., what a person can do in a standardized, controlled environment post-stroke) (7, 8). However, improvement in physical

capacity does not translate to improvement in physical performance (i.e., what a person actually does in his or her daily environment) (9). This suggests that improvement in the body structure and function domain may not necessarily translate to improvement in social participation or reintegration into pre-stroke life roles. Expanding the focus of post-stroke rehabilitation beyond the domain of body structure and function may therefore promote more meaningful outcomes that translate to real-world participation.

A relevant feature in the ICF model is the inclusion of contextual factors, including environmental and personal factors (10). The latter refers to factors that are not a part of an individual's health condition or health state. Personal factors include gender, age, co-morbidities, socioeconomic status, education, and behavioral characteristics such as self-efficacy and motivation (11). These personal factors relate to performance and participation outside of the clinical environment (12). Self-efficacy relates to "beliefs in one's capabilities to organize and execute courses of action required to produce given attainments" (13). Individuals with high self-efficacy post-stroke typically have greater confidence to participate in activities of daily living (ADLs), higher ability to overcome barriers in their recovery, and typically possess greater psychosocial functioning and well-being compared to those with low self-efficacy (14, 15). As recent work indicates baseline ADL function as an important prognostic factor of functional independence during early post-stroke recovery (16), self-efficacy also contributes to post-stroke recovery and rehabilitation outcomes. Closely related to self-efficacy is motivation, which refers to an individual's will to perform a certain behavior toward achieving their goal and is one of the processes through which self-efficacy affects human functioning and impacts post-stroke rehabilitation outcomes (17). An individual's level of self-efficacy influences their motivation as exemplified in the following ways: determination of goals that individuals set for themselves, determination of effort expended by an individual in achieving their goal(s), determination of how long an individual perseveres when faced with challenges, and determination of an individual's resilience to failure (18). Given the importance of self-efficacy and motivation in goal-setting, perseverance, and resilience, these personal factors are key contributors to recovery and rehabilitation processes, including those related to stroke.

Motor learning theories such as the Dynamic Systems Theory and OPTIMAL (Optimizing Performance through Intrinsic Motivation and Attention for Learning) Theory have incorporated personal factors to explain motor (re)learning post-stroke (19, 20), whereby the optimization of learning and recovery depend on an individual's level of self-efficacy and motivation. Interventions aimed at enhancing these personal factors have demonstrated a reduction in functional decline 3–12 months post-stroke (21), significant improvement in rehabilitation outcomes including the Reintegration to Normal Living Index and Activities-specific Balance Confidence (ABC) Scale (22), and significant functional recovery at 6 months post-stroke (23). Further, such interventions in individuals with chronic conditions, including stroke, demonstrated lasting improvement in coping strategies including symptom management, increased physical activity, less fatigue, and fewer hospital visits due to secondary complications (24).

The assessment of self-efficacy and motivation primarily entails self-report scales and questionnaires, which introduce limitations related to response bias and subjectivity with scoring (25, 26). Brain-based measures acquired through neuroimaging may provide greater objectivity. Past research examining neuroimaging-based biomarkers of stroke recovery have shown the utility of these measurements in describing post-stroke injury and behavioral status as well as predictive value in post-stroke recovery and treatment response (27–29). Expanding biomarker development to elucidate neural substrates subserving self-efficacy and motivation may hold important clinical implications. Identifying neural correlates of self-efficacy and motivation, for instance, may provide information beyond what conventional measures alone convey. This information may result in a more objective assessment of self-efficacy and motivation to better tailor motor (re)learning and treatment strategies. In this review, we identify potential neural substrates underlying motivation, self-efficacy, and constructs of self-efficacy such as self-agency from current neuroimaging literature, and discuss how leveraging these factors and their associated neural substrates has the potential to advance the field of stroke rehabilitation.

There are a number of systematic reviews on self-efficacy and motivation in stroke focusing on the role of these factors in stroke rehabilitation outcomes (30–32) and their implementation in treatment and intervention strategies (30, 33). Findings from these systematic reviews have demonstrated significant associations between self-efficacy and post-stroke outcomes such as quality of life, activities of daily living (ADLs), mobility, and depression (30, 31) and have encouraged the incorporation of these factors in rehabilitation programming (33) and medical curriculum (31). This review examines the roles of self-efficacy and motivation in stroke rehabilitation and recovery while distinguishing itself from other reviews by bridging topics of self-efficacy and motivation with neuroimaging and biomarker development.

AN OVERVIEW OF SELF-EFFICACY AND MOTIVATION

Albert Bandura's Social Cognitive Theory describes learning as a dynamic process arising from the interaction between person, environment, and behavior to explain goal-directed behavior and its maintenance across time (34, 35). Self-efficacy is an important feature of Social Cognitive Theory that refers to the control of human action through an individual's beliefs in their capabilities to produce desired outcomes by their actions (34).

Since self-efficacy impacts stroke rehabilitation (e.g., sustaining progress and coping with setbacks), understanding how self-efficacy beliefs originate is important. Self-efficacy beliefs arise from the following instances: (1) Performance mastery. Successful performance experiences raise mastery and efficacy expectations. Once established, enhanced self-efficacy tends to generalize to other situations in which performance was lacking (36). In individuals with stroke, the enhancement

of self-efficacy occurs through the accomplishment of therapy goals through independent effort. (2) Vicarious experience. Observing others perform activities generates expectations in observers that they may achieve similar outcomes with persistent effort (37). (3) Verbal persuasion. Individuals believe in their ability to successfully cope with adverse experiences based on the encouragement from others, including health care professionals and family members (38). (4) Emotional arousal. An individual's emotional state influences their level of self-efficacy (38). For example, stressful situations may perpetuate emotions that negatively affects an individual's self-efficacy or their perceived ability to accomplish rehabilitation goals.

While performance mastery, vicarious experiences, verbal persuasion, and emotional arousal shape one's degree of self-efficacy, self-efficacy impacts human functioning through several psychological processes (39). (1) Cognitive processes. Individuals' self-efficacy influences the anticipatory scenarios that they mentally construct and rehearse. In rehabilitation settings, for example, individuals with high self-efficacy, visualize successful scenarios entailing positive rehabilitation outcomes, whereas those with low self-efficacy, visualize failure scenarios. In adverse situations, those with low self-efficacy tend to lower their aspirations, which negatively impacts their performance. In contrast, those with high self-efficacy, typically establish and pursue ambitious goals for themselves (40). (2) Motivational processes. Self-efficacy is key in the self-regulation of motivation (41). Individuals motivate themselves and guide their actions based on their beliefs of what they can do and set goals for themselves and plan the course of action accordingly. Thus, high self-efficacy results in greater motivation to set ambitious yet attainable rehabilitation goals along with effective planning to execute behaviors necessary to achieve those goals. (3) Affective processes. Self-efficacy is also key in anxiety arousal. Individuals with high self-efficacy typically manage anxiety and stressful conditions in a productive manner during rehabilitation; whereas, those with low self-efficacy cannot (42). (4) Selection processes. Self-efficacy influences the types of activities that individuals decide to pursue (42). Those with diminished self-efficacy actively avoid activities during rehabilitation that they believe exceed their capabilities (42). In contrast, those with heightened self-efficacy readily undertake challenging activities and select situations that they judge themselves capable of handling. A construct of self-efficacy relevant to stroke rehabilitation discussed below is *self-agency*, which refers to the belief that one's action is the consequence of one's intention (43). Bandura's Social Cognitive Theory describes *agency* as an individual's ability to control and regulate their thinking, motivation, and behavior with existing self-beliefs (i.e., self-efficacy) (43). Motivation, self-efficacy, and constructs of self-efficacy such as self-agency therefore play a central role in post-stroke recovery and rehabilitation outcomes.

SELF-EFFICACY AND MOTIVATION IN STROKE REHABILITATION

Until recent years, stroke rehabilitation often emphasized impairment mitigation; however, evidence suggests that impairment mitigation does not necessarily translate to improved participation in daily activities or enhanced quality of life (9). Thus, it is necessary to consider and evaluate all aspects of the ICF model to develop a more thorough understanding of stroke recovery. Further, as rehabilitation outcomes depend on patients' attitudes, self-beliefs, and motivation, post-stroke outcomes are therefore contingent on an individual's ability to actively participate in the rehabilitation process. Yet, barriers to post-stroke recovery, including depression (44) and anxiety (45), may compromise an individual's level of self-efficacy and motivation thereby impacting physical capacity and participation (46) and resulting in lower engagement during rehabilitation (47). For instance, recent work by Stewart et al. (48) that examined self-efficacy for reach speed and accuracy in individuals with chronic stroke displaying mild motor impairment found self-efficacy to be a significant predictor of affected arm reaching performance (48). Complimenting these findings is work showing a significant positive association between individuals' level of motivation at the start of inpatient post-stroke rehabilitation and level of independence with ADLs at the end of rehabilitation as measured by the Functional Independent Measurement scale (49). In addition to engagement in the rehabilitation process, low self-efficacy and motivation may also negatively influence treatment adherence (50, 51). Work by Caetano et al. (52) revealed that self-efficacy for walking, along with walking ability, explained 80% of the variance in exercise adherence in individuals post-stroke (52). As these collective findings imply, self-efficacy and motivation influence rehabilitation outcomes, and this likely occurs through several routes. First, as a primary focus of stroke rehabilitation is to facilitate an individual's volitional movement, a patient's motivation and self-efficacy beliefs influence their motor behavior (20). High self-efficacy and motivation enhance future expectations and generate autonomy, which may translate to individuals setting ambitious rehabilitation goals and a stronger commitment to achieve those goals (20). Second, self-efficacy and motivation influence the perceived demand related to task performance, which may further impact an individual's task preparation during rehabilitation (53). Individuals with high self-efficacy and motivation thus focus more on achievable elements of the task and less on potential shortcomings. Third, enhanced expectations arising from high self-efficacy positively impact cognitive processes such as working memory and attention (54), which are imperative for effective (re)learning following stroke. Lastly, enhanced expectations are related to increased dopaminergic mediation, which modulates motivation to guide future behavior (55). Thus, self-efficacy and motivation can enhance post-stroke rehabilitation outcomes and participation by influencing various motivational, cognitive and physiological aspects to ensure that goals are effectively coupled with desired actions in real-life.

Self-efficacy and motivation are also incorporated in self-management and home-based rehabilitation programs to promote long-term behavioral change and its maintenance over time following inpatient hospitalization (56). Post-stroke self-management programs led by therapists incorporating self-efficacy and motivation factors focus on goal-setting and empowering individuals with information, support and

resources to facilitate post-acute care transition and symptom management (15, 57, 58). Such self-management strategies have resulted in improved confidence in recovery, better long-term health outcomes, and a reduction in post-stroke complications (33, 59, 60) as evidenced by increased physical activity, improved self-reported mobility and fine motor-skill performance, and elevated balance confidence (61, 62). The recent Taking Charge after Stroke (TaCAS) study examined a novel self-management program in community dwelling individuals within 16 weeks post-stroke (63). As a departure from the SMART (Specific, Measurable, Achievable, Realistic/relevant, and Timed) approach, the Take Charge intervention instead incorporated elements of Self-Determination Theory (64) by fostering autonomy, confidence, and purpose. Participants explored and discussed important aspects of their lives, including people, along with priorities that they hoped to address over the next 12 months. Compared to control participants that received written stroke education, individuals completing the Take Charge intervention demonstrated significantly higher quality of life scores (Short Form 36 Physical Component Summary, SF-36) and significantly lower odds of dependency (modified Rankin scale 3–5) at 12 months post-stroke. A notable finding of the TaCAS study was a significant dose effect with higher quality of life scores observed with an additional Take Charge session (63).

Other interventions incorporating self-efficacy and motivation factors delivered by rehabilitation therapists include individualized coaching (65) and cognitive strategy training (66). Individualized coaching is a patient-centered process that aims to facilitate and empower the individual to achieve self-determined goals related to their health and wellness (67). In individuals with stroke, personalized coaching involving goal-setting, monitoring of goals, and motivation counseling resulted in improved physical activity behavior and participation as measured by the number of weekly exercise sessions, intensity and duration of exercise, and step count at 1 year post-stroke (68). Similarly, cognitive strategy training incorporates an integrated approach from behavioral and cognitive psychology fields. Here, a therapist guides the patient in goal-setting and facilitates skill acquisition through a guided recovery process where the patient (learner) identifies a problem and uses feedback and guidance from the therapist to generate potential solutions (69). Such training enhanced patients' self-monitoring capabilities and problem-solving skills that led to successful rehabilitation outcomes (70–72). Rehabilitation approaches and strategies integrating concepts of self-efficacy and motivation therefore have the potential to optimize post-stroke recovery outcomes through enhanced patient autonomy and participation during the recovery process.

ASSESSMENT OF SELF-EFFICACY AND MOTIVATION

Measurement of self-efficacy typically occurs through self-reports and questionnaires whereby individuals rate their degree of confidence in performing a specific task (73). One measure of self-efficacy, referred to as *self-efficacy magnitude,* is determined by summing the total positive or *yes* responses from an individual wherein a greater number of positive responses implies greater self-efficacy (73). Another measure, *self-efficacy strength*, is determined by summing the confidence ratings across all performance levels with higher scores representing greater confidence levels (74). For example, the General Self-Efficacy Scale (GSES) (75) is a 10-item psychometric scale that rates an individual's level of self-efficacy based on their self-beliefs of meeting task demands in a broad array of contexts. Responses utilize a 4-point Likert Scale with scores ranging between 10 and 40 (higher scores suggest higher self-efficacy). Similarly, several subjective patient-based measures of motivation exist (25, 76). However, these scales demonstrate limited reliability and validity with notable methodological limitations (77). The overall subjective nature of self-efficacy and motivation questionnaires therefore likely limits their widespread use in rehabilitation. Establishing greater objectivity in the assessment of self-efficacy and motivation would benefit both research and clinical settings by providing a more holistic understanding of the individual.

NEUROIMAGING AND BIOMARKER DEVELOPMENT

The application of structural and functional neuroimaging in stroke rehabilitation propelled the development of biomarkers or measurements reflecting underlying cellular and molecular events associated with clinical status and/or evolution (27). Stroke recovery biomarkers have the potential to enhance the accuracy of post-stroke recovery and treatment response prediction (27). For instance, structural neuroimaging measures derived from magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and transcranial magnetic stimulation that convey corticospinal tract integrity have informed motor recovery and treatment outcomes in stroke (78–80). Similarly, functional neuroimaging measures reflecting cortical oscillatory activity and functional connectivity as measured by electroencephalography, magnetoencephalography, and functional MRI, respectively, have also demonstrated similar associations with post-stroke recovery of motor (81), somatosensory (82), language (83), and cognitive function (84). Collectively, these measurements of brain structure and physiological function have provided a more comprehensive understanding of stroke recovery. Additionally, evidence also suggests greater prediction accuracy with the use of neuroimaging biomarkers in conjunction with clinical outcome measures vs. clinical outcome measures alone (85). While the emphasis of these neuroimaging measures has encompassed mostly improvement and recovery of impairment and function, the utility of these measures may also apply to the assessment of personal factors such as self-efficacy and motivation. The identification of pertinent neural correlates (i.e., relevant neural structures and connections) of self-efficacy and motivation may enhance the accuracy of existing post-stroke recovery prediction models.

TABLE 1 | Neural correlates of self-efficacy identified in healthy individuals.

References	N	Age (years)	Imaging	Neural correlate(s)
Farrer and Frith (86)	12	29	fMRI	AIC, R IPL
Yomogida et al. (87)	28	18–24	fMRI	SMA, L CB, R PPC, R EBA
Nahab et al. (88)	20	18–33	fMRI	PPC, STS, DLPFC, pre-SMA, precuneus, insula, CB
Davis et al. (89)	79	65–75	MRI	Total brain and gray matter volumes
Kang et al. (90)	19	22–35	EEG	Alpha (8–12 Hz) band oscillations, anterior frontal area
Nakagawa et al. (91)	1,204	20.7 ± 1.8	MRI	Lenticular nucleus
Hirao (92)	89	19.7 ± 0.6	fNIRS	L PFC

Age presented as range or mean ± standard deviation. N, Number of study participants; AIC, anterior insular cortex; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; EBA, extrastriate body area; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; IPL, inferior parietal lobule; L, left; MRI, magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; PFC, prefrontal cortex; PPC, posterior parietal cortex; R, right; SMA, supplementary motor area; STS, superior temporal sulcus.

NEURAL CORRELATES OF SELF-EFFICACY

There is a limited but growing body of literature utilizing neuroimaging to identify potential neurological correlates of self-efficacy and its constructs such as self-agency (**Table 1**). Most studies in existence predominantly involve young adults with no significant neurological history. One of the largest studies to date conducted by Nakagawa et al. (91) involved 1,204 young adults (91). Using a combination of MRI and DTI measures, the investigators determined that higher general self-efficacy scores related to lower mean diffusivity (higher neuronal density) from the lenticular nucleus (putamen and globus pallidus). These findings compliment previous work demonstrating contributions from the putamen to motor control and skill acquisition (93, 94). Previous research findings have also shown that putamen volume positively correlates with perceptual-motor performance and that functional connections between the sensorimotor cortex and the posterior putamen strengthen in parallel with learning (95). Collectively, these findings substantiate the contributions of the putamen in both motor learning and self-efficacy processes. The findings by Nakagawa et al. (91) also align with work illustrating contributions from the globus pallidus in the development and control of learning in humans (96). The corticostriatal loop connects cortical motor planning regions with subcortical structures, including the thalamus, putamen, and globus pallidus to efficiently execute and control motor behavior (97). Together, these findings underscore the importance and relevance of the lenticular nucleus as a neural substrate of both self-efficacy and motor learning and control.

In addition to subcortical structures, Hirao (92) also identified the prefrontal cortex as a crucial region of self-efficacy. Using functional near-infrared spectroscopy (fNIRS), they compared changes in prefrontal activation during a verbal fluency task across 89 healthy young adults previously categorized into low, moderate, and high self-efficacy groups. Investigators found significantly less left prefrontal activation in the low self-efficacy group as compared to the moderate self-efficacy group, which infers potential involvement of prefrontal cortical activity in self-efficacy. These findings supplement past work showing contributions from prefrontal cortex in self-regulation or behaviors that result in the fulfillment of one's intended goals (98, 99). Combined, these findings suggest the importance of prefrontal cortex in both self-efficacy and self-regulation in goal-directed behavior. Future investigation is necessary to determine how these findings translate to the rehabilitation environment where outcomes depend on the consistency of goal-directed behavior. In a study in 79 community-dwelling older women, Davis et al. (89) specifically assessed self-efficacy related to falls using the ABC Scale and found that falls self-efficacy positively correlated with both total brain and gray matter volumes. These findings resonate with previous findings that found that increased risk of falls in those with advancing age occurs in part due to decreases in brain volume and reduced cognition (100). Given the occurrence of falls post-stroke and the impact of stroke on brain volume (101), determining the predictive value of total brain volume on falls self-efficacy may be an effective future research direction.

While the aforementioned studies focus on neural correlates of self-efficacy, several studies of young adults with no neurological conditions (86–88, 90) have also examined neural correlates of self-agency. As previously defined, self-agency is a construct of self-efficacy that refers to an individual's ability to influence their own functioning by regulating their thinking, motivation, and behavior with existing self-beliefs to achieve desired outcomes (43). Work employing functional MRI (fMRI), identified several cortical regions and neural structures associated with self-agency (86–88): anterior insula and the right inferior parietal lobule, posterior parietal cortex (PPC), superior temporal sulcus (STS), dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (pre-SMA), precuneus, insula, cerebellum, supplementary motor area (SMA), right posterior parietal cortex (PPC), and right extra striate body area (EBA). Relatedly, a meta-analysis encompassing 15 fMRI studies across 228 study participants identified activation of the insula as a neural correlate of self-agency (102).

As expected, several regions associated with self-efficacy also relate to self-agency, and these regions, in turn, contribute to motor system function (ventral premotor cortex, SMA, pre-SMA, and cerebellum) and to cognition and information processing (DLPFC, PPC, and insula) (103). The anterior insula, for instance, shares connections with sub-regions of the prefrontal cortex, such as the dorsolateral and ventromedial prefrontal cortices, that control attention and working memory (104). These cognitive processes are imperative for motor relearning post-stroke and impact subsequent rehabilitation outcomes (105). Similarly, recent neurophysiological and neuroimaging evidence acknowledges the involvement of PPC and premotor regions in internal monitoring of self- and externally-generated movements (106), which are essential components in relearning and regaining movement post-stroke. Additional studies are needed

to provide a definitive understanding of how neural structures concomitantly involved in self-agency and motor and cognitive processing influence post-stroke rehabilitation outcomes.

Apart from the anatomical structures associated with self-agency, EEG work involving a virtual reality motor paradigm in a healthy cohort highlighted neural oscillatory activity in the alpha (8–12 Hz) band (90). Decreases in relative alpha power, specifically overlying central, bilateral parietal, and right temporal areas, related to greater self-agency. Additionally, significant decrease in alpha coherence (connectivity) involving regions overlying anterior frontal cortex negatively correlated with self-agency. Past work demonstrating the involvement of neural oscillations in the alpha frequency band in stroke recovery (107, 108) encourage additional work to validate these findings in a stroke cohort.

NEURAL CORRELATES OF MOTIVATION

Akin to the self-efficacy literature, most studies examining neural correlates of motivation involve fMRI in healthy adults (**Table 2**). Given the close relationship between self-efficacy and motivation, many of the anatomical regions previously reported above have also been identified in studies of motivation. In 161 young adults (19–24 years of age), Lee and Reeve (110) found that greater anterior insular cortex activation related to greater motivation (110), which aligns with other work highlighting greater interactions between anterior insular cortex and striatum associated with greater motivation (109, 114). Together, these findings substantiate past research showing contributions from the ventral and dorsal anterior insula to an individual's motivational state with the latter region specifically contributing to the updating of motivational states according to associated goal-directed actions (116). Other regions identified by fMRI include prefrontal, sensorimotor, middle cingulate, and visual cortices (111, 112, 115) along with nucleus accumbens and precuneous (112), with greater recruitment of these regions associated with greater motivation. Interestingly, in an effort to establish a causal link between motivation and frontopolar (FPC) cortex, Soutschek et al. (117) stimulated FPC with transcranial direct current stimulation (tDCS) in 141 healthy adults (117). Facilitation of this region with anodal tDCS increased participant motivation to put forth additional effort necessary to obtain a reward. This is consistent with prior work highlighting the FPC in goal-directed behavior (118). Determining how these findings extrapolate to neurorehabilitation is a necessary next step.

Emerging work in pediatric neuroimaging has also identified potential key regions associated with motivation particularly related to *grit* and *growth mindset* (113). The former refers to the long-term perseverance toward a goal and the latter refers to the belief that effort improves talent. The investigators found that *grit* positively correlated with ventral striatal networks including structural connectivity to medial prefrontal and rostral anterior cingulate cortices, implicated in perseverance and reward. Participants' *growth mindset* positively correlated with dorsal striatal structural connectivity (113). These findings pose significant implications in neurorehabilitation. Grit and growth mindset are essential to conditions with long-term recovery trajectories involving motor (re)learning, and identifying structural connections that subserve these constructs may spur the development of targeted therapeutic approaches.

TABLE 2 | Neural correlates of motivation identified in healthy individuals.

References	N	Age (years)	Imaging	Neural correlate(s)
Schmidt et al. (109)	20	19–27	fMRI	BG
Lee and Reeve (110)	161	19–24	fMRI	AIC
Quirin et al. (111)	17	23.6 ± 3.2	fMRI	L PFC
Radke et al. (112)	36	19–48	fMRI	NA, MCC, precuneus
Myers et al. (113)	20	11.2 ± 2.1	fMRI	Connectivity between striatum and medial PFC and dorsal/rostral ACC
Lee and Reeve (114)	22	22.9 ± 2.8	fMRI	Connectivity between AIC and striatum
Kohli et al. (115)	100	20–46	fMRI	Striatum, midbrain, sensorimotor and occipital cortices

Age presented as range or mean ± standard deviation. N, Number of study participants; AIC, anterior insular cortex; ACC, anterior cingulate cortex; BG, basal ganglia; fMRI, functional magnetic resonance imaging; L, left; MCC, middle cingulate cortex; NA, nucleus accumbens; PFC, prefrontal cortex.

DISCUSSION

This review serves as a point of integration for self-efficacy and motivation literature, stroke rehabilitation, and neuroimaging. There exists an extensive array of evidence in the literature highlighting the influence of self-efficacy and motivation on post-stroke rehabilitation outcomes, including individuals' engagement and adherence to rehabilitation. Limitations in current self-efficacy and motivation assessment methods, combined with recent application of neuroimaging-based biomarkers in stroke, prompted a review of the neuroimaging literature to identify potential neural substrates underlying motivation and self-efficacy. This particular objective distinguishes this review from others. Research findings utilizing fMRI, fNIRS, and EEG revealed several pertinent anatomical structures and regions–several of which were associated with learning. Identifying ways to enhance an individual's self-efficacy and motivation has the potential to advance post-stroke rehabilitation and promote lasting behavioral change (119). Ascertaining neural substrates subserving these personal factors may benefit this effort.

An increasing number of clinical research studies in stroke rehabilitation recognize the value of patient-centered measures, reporting interactions between self-efficacy, participation, capacity (120, 121). The consideration of personal factors such as self-efficacy and motivation may adjudicate the disconnect between functional improvement in rehabilitation settings and enhanced participation in the natural environment.

Additionally, factors of self-efficacy and motivation also determine how an individual copes with difficult situations during rehabilitation. Greater self-efficacy and motivation positively affect an individual's ability to manage and overcome stressful conditions (18, 42). As stroke rehabilitation focuses on an individual's voluntary movement, an individual's self-beliefs and attitudes are fundamental in determining rehabilitation outcomes. Moreover, these biopsychological factors also influence long term behavior change (122) and return to work post-stroke (123). Lastly, there is growing evidence of time and dose-dependent effects of rehabilitation on functional improvement post-stroke (124–126). As discussed earlier, self-efficacy and motivation influence an individual's engagement in and adherence to rehabilitation, and these factors may therefore also impact the treatment dosage that an individual receives. Therapists and other medical professionals involved in the rehabilitation process should therefore implement strategies in their clinical practice to foster self-efficacy and motivation among their patients (127). Components of the Take Charge intervention (63) and elements from ASAP (Accelerated Skills Acquisition Program) entailing the celebration of patient effort and collaboration between therapist and patient provide additional direction (128). Such strategies are particularly imperative in the inpatient rehabilitation setting where boredom is a common sentiment reported in individuals post-stroke (129). A systematic review examining inpatient post-stroke rehabilitation experiences from 560 participants across 10 countries attributed feelings of boredom, frustration, and powerlessness, in part, to the physical environment (i.e., rehabilitation setting) (130). Individuals frequently desired more activities, stimulation, and practice opportunities both during and after their therapy sessions. Purposeful structuring of the rehabilitation environment based on the individual may also cultivate motivation and self-efficacy during this critical period of recovery in addition to the patient-therapist relationship.

In order to leverage self-efficacy and motivation to advance stroke rehabilitation, there must first be accurate tools to assess these factors. Current assessment tools involve self-reported questionnaires wherein individuals must either response in yes or no or rate themselves on a Likert Scale. Considering the subjective nature of scoring and lack of standardization of scoring ranges in these assessments, these tools may have limited reliability and validity. Furthermore, such measures might have reduced accuracy in assessing self-efficacy and motivation due to possible response bias (131). This bias may be due to participant hesitancy or the need to give socially desirable answers. To mitigate these issues, utilizing neuroimaging-based measurements in conjunction with self-reported scores may provide more accurate characterization of self-efficacy and motivation post-stroke. Evidence supporting the use of neurologic biomarkers in combination with behavioral measure (85) along with recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR) to incorporate biomarker data into future stroke recovery research (27) encourage the expansion of biomarker development to self-efficacy and motivation assessment.

In addition to potentially enhancing the objectivity of self-efficacy and motivation assessment, neural correlates of self-efficacy and motivation may also foster a more person-centered approach in motor learning and rehabilitation. Our review of the neuroimaging literature resulted in the identification of several potentially important structures and regions that require further investigation in individuals with stroke as the literature predominantly involved young adults without significant neurological history. Future work should confirm if similar brain-behavior associations reside in individuals with stroke. Further, similar to how biomarkers may differentiate treatment "responders" from "non-responders," neural correlates of self-efficacy and motivation may also define those with varying levels of self-efficacy and motivation. Such information may inform an individual's treatment and recovery trajectory and also guide therapists in their delivery of feedback and structuring of tasks during therapy sessions. Neural structures and connections associated with self-efficacy and motivation may also guide clinical researchers in their development of stroke recovery prediction models and interventions. Given the relevance of self-efficacy and motivation in motor learning/control and stroke rehabilitation, inclusion of these personal factors in stroke recovery prediction models may enhance predictive performance and provide additional therapeutic targets.

The majority of studies reviewed utilized MRI and fMRI technologies. While these neuroimaging techniques have been widely utilized in stroke, their lack of accessibility and portability limit their application in a stroke rehabilitation setting. Technologies such as fNIRS and EEG may prove valuable in the examination of self-efficacy and motivation in a rehabilitation setting, particularly at the bedside, while also enabling researchers to examine various neural networks and connectivity-based measurements. Given the complexity of self-efficacy and motivation, it is likely that neural correlates underlying these factors extend beyond an anatomical structure.

To promote consistency across clinical trial methodology and outcomes research in stroke, the SRRR proposed a universal battery of assessments for researchers (132). Though the current battery does not contain participation measurements or baseline measures of self-efficacy or motivation, several function- and activity-specific measurements with documented psychometric properties exist: ABC Scale (133), Falls Efficacy Scale (134), Walk-12 (135), Short Self-Efficacy for Exercise Scale (136), and the Confidence in Arm and Hand Movement Questionnaire (137). For the purposes of obtaining a baseline measurement of general self-efficacy and/or motivation specific to stroke rehabilitation, we recommend the Stroke Self-Efficacy Questionnaire (SSEQ) (138) and the Stroke Rehabilitation Motivation Scale (SRMS) (25). Briefly, the 13-item SSEQ assesses self-efficacy beliefs related to everyday tasks and self-management (e.g., bed mobility, ambulation, dressing, coping with frustrations of stroke, and exercise adherence) (138). The questionnaire possesses high internal consistency (Cronbach's alpha $= 0.90$) and criterion validity with the Falls Efficacy Scale (Spearman's $r = 0.803$, $p < 0.001$) (138). The 28-item SRMS, adapted from the Sports Motivation Scale (139), assesses internal and external motivation (25). Though the scale demonstrated good inter-rater reliability

and internal consistency, it is important to note the small sample size ($n = 18$) involved in the initial testing (25). Despite previous acknowledgment regarding the limitations of current self-efficacy and motivation assessments, obtaining baseline measures of self-efficacy and/or motivation is important since these factors influence constructive behaviors, attitudes, and beliefs in post-stroke recovery. Baseline knowledge of one's self-efficacy and/or motivation may inform recovery potential and treatment and learning responses while also serving as a potential covariate in a clinical trial. Thus, assessment of self-efficacy and motivation using self-reported measures in conjunction with objective neuroimaging-based measures have implications in both stroke rehabilitation practice and research.

CONCLUSION

Self-efficacy and motivation are important factors in stroke recovery and rehabilitation. The therapist-patient relationship and rehabilitation setting play significant roles in nurturing self-efficacy and motivation in patients. The use of neuroimaging to identify potential neural substrates of self-efficacy and motivation will enrich our understanding of stroke recovery and rehabilitation. There is a limited but growing body of literature concerning neural substrates of self-efficacy and motivation, and this work collectively inspires additional work in clinical populations, including stroke, to generate novel research questions, experimental paradigms, and treatment targets to optimize post-stroke recovery and rehabilitation outcomes.

AUTHOR CONTRIBUTIONS

JMC conceptualized the paper. RG, ACa, and ACo conducted literature reviews. RG wrote the paper. ACa, ACo, and JMC edited the paper. All authors have read and approved the submitted version.

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Brain Functional Topology Alteration in Right Lateral Occipital Cortex Is Associated With Upper Extremity Motor Recovery

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Stroke is a chief cause of sudden brain damage that severely disrupts the whole-brain network. However, the potential mechanisms of motor recovery after stroke are uncertain and the prognosis of poststroke upper extremity recovery is still a challenge. This study investigated the global and local topological properties of the brain functional connectome in patients with subacute ischemic stroke and their associations with the clinical measurements. A total of 57 patients, consisting of 29 left-sided and 28 right-sided stroke patients, and 32 age- and gender-matched healthy controls (HCs) were recruited to undergo a resting-state functional magnetic resonance imaging (rs-fMRI) study; patients were also clinically evaluated with the Upper Extremity Fugl-Meyer Assessment (FMA_UE). The assessment was repeated at 15 weeks to assess upper extremity functional recovery for the patient remaining in the study (12 left- 20 right-sided stroke patients). Global graph topological disruption indices of stroke patients were significantly decreased compared with HCs but these indices were not significantly associated with FMA_UE. In addition, local brain network structure of stroke patients was altered, and the altered regions were dependent on the stroke site. Significant associations between local degree and motor performance and its recovery were observed in the right lateral occipital cortex (R LOC) in the right-sided stroke patients. Our findings suggested that brain functional topologies alterations in R LOC are promising as prognostic biomarkers for right-sided subacute stroke. This cortical area might be a potential target to be further validated for non-invasive brain stimulation treatment to improve poststroke upper extremity recovery.

Keywords: stroke, upper extremity recovery, resting-state fMRI, right lateral occipital cortex, functional connectivity network

INTRODUCTION

Stroke, a common medical emergency, remains the main cause of long-term disability and death in the world (1). Usually, stroke patients usually show hemiplegia, especially affecting the upper limb (2). Independence of the patients in activities of daily living depends on the recovery of their upper limb motor functions (3), and accurate prognosis of the recovery would enable realistic goal-setting and guide the allocation of rehabilitation resources. However, the prognosis of poststroke upper extremity recovery is still a challenge.

The most common neuroimaging biomarker to predict poststroke upper extremity recovery is measuring the integrity of the corticospinal tract (4–8). But neurological impairment poststroke can sometimes exceed expectations of stroke severity because stroke not only leads to focal, location-dependent neurological symptoms, but also causes widespread effects in remote hemispheres through functional networks (9–11). Researchers have recently discovered that along with the disorders of structural connectivity (12), reorganization of functional networks is related to the prognosis of patients (13–17). However, at present, there have been few reports on how the reorganization of brain functional networks predicts recovery of clinical motor function (18).

The properties of brain functional networks can be explored using graph theory. Resting-state fMRI (rs-fMRI) combined with network analysis demonstrated that the motor execution networks of convalescent stroke patients shifted to a more random topology (19); the local efficiency and small worldness of stroke patients were significantly higher and lower than those of healthy controls (HCs), respectively, and the latter was increased to a level close to that of the HCs during rehabilitation (20, 21). Moreover, an earlier study has shown functional network topological properties associated with poststroke outcomes in acute ischemic stroke patients (22). Therefore, we hypothesized that the brain functional topological properties were associated with an upper extremity motor recovery after stroke.

In this study, by taking advantage of a modest sample size (57 stroke patients and 32 age- and gender-matched HCs), global and local voxel-based graph theory analyses were performed and the correlation between brain network dysfunction and behavior in subacute stroke was fully investigated. First, after the patients were divided into two different subgroups based on stroke site, global graph properties of the two subgroups, and their association with clinical measurement were assessed independently. Following this, voxel-based degree maps between patients and their matched HCs were compared and association with clinical measurement was evaluated. Finally, using the significantly associated regions from the last step as regions of interest (ROIs), an ROI-based functional connectivity (FC) analysis was performed to explore the significantly different FC regions between patients and the HCs and found an ROI that can evaluate the extent to which upper extremity recovered postrehabilitation.

MATERIALS AND METHODS

Participants

We recruited 62 patients with first-time ischemic stroke between May 2017 and July 2020 at the Department of Physical Medicine and Rehabilitation in the Second Affiliated Hospital of Wenzhou Medical University, China. A total of five patients were removed from further data analyses because they did not pass our data quality control (see Section Quality control for details). To be eligible, participants must have (1) been between 30 and 85 years of age; (2) had their first stroke within the past month; (3) subcortical lesion restricted to the basal ganglia, internal capsule, corona radiate, or brainstem. Participants were excluded if they had the previous history of brain neurosurgery or epilepsy, or any MRI contraindications. The difference in lesion location of ischemic stroke is associated with different functional outcomes (23). Therefore, in this study, the stroke patients were divided into two subgroups: left-sided stroke patients and right-sided stroke patients.

In addition, 32 gender-, age-matched HCs were recruited. HCs were excluded if they (1) were <30 or more than 85 years old; (2) had psychiatric disease; (3) reported history of brain neurosurgical procedures and/or epilepsy; (4) were not suitable for MRI scan. All the stroke patients and HCs were right-handed. The demographical and clinical characteristics of stroke patients and HCs are detailed in **Table 1**.

This study was approved by the Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, China (Approval number: Clinical Scientific Research Ethical Review No. 2017LCKY-09) and all the participants provided written informed consent. All the research procedures were conducted in accordance with the Declaration of Helsinki.

Clinical Assessment and Rehabilitation

Clinical measurement related to motion performance was assessed. FMA_UE was used to measure upper limb movement, a highly recommended clinical tool for evaluating changes in motor impairment after stroke (range: 0–66) (24, 25). The upper extremity motor domain includes movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, and hand (24) and each item has a 3-point ordinal scale (0-cannot perform, 1-performs partially, and 2-performs fully) (25). All the patients received two assessments of FMA_UE at the following time points: immediately following enrollment (baseline FMA_UE) and a follow-up 15 weeks after enrollment (follow-up FMA_UE). To evaluate the extent to which upper extremity was recovered postrehabilitation, FMA_UE recovery ratio was defined as

$$\text{rFMA\_UE} = \frac{\text{follow} - \text{up FMA\_UE} - \text{baseline FMA\_UE}}{\text{baseline FMA\_UE}}$$

and referred to as rFMA_UE. The positive and negative signs of rFMA_UE indicated improvement and deterioration of the upper extremity, respectively.

The FMA_UE assessments were evaluated by the same physician and collected on an electronic tablet device using Research Electronic Data Capture (REDCap) (26), a secure,

TABLE 1 | Demographic and clinical characteristics of left-sided and right-sided stroke patients and HCs.

	Left-sided ($n = 29$)		Right-sided ($n = 28$)		HCs ($n = 32$)		Left-sided vs. HCs *p*-value	Right-sided vs. HCs*p*-value	Left- vs. Right-sided *p*-value
Age, mean (SD), years[a]	62.38	(11.10)	64.71	(8.56)	65.22	(3.07)	0.192	0.770	0.379
Gender, male (%)[b]	19	(65.52)	15	(53.57)	15	(46.88)	0.143	0.605	0.358
Right handedness (%)	29	(100)	28	(100)	32	(100)	1.000	1.000	1.000
Time after stroke, mean (SD), days	15.62	(7.09)	18.18	(8.31)		–	–	–	0.216
Hypertension (%)	22	(75.86)	20	(71.43)		–	–	–	0.704
Diabetes (%)	12	(41.38)	19	(67.86)		–	–	–	0.045
Baseline FMA_UE, mean (SD)	33.79	(23.65)	28.79	(16.62)		–	–	–	0.339
Follow-up FMA_UE, mean (SD)*	49.42	(22.52)	46.60	(19.46)		–	–	–	0.711

[a]*Independent samples t-test.*

[b]*Chi-squared analysis.*

SD, standard deviation; FMA_UE, Upper Extremity Fugl-Meyer Assessment.

*– Unavailable; *Follow-up assessment was performed for 12 left-sided and 20 right-sided stroke patients.*

convenient, and efficient web application for capturing electronic survey data.

All the patients received standard rehabilitation treatments after enrollment. The treatment program consists of physical and occupational therapy, including grips and finger movements, gross movement, stretching, and training in daily life activities.

Magnetic Resonance Imaging Data Acquisition

Subjects were scanned on a 3 Tesla GE-Discovery 750 scanner with the following parameters: for anatomical T1-MRI data: TR/TE = 7.7/3.4 ms, flip angle = 12°, FOV = 256 × 256 mm, resolution = 256 × 256, slice per volume = 176, slice thickness = 1 mm; for fMRI data with odd interleave slice acquisition scheme: TE/TR = 30/2,500 ms, voxel size = 3.4375 × 3.4375 × 3.5 mm^3, in-plane resolution = 64 × 64, number of volumes = 230, and flip angle = 90°.

FMRI Data Preprocessing and Registration

A scrubbing-based preprocessing method (27) was applied to all rs-fMRI data with the following steps: discard first four volumes; motion correction; slice-time correction; intensity normalization; high-pass temporal filtering (0.008 Hz) for correcting low-frequency signal drift; regression of six motion vectors, cerebrospinal fluid (CSF) signal-averaged overall voxels of eroded ventricle region, averaged white matter (WM) signal, and averaged global signal of whole brain; motion-volume censoring by detecting volumes with frame-wise displacement (FD) larger than 0.5 mm, derivative variance root mean square (DVARS) after Z normalization larger than 2.3, and SD after Z normalization larger than 2.3, and scrubbing above detected (number of volume = i) and adjacent four volumes (i–2, i–1, i, i+1, i+2) (27, 28). FD is a measure of head motion from one volume to the next, and is calculated as the sum of absolute value of three translational displacements in x, y, z axis and three rotational displacements in *pitch*, *yaw*, and *roll* (units of radians), which were multiplied 50 to convert to similar units to translational displacements (27). DVARS is a measure of the change in volume intensity within a predefined gray matter (GM) mask from one volume to the next, calculated as the root mean square of the backward differentiated volumes; SD is a measure of deviation of volume intensity within the predefined GM mask. Because we were interested in the low-frequency fluctuations of resting-state fMRI signal, the aforementioned scrubbed time series were band-pass filtered (0.008–0.1 Hz) by applying a 4th-order Butterworth filter.

All the preprocessed fMRI data were registered to MNI152 2 mm template using a two-step procedure [ref. https://www.fmrib.ox.ac.uk/datasets/techrep/tr07ja2/tr07ja2.pdf]: the mean of preprocessed fMRI data were registered with a seven degrees of freedom affine transformation to its corresponding anatomical brain (FLIRT). Transformation parameters were also computed by non-linearly registering the individual brain to the MNI152 template (FNIRT). Combining the two transformations by matrix multiplication yielded transformation parameters normalizing fMRI data to standard space. All the final registered images were manually examined. Because the network analysis was voxel-wise-based, all registered images were down-sampled with linear interpolation to 6 × 6 × 6 mm^3 for decreasing computational intensity.

We used 157 healthy subjects to generate an in-house 6 × 6 × 6 gray matter template. The procedure was briefly introduced, for each subject, first skull-stripped T1-brain image was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) (FSL/FAST); second, GM was nonlinearly registered to MNI152_222 template (FSL/FNIRT); third, the 157 registered GMs were merged and averaged across subjects; the averaged GM was threshholded by 50% probability (the voxels were excluded if less than 79 subjects were covered). Final, the thresholded GM was downsampled to 6 × 6 × 6.

Quality Control

After preprocessing, fMRI data were assessed for excessive motion. The number of censored motion volumes after preprocessing reflects the extent of motion of a subject during scanning. Any subject with <120 remaining volumes was excluded, which guaranteed a minimum of 5-min-scanning images for FC analysis (29).

Brain Functional Connectivity Network and Global Graph Properties

Brain FC network that covered whole gray matter was constructed before global graph properties were computed. First, blood oxygenation level-dependent (BOLD) signal was extracted from each gray matter voxel in registered $6 \times 6 \times 6$ m^3 rs-fMRI data. Following this, a correlation matrix was generated by calculating voxel-based pairwise Pearson correlation coefficients of BOLD signals. Fisher's z transformation was applied to convert the Pearson correlation coefficient. To normalize the variation of strength of brain FC across individuals, a link density, the percentage of links with respect to the maximum number of possible links, was predetermined, which corresponds to a threshold (30, 31). In this study, 10 link densities (from 1 to 10%) were applied. Consequently, an indirectly connected brain FC network was generated after the correlation matrix was binarized by the subject-dependent threshold.

For each predetermined link density and each subject, five voxel-level graph properties were, respectively, computed using the brain connectivity toolbox (BCT) (32): "degree"—a measure of network hubness, "clustering coefficient"—a measure of network segregation, "betweenness centrality"—a measure of within-network communication, "efficiency"—a measure of network integration, and "participation coefficient"—a measure of diversity within a network.

Graph Topological Disruption Index (K_D) Comparison and Association With FMA_UE

K_D is used to measure the extent of brain functional reorganization, describing the topological changes of individual brain networks with respect to referential network topology (31), and indicating brain network property changes of a subject in some regions with the opposite trend in other regions (30, 33, 34). In this study, using brain of HCs as a normative reference, five graph topological disruption indices were computed: degree (D), betweenness centrality (BC), clustering coefficient (CC), efficiency (E), and participation coefficient (PC), and referred as K_D_D, K_D_BC, K_D_CC, K_D_E, and K_D_PC, respectively. For each graph topological disruption index, a repeated measures analysis of covariance (ANCOVA) with age and gender as covariates of no interest across all link density was performed to determine if there exists a significant difference between stroke patients (left-sided and right-sided, independently) and HCs. In addition, a Spearman correlation with age and gender as covariates was applied to examine if there exists a significant association between graph topological disruption indices and FMA_UE.

Local Degree Comparison and Association With FMA_UE

Because the five graph topological disruption indices are significantly correlated (35) and degree is an important marker of network development and resilience (32), degree was used for exploring brain FC locally. Degree map was generated from the brain FC network by counting the number of functional links on the gray matter at each voxel. To decrease the effect of motion on local FC (27), the links within two adjacent voxels were excluded. To identify voxel-wise degree differences between patients (life-sided or right-sided) and HCs, the script of *randomize* in FSL is performed to generate 5,000 permutations of the data while controlling for age and gender as confounds; family-wise correction (corrected $p = 0.05$) was applied with threshold-free cluster enhancement (TFCE) (36). In addition, for each significant cluster found earlier, we further analyzed the association between the average degree count extracted from the cluster and FMA_UE. Using the script of *fslmeants* in FSL, the mean degree count across patient groups within each significant cluster was extracted, and Spearman correlation analysis was applied to examine if there exists a significant association between degree count and FMA_UE.

Functional Connectivity Between Right Lateral Occipital Cortex (R LOC) and Other Nodes in the Subgroup of Right-Sided Stroke Patients

After R LOC was discovered as the only region in which there existed significant association between local degree count and FMA_UE in the right-sided stroke patient subgroup, to explore which regions R LOC connected to and if these regions were significantly different between right-sided stroke patients and their age- and gender-matched HCs, R LOC was used as a region of interest (ROI) to generate ROI-based degree maps for both right-sided stroke patients and HCs. To identify the difference of ROI-based degree map between right-sided stroke patients and HCs, the script of *randomize* in FSL is performed to generate 5,000 permutations of the data while controlling for age and gender as confounds; family-wise correction (corrected $p = 0.05$) was applied with threshold-free cluster enhancement (TFCE) (36).

Software

All statistical analyses were performed using MATLAB 2016a, SPSS 23 (IBM Corp. in Armonk, NY), and FSL (www.fmrib.ox.ac.uk/fsl). Brain schemas of ROI and FC network were visualized on a surface rendering of a human brain atlas with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (37).

RESULTS

Comparisons of Demographics Between Stroke Patients and HCs and Clinical Characteristics of the Patients

As shown in **Table 1**, all 57 stroke patients were diagnosed with ischemic stroke. Of the 57 patients, 29 stroke patients had a left-sided stroke and the other 28 had a right-sided stroke, there were no statistical differences in age ($p = 0.192$, 0.770) or gender ($p = 0.143$, 0.605) between patients and their corresponding HCs. A total of 17 left- and 8 right-sided stroke patients did not participate in the follow-up assessment of FMA_UE.

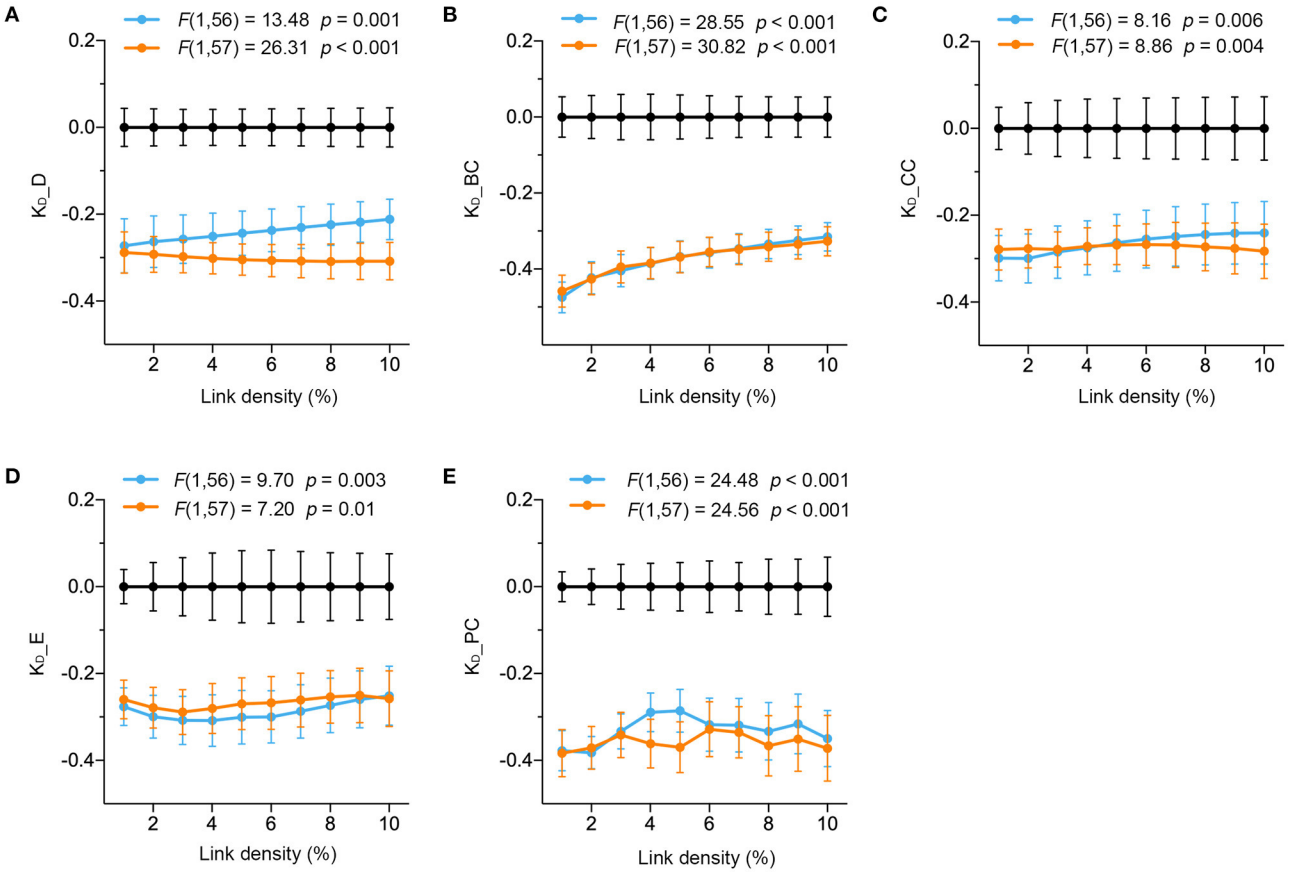

FIGURE 1 | Significantly altered global connectivity was observed in left- and right-sided stroke patients. A repeated measure ANCOVA with age and gender as covariates of no interest determined that **(A)** K_D_D [$F_{(1,57)} = 26.31$, $p < 0.001$], **(B)** K_D_BC [$F_{(1,57)} = 30.82$, $p < 0.001$], **(C)** K_D_CC [$F_{(1,57)} = 8.86$, $p = 0.004$], **(D)** K_D_E [$F_{(1,57)} = 7.20$, $p = 0.01$] and **(E)** K_D_PC [$F_{(1,57)} = 24.56$, $p < 0.001$] of left-sided stroke patients (orange) and **(A)** K_D_D [$F_{(1,56)} = 13.48$, $p = 0.001$], **(B)** K_D_BC [$F_{(1,56)} = 28.55$, $p < 0.001$], **(C)** K_D_CC [$F_{(1,56)} = 8.16$, $p = 0.006$], **(D)** K_D_E [$F_{(1,56)} = 9.70$, $p = 0.003$] and **(E)** K_D_PC [$F_{(1,56)} = 24.48$, $p < 0.001$] of right-sided stroke patients (cyan) significantly decreased compared to HCs across all link densities. Data plotted as mean ± SE.

Significantly Disrupted Global Brain Connectivity in Stroke Patients

A repeated measures ANCOVA with age and gender as covariates of no interest determined that significant global altered connectivity was observed in stroke patients. All five graph topological disruption indexes of the left-sided stroke patients statistically significantly decreased compared to HCs across all link densities (from 1 to 10%) (see **Figure 1**, orange). The same significant decrease was also observed in the right-sided stroke patients (see **Figure 1**, cyan). Therefore, we may conclude that global brain connectivity in both right- and left-sided stroke patients was significantly disrupted compared with that in HCs. However, across all the link densities, these five disruption indexes were not significantly associated with baseline FMA_UE for both right- and left-sided stroke patients (see **Table 2**), indicating that none of the global disruption indexes are promising predictors of motor impairment after stroke.

TABLE 2 | No significant correlations between the 5 disruption indexes in 2 subgroups and baseline FMA_UE at link density = 10%.

	K_D_D	K_D_BC	K_D_CC	K_D_E	K_D_PC
Left_sided					
R	−0.091	0.042	0.032	−0.088	0.228
p-value	0.651	0.835	0.876	0.661	0.254
Right_sided					
R	0.202	−0.035	0.111	0.130	−0.056
p-value	0.321	0.867	0.588	0.525	0.785

K_D_D, disruption index of degree; K_D_BC, of betweenness centrality; K_D_CC, of clustering coefficient; K_D_E, of efficiency; K_D_PC, of participation coefficient.

Significantly Altered Local Connectivity in Stroke Patients

In addition to the global connectivity alteration observed in stroke patients, we also found altered local connectivity measured by degree in stroke patients. Compared with HCs, patients with

TABLE 3 | Brain regions with significant local degree differences between stroke patients and HCs.

Brain regions	MNI coordinates			Cluster size (mm^3)	$t_{(59)}$-value	*p*-value
	X	Y	Z			
(A) Brain regions with significant local degree differences between left-sided patients and HCs at 10% link density						
Stroke Patients > HCs						
Left precentral gyrus	−42	−6	36	1,296	4.12	**< 0.001**
Right amygdala	30	0	−24	864	4.17	**< 0.001**
Stroke Patients < HCs						
Left precuneous cortex	0	−60	42	9,504	4.25	**< 0.001**
Right lateral occipital cortex‡	18	−84	42	3,240	4.77	**< 0.001**
Right supramarginal gyrus‡	60	−42	36	2,808	4.42	**< 0.001**
Left occipital pole‡	−18	−90	36	1,944	4.29	**< 0.001**
Right lateral occipital cortex‡	60	−66	0	1,080	3.90	**< 0.001**
Left lateral occipital cortex	−48	−78	6	648	3.64	**< 0.001**
$t_{(59)}$: 59 represents degree of freedom. ‡: overlapped region with that from right-sided patients						
(B) Brain regions with significant local degree differences between right-sided patients and HCs at 10% link density						
Stroke Patients > HCs						
Left precentral gyrus	−12	−30	48	1,512	4.77	**<0.001**
Right inferior frontal gyrus	48	18	18	864	3.19	**0.002**
Left superior temporal gyrus	−60	−18	0	648	4.38	**<0.001**
Left inferior frontal gyrus	−42	18	12	648	3.95	**<0.001**
Stroke Patients < HCs						
Right occipital pole‡	24	−90	36	6,264	4.49	**<0.001**
Right supramarginal gyrus‡	66	−30	30	3,024	4.09	**<0.001**
Right lateral occipital cortex‡	60	−66	6	2,592	4.65	**<0.001**
Left lateral occipital cortex‡	−18	−84	24	864	3.30	**0.002**

$t_{(58)}$, 58 represents degree of freedom; ‡Overlapped region with that from left-sided patients. Bold values of p-value represents statistically significance ($p < 0.05$).

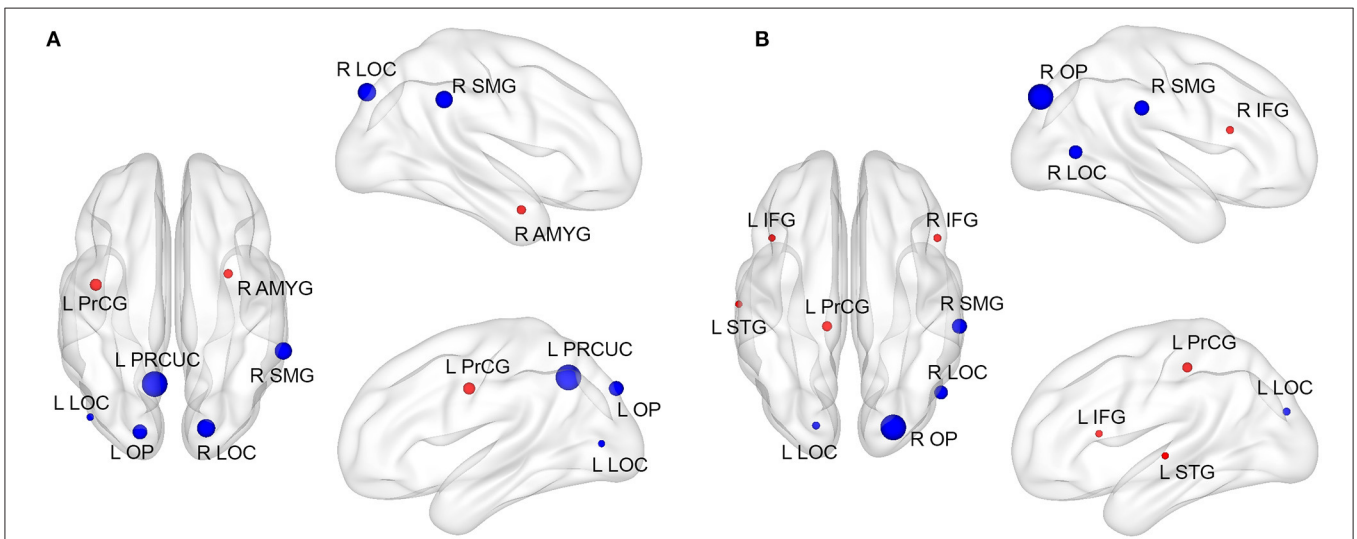

FIGURE 2 | Significant local altered connectivity was observed in left- and right-sided stroke patients. Compared with HCs, the location and cluster size of regions with increased (red) and decreased (blue) local degree was depicted in **(A)** for the left-sided stroke patients, **(B)** for right-sided stroke patients. Red and blue nodes represented where nodal degree of stroke patients was greater and less than HCs, respectively. The size of the node represents cluster size. Significant level was set at $p < 0.05$ after multiple comparison corrections.

left-sided stroke exhibited significantly increased nodal degree in the left precentral gyrus (L PrCG) and right amygdala (R AMYG), and the decreased nodal degree in the left precuneous cortex (L PRCUC), right supramarginal gyrus (R SMG), left occipital pole (LOP), right lateral occipital cortex (R LOC), and L LOC (**Table 3A**; **Figure 2A**). Patients with right-side stroke

showed significantly increased nodal degree in the L PrCG, right inferior frontal gyrus (R IFG), left superior temporal gyrus (L STG) and L IFG, and the decreased nodal degree in the right occipital pole (R OP), R SMG, R LOC, and L LOC (**Table 3B**; **Figure 2B**).

Degree in R LOC Was Associated With Baseline FMA_UE and Predicted the Extent of Motion Recovery in the Right-Sided Stroke Patients

We further analyzed the associations between the local degree count extracted from significant brain regions (**Table 2B**; **Figure 3**) in both left- and right-sided stroke patients and their baseline FMA_UEs. Only R LOC in the group of the right-sided stroke patient was significant after a Bonferroni correction ($p_{\text{Bonferroni}} = 0.006$) ($\rho = -0.861$, $p < 0.001$, **Figure 3A**). Moreover, the degree in R LOC was able to predict rFMA_UE, the extent of upper extremity recovery after rehabilitation ($\rho = 0.691$, $p = 0.001$, **Figure 3B**).

ROI-Based FC Analysis Revealed Regions With Significantly Different FC in Right-Sided Stroke Patients

By using R LOC as an ROI, the region in which local degree alteration was associated with motor performance, an ROI-based FC analysis revealed regions with significantly different FC in right-sided stroke patients compared with HCs. The regions with increased degree connectivity to R LOC were L PRCUC, right middle frontal gyrus (R MFG), and left middle frontal gyrus (L MFG). The regions with decreased degree connectivity to R LOC are the left supplementary motor cortex (L SMA), left postcentral gyrus (L PoCG), R SMG, R PrCG, and right superior frontal gyrus (R SFG) (**Figure 4**). The detailed MNI coordinates and the cluster size are listed in **Table 4**.

DISCUSSION

A key theoretical and clinical question of interest is the nature of any topological abnormalities in the brain network organization of stroke patients which might relate to their motor performance; assessing this would shed light on which aspects of normal brain network organization might be critical for upper limb motor recovery.

In this study, we applied graph-based theoretical approaches to rs-fMRI to analyze the brain functional connectome topology in subacute ischemic stroke compared with HCs. Our main findings are summarized as follows: (1) at the global level, using brain of HC as a normative reference, there exists significantly disrupted global brain connectivity in subacute stroke patients compared with HCs, but no correlation between global disruption indexes and clinical measurements was found; (2) at the local nodal level, by measuring degree, significant local degree differences between stroke patients and HCs were found, among which baseline FMA_UE and rFMA_UE were significantly correlated to the degree count in R LOC in right-sided stroke patients.

We found that whole-brain network structure of the stroke patients was altered, regardless of stroke site. Graph disruption indices derived from five network topological measurements, degree, clustering coefficient, participation coefficient, betweenness centrality and efficiency, which, respectively, represent network hubness, segregation, diversity, within-network communication, and integration, were significantly decreased compared with HCs across all predefined link densities in two subgroups. The results, in accord with findings of Termenon et al. (33) of significantly lower K_D in the contralesional hemispheres of brain networks of the patients, indicates that stroke-induced whole brain reorganization, suggesting that FC and other network properties vary in the certain regions at the subacute stage. The failure to observe any significant association between global hub disruption and FMA_UE across two subgroups reveals that although global hub disruption is a more reliable and sensitive metric than graph metrics to detect brain reorganization (33), it is not a biomarker to predict the motor dysfunction caused by stroke at the subacute stage, which implies that the clinical measurement reflecting motor dysfunction might only be related to brain reorganization within brain network(s) rather than whole brain reorganization.

We found that local-brain network structure of stroke patients was altered in terms of degree compared with HCs. From data shown in **Figure 2**, we conclude that the local altered regions were not identical across two subgroups. In general, the increased degree was mainly located in the temporal and frontal lobes, decreased in the occipital lobe, and altered regions were located not only in the hemisphere of the lesion, but also in the contralesional hemisphere. These findings might reflect the overall impact of local lesions on the long-distance functional connective area and indicate that the visual, motor, emotional, language processing, and cognitive processes of patients with subacute ischemic stroke were damaged or at least degraded.

The right-sided stroke patients, where the degree extracted from degree-altered regions was significantly correlated to the upper extremity motor function, showed significantly decreased degree in the occipital cortex and right supramarginal gurus, and increased degree mainly in the L PrCG, R IFG, L STG, and L IFG (see **Figure 2B**; **Table 3B**). The observation of decrement of degree in the occipital cortex is consistent with findings in patients with transient ischemic attack (TIA) (38) and ischemic stroke patients (39), as this region is a part of the visual dorsal stream and is involved in object localization (40). The right-sided stroke patients with more severe paralysis (lower FMA_UE) had more FC in the R-LOC (**Figure 3A**), which could be attributed to functional compensation after the onset of stroke (41). Similarly, for the regions with increased degree, previous studies have demonstrated that altered organization of connectivity in the middle frontal gyrus in patients with subcortical stroke reflected the role of the frontal lobe in higher-order movement planning (42, 43), as the frontal lobe is associated with the multiple forms of olfaction and higher-order cognition, including working memory, inhibitory control, conflict monitoring, and shifting between rule sets (44), and that the L PrCG is in the sensorimotor network (SMN), a network with multifunctional characteristics and vulnerable not only to neurodegenerative diseases, but also to

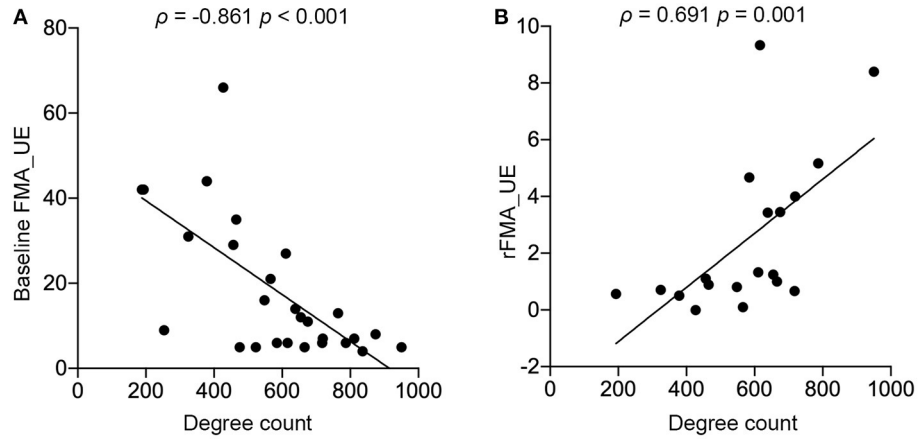

FIGURE 3 | Significant associations between degree and upper extremity motor performance were discovered in R LOC in the right-sided stroke patients. **(A)** Baseline FMA_UE scores significantly correlated to local degree in R LOC; **(B)** rFMA_UE significantly correlated to local degree in R LOC.

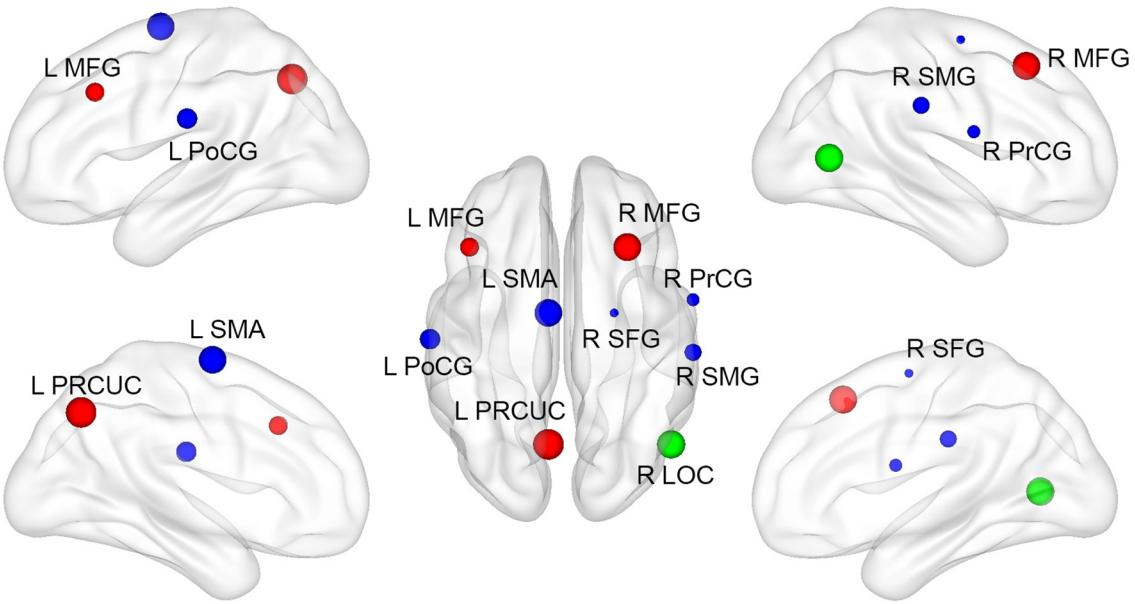

FIGURE 4 | Regions with significantly different ROI-based functional connectivity in right-sided stroke patients. Compared to HCs, the location and cluster size of regions with significantly different R LOC-based functional connectivity. Red and blue nodes represent those regions of which functional connections were greater and less than HCs, respectively. The green node represents the seed ROI (R LOC).

cerebrovascular diseases (45, 46). The compensatory mechanism for motor impairment might contribute to this degree increment. However, we did not observe the same associations in the left-sided stroke patients. One of the possible reasons might be that left- and right-side stroke patients have significantly different topological properties (47, 48). Left-lateralization in the language process (49) and the left hemisphere being the dominant hemisphere of right-handers might result in the left-side stroke patients having more complex FC changes poststroke.

Our finding that the degree extracted from the R LOC region was significantly associated with upper extremity motor recovery [i.e., right-sided stroke patients with more severe paralysis had more potential to benefit from the compensatory mechanism, leading to a higher chance of FC in R LOC after 15 weeks rehabilitation (**Figure 3B**)], assists our understanding of the importance of eyehand coordination in the rehabilitation of upper limb motor function. The R LOC is part of the visual cortex (40) that connects with the amygdala, hippocampus, and *via* intrathalamic pathways with mediofrontal areas (50). The R LOC also receives top–down modulation from frontal and parietal areas in relation to visual attention (51). Previous studies indicate visual feedback can enhance motor function

TABLE 4 | Brain regions with significant differences in R LOC functional connectivity between right-sided stroke patients and HCs.

	MNI coordinates			Cluster size (mm^3)	$t_{(58)}$-value	*p*-value
	X	Y	Z			
Stroke Patients > HCs						
Left precuneus	−6	−66	42	8,640	4.19	**<0.001**
Right middle frontal gyrus	30	24	48	6,264	5.64	**<0.001**
Left middle frontal gyrus	−42	24	36	2,160	3.57	**<0.001**
Stroke Patients < HCs						
Left supplementary motor cortex	−6	−6	66	6,048	3.53	**<0.001**
Left postcentral gyrus	−60	−18	24	2,592	4.51	**<0.001**
Right supramarginal gyrus	66	−24	30	1,728	4.03	**<0.001**
Right precentral gyrus	60	0	18	1,080	4.07	**<0.001**
Right superior frontal gyrus	24	−6	60	648	3.30	**0.002**

Bold values of p-value represents statistically significance ($p < 0.05$).

(52, 53) so that during rehabilitation, dependence on visual feedback increases (54, 55) and viewing motion stimuli leads to activity increases in regions of the extrastriate visual cortex (56). Moreover, multimodal fMRI experiments in (57) revealed that passive touch significantly activated the object selective parts of LOC and that the coupling was specific to hand and shoulder stimulation, suggesting that LOC is functionally connected to the hand area of primary somatosensory. While our data cannot provide causality direction between R LOC and upper extremity motor recovery, thereby preventing us from identifying it as a sure brain region to target for treatment, together, these findings, and the previous finding point to the R LOC as an important region to further probe for intervention methods of poststroke motor rehabilitation.

By virtue of an R LOC-based FC analysis, we identified the regions that connected to R LOC and the degree extracted from which was significantly increased compared to HCs at the subacute stage poststroke, left PRCUC and left and right MFG, and the regions with decreased connectivity, L SMA, L PoCG, R SMG, R PrCG, and R SFG. These regions correlated with the motor recovery after stroke (20, 58, 59). Combined with the discovery that the more the degree was extracted from the R LOC, the better motor function recovery the patient demonstrated, these widespread regions in both hemispheres might provide subacute stroke patients with a motor compensation mechanism after the onset of stroke.

There are limitations in this study. First, in our study, 74 and 54% of patients had hypertension, and diabetes, respectively, so variances in brain structure and function caused by hypertension (60), diabetes (61), and stroke are difficult to delineate. In the future, we will have a cross-sectional study on the differences between groups of stroke patients with and without hypertension and diabetes. Second, participants were not divided into groups according to the severity of motor dysfunction. Third, our sample size of 28 right-sided stroke patients is relatively small; future work will include a larger cohort of patients; and focus on the analysis of longitudinal changes in brain regions critical to stroke outcomes captured through brain functional topological properties. Fourth, we did not collect fMRI data during the follow-up period, and thus cannot detect how brain networks reorganize as stroke continues to evolve. Fifth, we did not collect language-related measurements, which prevented us from further investigating why left- and right-sided stroke patients had different associations between the degree extracted from R LOC and the upper extremity motor recovery.

CONCLUSIONS

In conclusion, the five global graph topological disruption indices of stroke patients were significantly decreased in two subgroups compared with HCs. Correlation analysis revealed that these global disruption indices were not significantly associated with FMA_UE. Local brain FC in terms of degree was explored and it was found that local brain network structure of the stroke patients was altered and significant associations between region degree and upper extremity motor functional recovery were observed in R LOC in the subgroup of right-sided stroke patients. These findings suggest that the topological properties of functional brain networks may provide prognostic value for motor functional recovery after stroke.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SJ, LH, and QH contributed to conception and study design. WT, DL, YC, YJ, and LF contributed to acquisition of data. QH, LH, SH, and BW analyzed functional images and statistical analysis. LH and QH drafted and edited the manuscript. All authors approved the final manuscript version to be published.

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Functional Remodeling Associated With Language Recovery After Repetitive Transcranial Magnetic Stimulation in Chronic Aphasic Stroke

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Background: Repetitive transcranial magnetic stimulation (rTMS) has shown promising efficacy in improving the language functions in poststroke aphasia. However, randomized controlled trials were lacking to investigate the rTMS-related neuroimaging changes underlying the therapeutic effects on language improvement in chronic aphasia.

Objective: In this study, we aimed to evaluate the effects of low-frequency rTMS (LF-rTMS) on chronic poststroke aphasia. We hypothesized that the deactivation of the right pars triangularis could restore the balance of interhemispheric inhibition and, hence, facilitated the functional remodeling of language networks in both the hemispheres. Furthermore, the rTMS-induced functional reorganization should underpin the language recovery after rTMS.

Methods: A total of 33 patients (22 males; age: 58.70 ± 13.77 years) with chronic stroke in the left hemisphere and nonfluent aphasia were recruited in this randomized double-blinded study. The ratio of randomization between the rTMS and sham groups is 17:16. All the patients received real 1-Hz rTMS or sham stimulation (placebo coil delivered < 5% of magnetic output with similar audible click-on discharge) at the right posterior pars triangularis for 10 consecutive weekdays (stroke onset to the first stimulation: 10.97 ± 10.35 months). Functional connectivity of language networks measured by resting-state fMRI was calculated and correlated to the scores of the Concise Chinese Aphasia Test by using the stepwise regression analysis.

Results: After LF-rTMS intervention, significant improvement in language functions in terms of comprehension and expression abilities was observed compared with the sham group. The rTMS group showed a significant decrease of coupling strength between right pars triangularis and pars opercularis with a strengthened connection between right pars orbitalis and angular gyrus. Furthermore, the LF-rTMS significantly enhanced the coupling strength associated with left Wernicke area. Results of regression analysis showed that the identified functional remodeling involving both the hemispheres could support and predict the language recovery after LF-rTMS treatment.

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Conclusion: We reported the therapeutic effects of LF-rTMS and corresponding functional remodeling in chronic poststroke aphasia. Our results provided neuroimage evidence reflecting the rebalance of interhemispheric inhibition induced by LF-rTMS, which could facilitate future research in the refinement of rTMS protocol to optimize the neuromodulation efficacy and benefit the clinical management of patients with stroke.

Keywords: aphasia, stroke, repetitive transcranial magnetic stimulation, fMRI, functional connectivity

INTRODUCTION

Poststroke nonfluent aphasia is characterized by a disabling linguistic output resulting from the damage of language-related circuits in the brain. Patients with this condition have difficulty in performing basic communication tasks and recovering previous daily status (1). Studies have demonstrated the promising efficacy of repetitive transcranial magnetic stimulation (rTMS) as a non-invasive neuromodulatory intervention to treat stroke-related aphasia (2, 3). According to the rationale of paradoxical functional facilitation and the theory of interhemispheric imbalance in poststroke recovery, many randomized controlled studies have reported that the application of an inhibitory low-frequency rTMS (LF-rTMS) protocol over the contralesional homologous Broca area results in substantial language improvement (4–11). This finding provides an alternative option for patients with chronic aphasic who have less spontaneous recovery in the subacute phase.

Neuroplasticity associated with language recovery after aphasic stroke involves both the left and right hemispheres (12, 13). However, the roles of left and right hemispheres in language recovery have been under debate for decades (14). Previous studies revealed that the overactivation of the right pars triangularis impeded language performance after a stroke involving the left inferior frontal gyrus (5, 7, 14). A task functional MRI (fMRI) study of six patients with chronic poststroke aphasia found that the naming improvement after LF-rTMS treatment in chronic was correlated with remodeling of functional activation in bilateral networks (15). Increased activations in the left hemisphere, including the medial frontal, cingulate, supplementary motor, and fusiform gyrus areas, were observed during the naming task after the LF-rTMS treatment. However, the activation of the right pars triangularis (target of LF-rTMS) shifted to the right pars opercularis during the naming task (15). A meta-analysis study further concluded that the activation of perilesional and spared language areas in the left hemisphere facilitated the naming performance, whereas the activation of right language areas impeded the naming performance (16). However, the functional reorganization involves both the hemispheres after the inhibitory LF-rTMS remains inconclusive because of the lack of randomized controlled trials (RCTs). Therefore, a formal RCT with neuroimaging assessment is required to determine bilateral and intercortical changes after the rTMS treatment to elucidate the relationship between the network reorganization and language improvement in patients with aphasic stroke.

Resting-state fMRI (rs-fMRI) has been widely used to provide evidence of functional changes after stroke. Unlike task-based fMRI methods, rs-fMRI measures the intrinsic fluctuation of brain activities and provides a more flexible approach to investigate functional networks (17). Recent evidence indicates that aphasia is a network disorder with extensive involvement of altered functional connectivity (FC) rather than local damage caused by stroke (18). Accordingly, rs-fMRI analysis may help to comprehensively evaluate the disruption of language networks after stroke and remodeling with recovery. Several functional studies have reported that the secondary language circuits, including left spared cortices, perilesional tissues, and right homologous areas, might take over the language function after the primary language cortices are damaged (19, 20). The temporal shift of resting-state hemodynamic profiles may correspond to language performance after stroke (21). Moreover, lesion distribution may influence network remodeling and language performance after a stroke (19, 21). However, no RCT has evaluated the functional reorganization of language networks by using rs-fMRI after LF-rTMS treatment in patients with chronic poststroke aphasia.

In this RCT, we evaluated the therapeutic effects of LF-rTMS and associated functional remodeling in patients with chronic poststroke aphasia. Patients were randomly allocated to the rTMS or sham groups. We hypothesized that the deactivation of the right pars triangularis would restore the balance of interhemispheric inhibition, thus facilitating the functional remodeling of language networks in both the brain hemispheres. Furthermore, we anticipated that the rTMS-induced functional reorganization, which involves FC enhancement in the left hemisphere and corresponding modulation in the right hemisphere, could support language recovery after rTMS. Considering the predominant lateralization of language functions and aphasia as a network disorder, we investigated the modulation of the bilateral networks and effects on language improvement relevant to treatment-induced recovery.

MATERIALS AND METHODS

Participants

A total of 54 patients who had chronic left hemispheric stroke with nonfluent aphasia and who were admitted to the stroke unit of a tertiary Medical Center were evaluated. The final cohort, including 33 patients with Chinese as their first language, was selected based on the following inclusion criteria: (1) a first ischemic stroke affecting the left territory of the middle cerebral artery as confirmed through MRI; (2) at least 3 months after

stroke onset; (3) no history of dementia, affective disorders, or other neurodegenerative diseases; and (4) absence of rTMS contraindications. Nonfluent aphasia is characterized by anomia, short phrase length (0–5 words per breath unit), with or without auditory comprehension, or repetition impairment (22). Phrase length is defined as the average of the three longest meaningful utterances produced when a picture scene is described [e.g., "Cookie theft" in the Concise Chinese Aphasia Test (CCAT)] or when responding to an open-ended question. All the participants provided a written informed consent prior to study participation and the study protocol was in accordance with the 2008 Declaration of Helsinki and approved by the local institutional review board. This clinical trial was preregistered with the identifier of NCT03059225 (https://clinicaltrials.gov/ct2/show/NCT03059225). All the patients were right-handed and had scores of > 90 in the Edinburgh Inventory (23). **Figure 1** presents the lesion distribution of the 33 recruited patients.

The enrolled patients were randomly allocated into one of the study groups (**Figure 2**) and either treated with inhibitory 1-Hz LF-rTMS on the contralesional pars triangularis (rTMS group, $n = 17$) for 10 daily sessions or untreated (sham group, $n = 16$). **Table 1** presents the demographics and clinical assessment results of enrolled patients. No significant differences in age ($p = 0.086$, two sample t-test), sex ($p = 0.805$, chi-square test), and pretreatment language performance measured by the CCAT ($p = 0.203$, two sample t-test) were observed between the rTMS and sham groups. All the statistical analyses were performed by using the statistics toolbox in MATLAB R2020 environment.

Protocol for rTMS

We performed rTMS by using Magstim Rapid^2 (Magstim Company, Withland, Dyfed, UK) with a 70-mm figure-of-eight coil. A Dantec keypoint electromyograph (Dantec, Skovlunde, Denmark, UK) was connected to the stimulator to record the motor-evoked potentials (MEPs) of the left first dorsal interosseous muscle. We recorded MEPs by using surface Ag/AgCl electrodes, probing the resting motor threshold (rMT) on a 9 cm × 9 cm grid over the motor cortex in the frontal area. The amplified (100 μV−1 mV/div) and bandpass-filtered (20–2,000 Hz) signals were digitized at a sampling rate of 20 kHz. Subsequently, rMT was defined as the minimum intensity at which MEPs with amplitudes of at least 50 μV could be elicited in half of the 10 consecutive trials. 3T-MRI revealed that the target area of the right posterior pars triangularis was located on the rostral part of the vertical ascending ramus of the Sylvian fissure and on the caudal part of the triangular gyrus (6, 24). Studies have indicated that the optimal stimulation location of LF-rTMS is the right posterior pars triangularis with the highest naming performance after suppression (4, 25). A frameless stereotaxic system (Brainsight, Rogue Research, Montreal, Canada) was used to coregister the stimulation target in relation to the anatomical marks of a patient's head on a real-time feedback presentation system. The employed neuronavigational system was precise to the millimeter level to locate the rTMS coil at the posterior pars triangularis (26). We applied 1-Hz LF-rTMS trains at 90% of rMT to the contralesional pars triangularis for 15 min (900 pulses) *per session*. The applied stimulation protocol was mainly based on studies by Naeser et al. (4, 5).

The stimulation protocol for the sham group was identical to that of the rTMS group, except that a placebo coil (Magstim) was used for the sham stimulation; in this approach, < 5% of the magnetic output was delivered and minimal scalp current sensation was induced. The placebo coil was identical in shape and size to the real stimulation coil and produced the same audible click on discharge as the real coil. Because none of the patients had ever undergone rTMS, they could not identify whether the stimulation was real or sham. During the initial assessment for rMT, we also used the sham coil to provide a consistent sensation as during the treatment sessions. Each patient alternately received intervention in a separate room at an appointed time to avoid conversation. Intervention for both the groups consisted of 10 daily sessions (from Monday to Friday for 2 weeks) by another TMS operator different from the one who assessed the rMT. The TMS operator was blinded to patient grouping. At the end of the first and final treatment, patients were asked to state whether they could tell if the treatment they were receiving was a real or sham stimulation. All the patients reported that they could not differentiate the type of stimulation at both the time points.

No accompanying language rehabilitation training was performed during the rTMS intervention in either the rTMS or sham groups. All the participants underwent a 40-min training program by a speech-language pathologist, who was blinded to patient grouping. The training program was performed 10 min after the rTMS intervention on Monday (once a week). The training program emphasized verbal expressive skills, including repetition, phonemic training, semantic training, naming, conversation, picture description tasks, and phrase-generation tasks.

Language Assessment

A blinded speech and language therapist determined the language performance before and after rTMS intervention by using the CCAT (27), which was at that time the only validated Chinese aphasic assessment tool. It comprised nine subtests: simple response, expository speech, matching, auditory comprehension, naming, reading comprehension, repetition, copying, and spontaneous writing. Each item was scored from 0 to 12 and all the subtest points were averaged to obtain the total CCAT score. Two more composite scores −4-expression (calculated as the sum of the scores for simple response, expository speech, naming, and imitation writing) and 3-comprehension (calculated as the sum of the scores for matching, auditory comprehension, and reading comprehension)—were also acquired.

A paired t-test was used to assess the time effects on the 12 items of the CCAT (including total score and two composite scores) within each group and a two-sample t-test was used to identify the significant difference of change scores (post- and pre- assessment) between the rTMS and sham groups. Cohen's d, i.e., the standardized mean difference, was further calculated

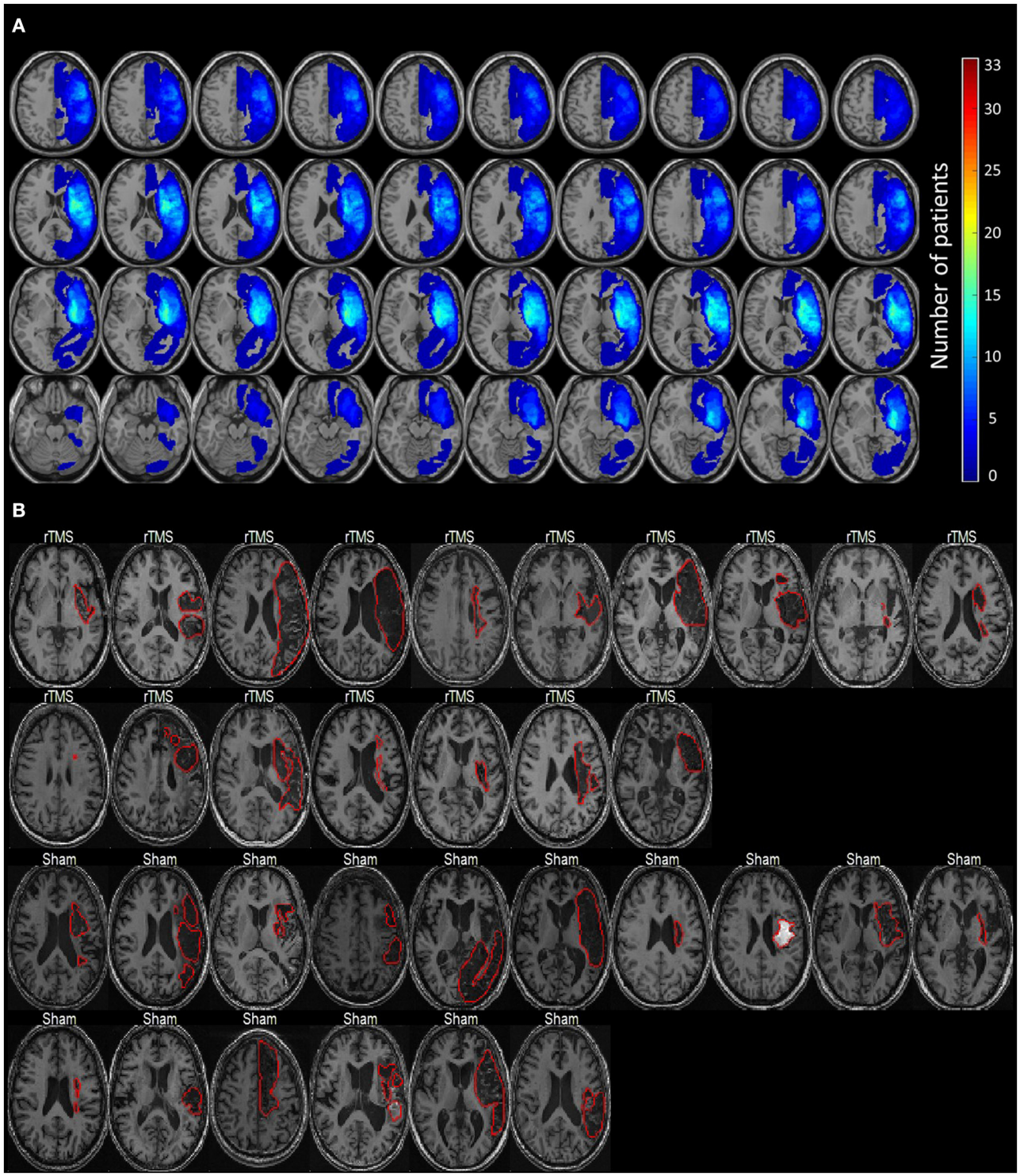

FIGURE 1 | The lesion distribution of the study cohort. **(A)** The overlapping maps of lesion distribution among 33 patients. **(B)** The individual lesion pattern of each patient (delineated by the red contours). Lesions are all located in the left hemisphere.

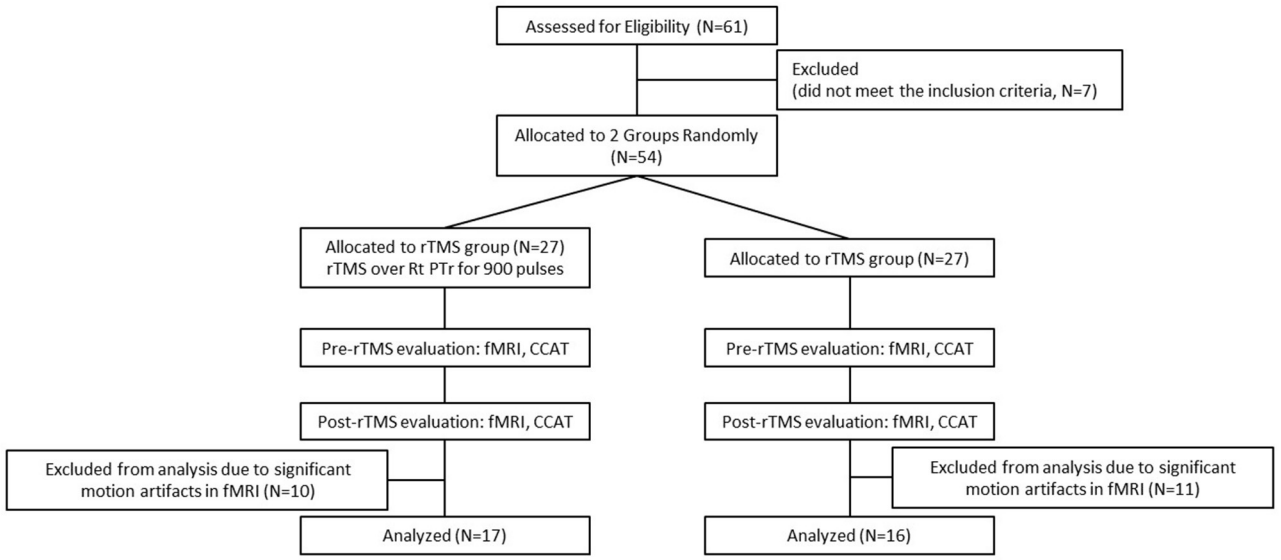

FIGURE 2 | Flowchart of patient inclusion.

TABLE 1 | Demographic data and clinical assessment of all the subjects.

	rTMS group (n = 17)	Sham group (n = 16)	P-values
Age	54.71 ± 12.03	62.94 ± 14.59	0.086
Gender (M:F)	11:6	11:5	0.805
Scores of concise chinese aphasia test	7.65 ± 2.39	6.61 ± 2.18	0.203
Months post-stroke	9.41 ± 7.27	12.63 ± 12.90	0.381

to estimate the effect size (28).

$$d = \frac{M_{rTMS} - M_{Sham}}{\sqrt{\left({S_{rTMS}}^2 + {S_{Sham}}^2\right)/2}} \times \left(\frac{N-3}{N-2.25}\right) \times \sqrt{\frac{N-2}{N}} \quad (1)$$

where M_{rTMS} and M_{Sham} are the means of the rTMS and sham groups, respectively, and S_{rTMS} and S_{Sham} are the SDs of the rTMS and sham groups, respectively. Considering the sample size (N) of this study was relatively small, we applied the last two terms of the equation to adjust the Cohen's d ($N = 33$ in this study) (28).

Analysis of Resting-State FC

Magnetic resonance imaging data, including three-dimensional fast spoiled gradient recalled acquisition in the steady state (3D-FSPGR) T1-weighted images [repetition time/echo time (TR/TE): 9.4/4.0 ms and voxel size: 1.0 mm × 1.0 mm × 1.0 mm] and blood oxygenation-level dependent (BOLD) rs-fMRI images (TR/TE: 2,500/30 ms, voxel size: 3.5 mm × 3.5 mm × 3.5 mm, 200 volumes, and eye closed) were acquired on a 3T MRI scanner (GE Discovery MR750) by using an 8-channel head coil. Each patient received two MRI scans before and after the treatment to evaluate the changes in brain functional networks. The average duration between pre- and post- treatment MRI was 25.67 ± 20.89 days based on the scanner and patient's schedule (the rTMS treatment took 2 weeks). The fMRI data were preprocessed based on the standard procedures (29). The average BOLD signals were calculated from the 32 selected language areas (**Supplementary Table S1**) with a bandpass filter (0.01–0.1 Hz) followed by the calculation of Pearson's correlation coefficients between any pair of language areas. The r-to-z Fisher transformation was applied to ensure the normal distribution. The overlapping rates between selected language areas (excluding cerebellar regions) and stroke lesions are given in **Supplementary Figure S1**. We categorized the changes in FC after treatment into two conditions, namely, increase of coupling strength (including increase in synchronization and increase in antisynchronization) and decrease of coupling strength (including loss of synchronization and loss of antisynchronization) (**Supplementary Table S2**). We would emphasize that increase of synchronization (commonly observed in short-distance or homologous FCs) or antisynchronization (commonly found in long-distance FCs) both represents a stronger coupling strength (30). The language networks were separately examined in the following connectivity sets: (1) FCs in the left (ipsilesional) hemisphere, (2) FCs in the right (contralesional) hemisphere, and (3) interhemispheric FCs (including FCs between homologous regions and between cortical regions to the contralateral cerebellum based on the previous studies (31–33).

For comparing posttreatment and pretreatment FCs for each group (intragroup test), a paired t-test was conducted to examine the time effect. The significance of FC changes with control of family-wise errors was examined by using the following procedures (34). First, the FCs with $p < 0.05$ according to

the t-test results were initially filtered out and regarded as the potential differential expressed networks between conditions in each connectivity set. Second, the candidate networks were assessed by using permutation testing to control family-wise errors. We shuffled the time/group labels for each patient 5,000 times and calculated p-values of the candidate networks by using t-tests at each shuffling t. The combined/representative p-value of the candidate network was calculated by using Fisher's method (35). We denoted the combined p-value at shuffling t as p_t and that without any permutation (original labeling) as p_0. Finally, the permutation p-value was calculated by dividing the number of p_t that was smaller than p_0 by the total shuffling time ($T = 5{,}000$) and permutation $p = \#(p_t < p_0)/T$. FC changes were considered significant if permutation $p < 0.001$.

For intergroup comparison, a two-sample t-test ($p < 0.05$) was first applied to identify the significant difference of coupling strength changes (post-FCs and pre-FCs). We further performed a one-way multivariate ANOVA (MANOVA) ($p < 0.05$) to investigate whether the significant difference of coupling strength changes could be identified between the two groups by considering the brain as an integrated network (36). Detailed descriptions of fMRI acquisition, imaging preprocessing, and statistical analyses are provided in the **Supplementary Materials**.

Stepwise Linear Regression Analysis Between Language Improvement and Altered FCs

We further performed stepwise linear regression analysis to investigate the relationship between the altered functional networks and language improvement in the rTMS group (37). Considering that the connectivity within the language network may interact mutually and jointly influence the language abilities, the multivariate regression analysis that could model the relationship between multiple independent variables (multiple FCs in this case) and the dependent variable (the CCAT score) was applied. Only the change score (post and pre) of each significantly improved CCAT item was used as the dependent variable (response) and the change scores of significantly altered FCs were input as independent variables into the linear regression analysis. The performance of generated linear regression models was evaluated by the goodness-of-fit (based on R-square, R^2) and F statistic vs. a constant model (with $p < 0.05$ as significance). The influence of each dependent variable (i.e., the change score of FC) on the prediction of language improvement was considered significant if $p < 0.05$.

RESULTS

Language Performance

The changes in the CCAT scores were obtained by subtracting the pretreatment assessment scores from the posttreatment assessment scores. Results of the t-test revealed that the improvements in total CCAT ($P < 0.001$, $d = 1.564$), auditory comprehension ($P = 0.027$, $d = 0.767$), naming ($P = 0.003$, $d = 1.049$), imitation writing ($P = 0.038$, $d = 0.721$), 4-expression ($P = 0.008$, $d = 0.938$), and 3-comprehension ($P = 0.045$, $d = 0.730$) were significantly greater in the rTMS group than that in the sham group (**Table 2**). In Sections Alterations of Resting-state Functional Network After LF-rTMS and Regression Analysis Between Altered FCs and Language Improvement, we focus on unraveling the changes of FCs and their relationships with the language improvement after LF-rTMS treatment.

Alterations of Resting-State Functional Network After LF-rTMS

Based on the intragroup and intergroup tests, we identified a language subnetwork with the significant difference ($p = 0.018$, MANOVA) of functional remodeling between the rTMS and sham groups (**Figure 3**). The identified functional remodeling involved coupling strength changes of 11 FCs ($p < 0.05$, intergroup two-sample test, **Supplementary Table S4**) within left and right hemispheres. In the right hemisphere, the rTMS group showed a significant decrease of coupling strength between right pars triangularis and pars opercularis, whereas the sham group presented an increase of this connectivity. We also noticed that strengthened connections between right pars orbitalis and angular gyrus and between right superior temporal gyrus and caudate were presented in the rTMS group. In the left hemisphere, several connectivities associated with the Wernicke area (superior temporal gyrus) from the pars orbitalis and angular gyrus significantly increased coupling strength after the rTMS treatment compared to the sham group.

Regression Analysis Between Altered FCs and Language Improvement

Among the six CCAT items with significant improvement in the rTMS group compared to the sham group (as listed in **Table 2**), stepwise regression analysis showed that four of them (including auditory comprehension, total score, 4-expression, and 3-comprehension) could be predicted by the change score of FCs. Specifically, the fitting performance of regression models for the auditory comprehension, 4-expression, and total score all achieved $R^2 > 0.729$ and $p < 0.023$ (**Figures 4A–C**). For the 3-comprehension, the regression models showed $R^2 = 0.518$ and $p = 0.028$ (**Figure 4D**). **Figure 4** demonstrates that the predicted change scores of the CCAT items (ΔCCAT) based on the FC changes are consistent with the measured/actual CCAT change scores (the data points in **Figure 4** locate around the dashed diagonal lines). The detailed fitting coefficients and corresponding p-values for each FC are given in **Supplementary Table S5**. All the significant correlated FCs ($p < 0.05$) with at least one CCAT item were within left or right hemispheres (i.e., intrahemispheric FCs shown in **Figure 3**). No interhemispheric FC showed a significant difference between the two groups or the significant correlation with the language improvement.

DISCUSSION

We conducted an RCT study with neuroimaging investigation to confirm the effectiveness of LF-rTMS in enhancing speech recovery and remodeling functional networks in chronic

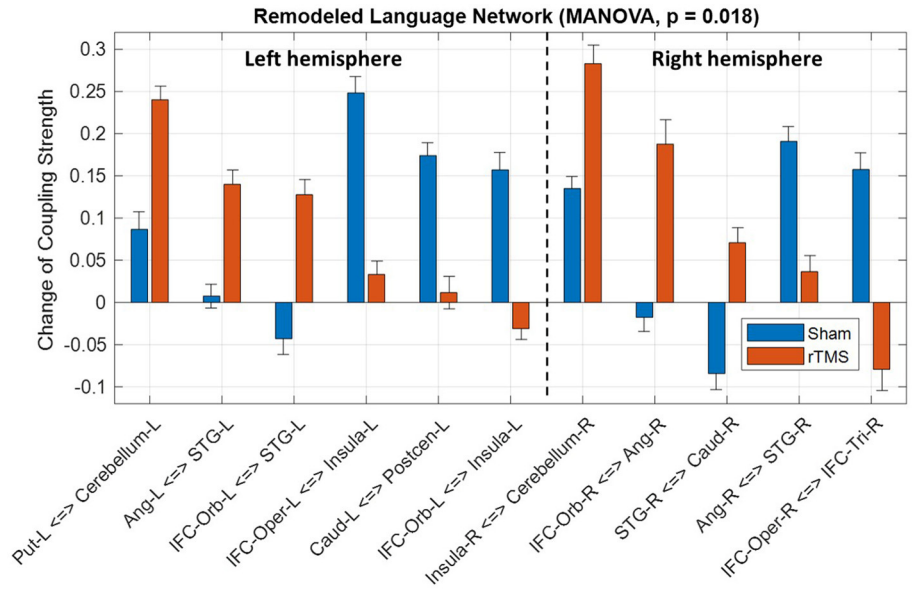

FIGURE 3 | Significant difference of language network remodeling between the repetitive transcranial magnetic stimulation (rTMS) and sham groups. IFC, inferior frontal cortex; Tri, pars triangularis; Oper, pars opercularis; Orb, pars orbitalis; STG, superior temporal gyrus; Precen, precentral gyrus; Postcen, postcentral gyrus; Ang, angular gyrus; Caud, caudate; Put, putamen; L, left; and R, right.

TABLE 2 | Language performance of the studied cohorts.

	rTMS group (n = 17)			Sham group (n = 16)			Change scores (post-pre)			
Items	**pre**	**post**	***P*-values**	**pre**	**post**	***P*-values**	**rTMS group**	**Sham group**	***P*-values**	**Cohen's d**
CCAT total score	7.65 ± 2.39	8.42 ± 2.35	<0.001*	6.61 ± 2.18	6.70 ± 2.24	0.245	0.59 ± 0.31	0.09 ± 0.29	<0.001*	1.564
Simple response	7.00 ± 3.37	7.48 ± 3.57	0.003*	5.58 ± 3.02	5.72 ± 3.11	0.572	0.48 ± 0.57	0.14 ± 0.95	0.212	0.419
Expository speech	5.48 ± 2.95	6.17 ± 3.26	0.002*	4.24 ± 2.55	4.42 ± 2.54	0.411	0.69 ± 0.76	0.18 ± 0.86	0.079	0.598
Matching	11.1 ± 1.89	11.4 ± 1.38	0.147	11.5 ± 0.94	11.6 ± 0.78	0.295	0.26 ± 0.72	0.13 ± 0.46	0.513	0.218
Auditory comprehension	7.96 ± 2.41	8.78 ± 2.37	<0.001*	6.95 ± 2.71	7.14 ± 2.92	0.326	0.82 ± 0.77	0.19 ± 0.76	0.027*	0.767
Naming	6.86 ± 3.32	7.28 ± 3.50	0.008*	4.86 ± 3.14	4.76 ± 3.09	0.219	0.42 ± 0.57	−0.10 ± 0.31	0.003*	1.049
Reading comprehension	8.16 ± 2.87	8.85 ± 2.98	0.031*	7.14 ± 2.64	7.11 ± 2.91	0. 924	0.69 ± 1.15	−0.02 ± 0.82	0.070	0.666
Repetition	7.26 ± 2.87	7.69 ± 2.89	0.043*	5.64 ± 3.36	5.73 ± 3.26	0.513	0.44 ± 0.82	0.09 ± 0.52	0.158	0.476
Imitation writing	9.54 ± 2.36	10.3 ± 2.52	0.027*	9.01 ± 2.79	8.98 ± 3.04	0.864	0.71 ± 1.17	−0.03 ± 0.72	0.038*	0.721
Spontaneous writing	6.23 ± 2.45	6.6 ± 2.51	0.007*	5.08 ± 2.43	5.31 ± 2.33	0.045*	0.43 ± 0.53	0.23 ± 0.41	0.260	0.395
4-Expression	26.6 ± 1.69	28.6 ± 12.6	<0.001*	20.3 ± 11.1	20.6 ± 11.0	0.502	2.03 ± 1.69	0.31 ± 1.78	0.008*	0.938
3-Comprehension	27.8 ± 1.87	29.4 ± 5.77	0.004*	25.3 ± 5.83	25.6 ± 6.27	0.424	1.58 ± 1.87	0.31 ± 1.39	0.045*	0.730

**represents significant differences with p values < 0.05.*

poststroke aphasia. We identified the corresponding FC modulation between right pars triangularis and pars opercularis and the circuits associated with left Wernicke area and bilateral Geschwind areas (angular gyrus), which were correlated with the language improvement after rTMS treatment. Our findings provide insights into the neuroplastic mechanisms of functional recovery in chronic poststroke aphasia. The discussion of therapeutic mechanisms of rTMS, LF-rTMS-related FC changes, and the association between functional remodeling and language recovery are addressed in the following sections.

Mechanisms and Clinical Effects of rTMS

Both the left and right hemispheres contribute to language recovery to different extents under varied hypotheses following a stroke. Evidence from studies employing neuroimaging suggested that language recovery is primarily attributed to left hemisphere reorganization, whereas the right hemisphere assists in relevant tasks (38, 39). In the aforementioned studies, the increased activation of the right hemisphere persisted for several months following damage to the left hemisphere, which was regarded as either maladaptation or interferential compensation to the linguistic performance, whereas the activation of perilesional or spared areas in the left hemisphere facilitated language restoration during spontaneous recovery (38, 39). Stefaniak et al. proposed two potential recovery models after poststroke aphasia. The first model suggested that other cognitive networks may compensate the damaged language networks; the second model indicated that the

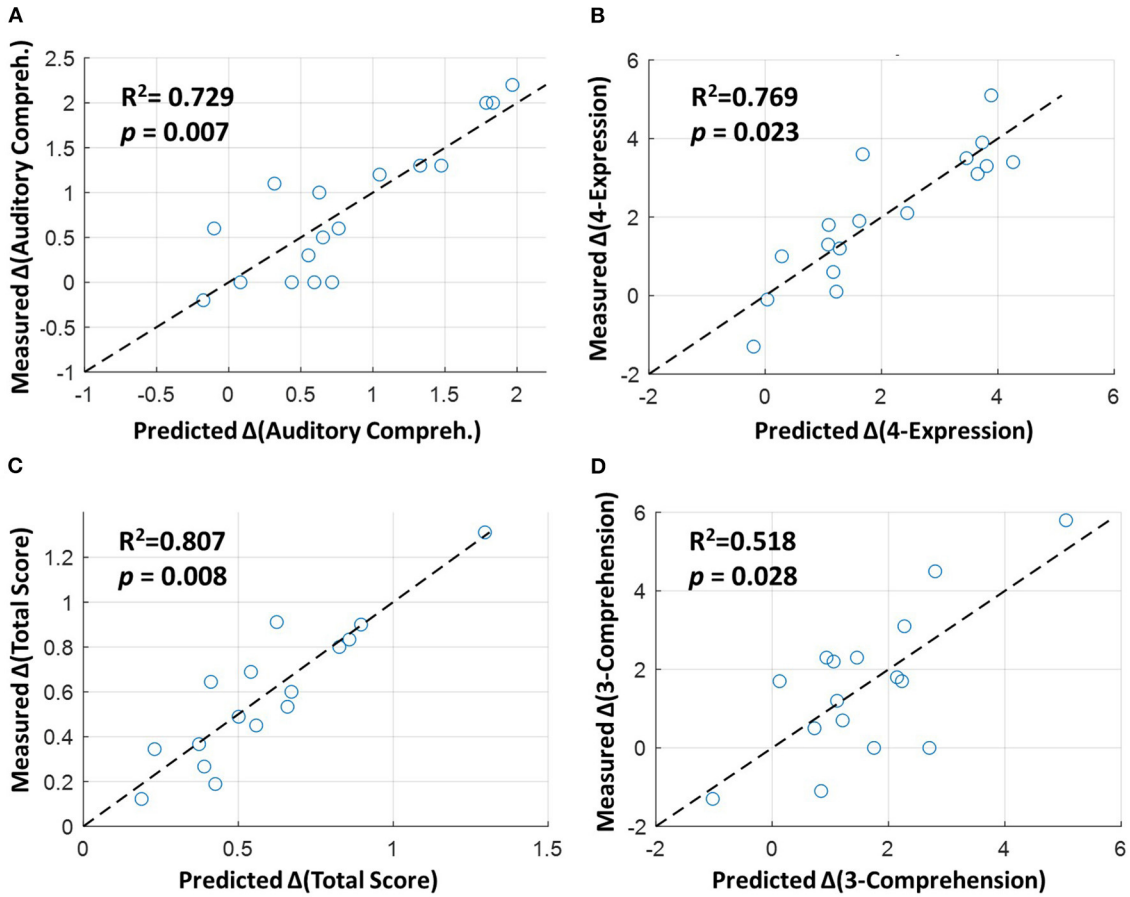

FIGURE 4 | Stepwise linear regression between altered functional connectivities (FCs) and language improvement in the rTMS group. The horizontal axes represent the predicted change scores of **(A)** auditory comprehension, **(B)** 4-expression, **(C)** total score, and **(D)** 3-comprehension based on the altered FCs (given in **Figure 3**), and the vertical axes represent the measured/actual change scores. The dashed diagonal lines indicate the perfect prediction between the predicted and measured values based on the regression models. The detailed coefficients and *p*-values for the independent variables (FCs) are shown in **Supplementary Table S5**.

ipsilesional and spared language-related areas may engage in the language function after the damage of primary core by the stroke (40).

Brain stimulation methods such as rTMS might alter neural plasticity and promote language restoration through long-term potentiation and long-term depression mechanisms (6, 8, 11, 15, 41). The excitatory (high-frequency) rTMS paradigm upregulates cortical excitability by facilitating synaptic transmission, whereas the LF-rTMS paradigm downregulates cortical excitability by attenuating synaptic strength (42). When applying LF-rTMS to the right homologous Broca area, specifically the pars triangularis, level B evidence revealed that LF-rTMS promoted language recovery in poststroke nonfluent aphasia through the improvement of interhemispheric imbalance from the overactive right homologous area (4, 10, 25, 39, 41, 43). Li et al. (2) reported that only naming exhibited a significant improvement after LF-rTMS treatment for mixed types of aphasia and different durations after stroke. Yao et al. (3) considered a relatively complete list of relevant LF-rTMS studies and suggested that naming, repetition, comprehension, and written language significantly improve after LF-rTMS. Their subgroup analysis further indicated that the therapeutic effects were significant among patients with chronic or acute stroke. The aforementioned meta-analyses not only confirmed the safety and treatment effects of LF-rTMS in poststroke aphasia, but also addressed the potential bias and influence of native speaker status and use of different assessment tools. In this study, we applied a well-validated assessment tool in Chinese, the CCAT, to reliably assess language functions for the recruited patients. Our results are consistent with those of studies reporting that LF-rTMS significantly improved linguistic performance in the domains of auditory comprehension, reading comprehension, naming, and verbal or writing output ability compared with baseline. Chieffo et al. (44) provided an opposite finding by comparing the effects of excitatory, inhibitory, and sham rTMS stimulation on the right inferior frontal gyrus in patients with chronic aphasia. Their results showed that only excitatory rTMS had a significant improvement of naming performance. However, this study only recruited five patients who underwent three different rTMS protocols with a 6-day washout period. The potential interactions

between three different rTMS protocols were not fully addressed and the number of stimulation session was not reported.

In this study, the rTMS group exhibited favorable outcomes in terms of the total CCAT score, reflected in auditory comprehension, naming, expression, and imitation writing compared with the sham group. We demonstrated the substantial effect of rTMS in multiple domains of language skills for treating chronic poststroke aphasia.

Low-Frequency Repetitive Transcranial Magnetic Stimulation-Related FC Changes in Chronic Poststroke Aphasia

Harvey et al. applied LF-rTMS to the contralesional par triangularis in nine patients with chronic aphasia following stroke and found a long-lasting improvement in naming coupled with activation changes in the right frontal region and left hemisphere in fMRI (15). This result indicated that LF-rTMS-mediated performance improvement may be closely linked to the alleviation of interhemispheric imbalance. However, few RCTs have employed neuroimaging to evaluate language improvement according to fMRI findings with the sham group. Furthermore, studies have mainly focused on local brain activation rather than the connectivity between brain areas. Therefore, we investigated the FC between the language-related areas and language performance to elucidate the network connectivity changes driven by LF-rTMS treatment.

In addition to the changes in local structure and functional activation after stroke, recent articles have addressed the alteration of interregional coupling measured by using FC and its association with the deficit in language functions (45, 46). Another study concluded that patients with aphasic stroke exhibit a decrease in FC between the left medial temporal and superior temporal gyri, which can be alleviated by language therapy, whereas the increase in FC between the left inferior frontal and medial temporal gyri after the therapy was associated with improvements in phonological and semantic processing of language functions (47). Furthermore, the cerebellum and basal ganglia connect with the inferior frontal and lateral temporal gyri to assist phonological processing (48).

Our results shown in **Figure 3** demonstrated that the rTMS group presented distinct FC remodeling compared to the sham group. First of all, the FCs between the perilesional and spared regions in the left hemisphere, such as the connectivity associated with Wernicke area, restored their connectivity strength, whereas the right cortical areas, such as the FC between right pars triangularis and pars opercularis, reduced its coupling strength. These findings are consistent with the abovementioned literatures that the effect of LF-rTMS may suppress the dominating role of right hemisphere and, hence, restore the interhemispheric inhibition to facilitate the functional remodeling in the left hemisphere.

Functional Remodeling Induced by LF-rTMS Supports Language Recovery

Because few studies have focused on LF-rTMS effects on patients with chronic stroke, rTMS-related neuroimaging evidence to support and elucidate language improvement remains unclear. In this study, we applied stepwise linear regression, in which we considered multiple independent variables (multiple FC changes) for investigating the relationship between functional remodeling and language improvement after rTMS treatment. Compared with the univariate correlation analysis between each FC change and language performance, the multivariate linear regression analysis is more flexible for considering the interactions between FCs and assess the comprehensive effect of network remodeling on language improvement (37). Among the six CCAT items that were significantly improved in the rTMS group compared with the sham group (**Table 2**), four (auditory comprehension, total score, 4-expression, and 3-comprehension) can be predicted or underpinned based on the rTMS-induced FC alterations (**Figure 4**). As given in **Supplementary Table S5**, each of these CCAT items could be predicted by multiple FCs rather than a single FC modulation with a satisfactory goodness-of-fit and significance.

The FCs selected in the regression models were associated with the Broca area, Wernicke area, Geschwind area, striatum, and cerebellum in both the hemispheres. Comprehension of spoken or written words requires the engagement of the superior temporal gyrus, whereas only the left hemisphere is involved in nonlexical phonemic recording (49). The left hemisphere plays a dominant role in tuning different types of auditory information, processing rapid acoustic transitions, and discriminating between different consonants. In addition to the core regions in cortical areas (Broca, Wernicke, and Geschwind) for language generation and comprehension, the modulating and integrating functions of the thalamus, striatum, and cerebellum are essential in language processing, especially after stroke damage (50). The thalamus and striatum are the relay centers within the corticostriatal–thalamocortical circuits that bidirectionally connect with language-related cortices (51–53). Accordingly, the altered FCs related to these circuits may be associated with language recovery after stroke.

It is worth to note that in a tonal language, such as Chinese, pitch can distinguish word meanings, while in a nontonal language, such as English, pitch is used to convey the lexical and intonation in phonetic (54). Previous studies revealed that the superior temporal gyrus participated in phonological processing to encode phonetic features (55). Our findings based on the CCAT assessment on Chinese speakers revealed that the comprehension ability was significantly improved and correlated with the FC of superior temporal gyrus after the LF-rTMS treatment. On the contrary, a previous meta-analysis that mixed studies of tonal and nontonal languages, including Chinese, English, German, and Polish, showed no significant improvement of the comprehension ability after the LF-rTMS treatment (2). Accordingly, the disparities of characteristics and neural substrates between tonal and nontonal languages should be considered to unravel the underlying mechanism of language recovery after treatments.

We summarized the neuroplastic mechanism underlying the LF-rTMS treatment based on our findings in **Figure 5**. With the LF-rTMS inhibition on the right pars triangularis, the rebalance of interhemispheric inhibitions between two hemispheres may

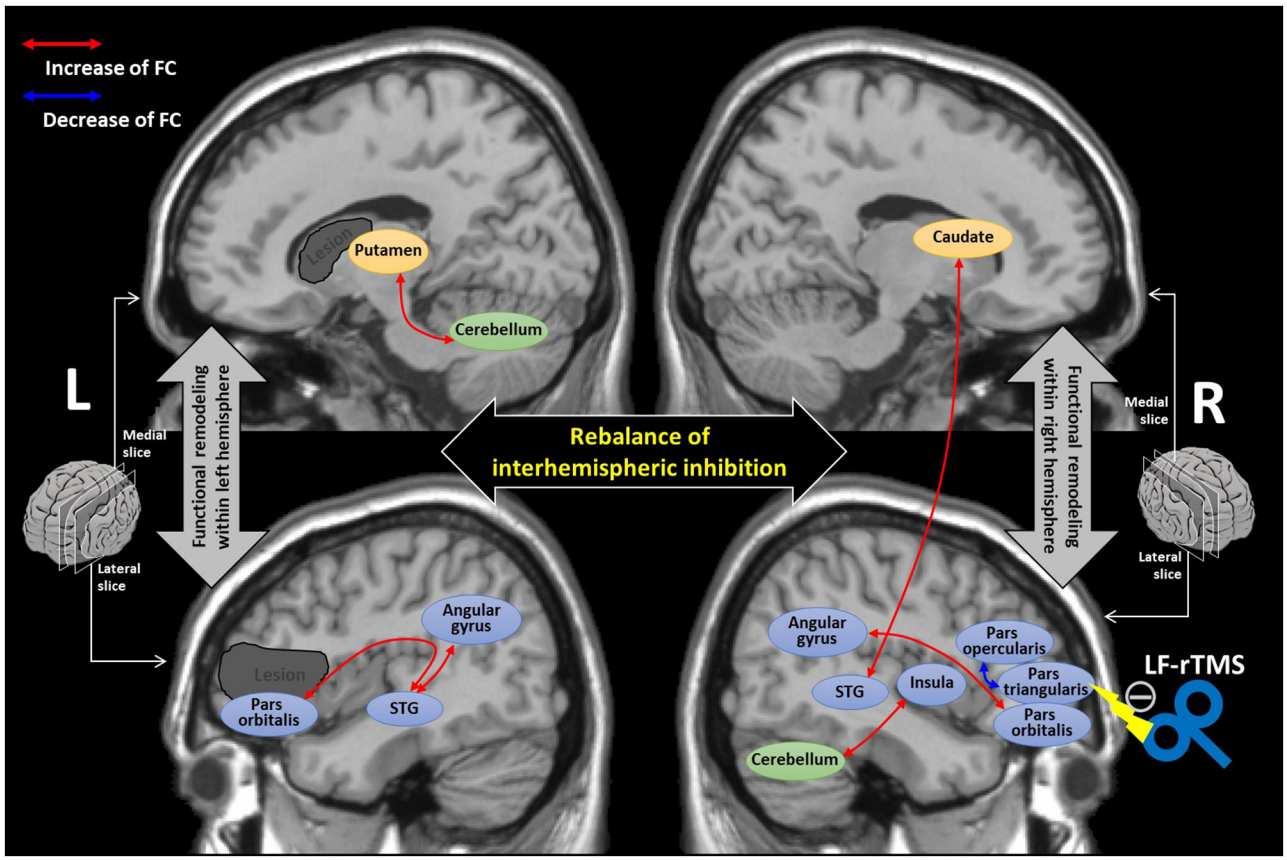

FIGURE 5 | The diagram summarizing the underlying neuroplastic mechanism of language recovery after the low-frequency-rTMS (LF-rTMS) treatment. The dark gray regions indicate the potential stroke lesions mainly involved in the left inferior frontal gyrus and striatum areas. The double arrows stand for the FCs with significant correlations (identified by the regression analysis) with language improvement after the LF-rTMS treatment. The cortical areas are colored blue; the striatum areas are colored yellow; the cerebellum is colored green. STG, superior temporal gyrus.

be restored to facilitate the network remodeling in both the hemispheres.

Limitations and Further Considerations

Several issues of this study should be further recognized. First, this study had a relatively high exclusion rate. We excluded 21 patients because of significant head motions during the fMRI scan. Some of the patients with stroke had difficulty in fixing the head position. Despite the high exclusion rate, the final number of included participants (33 patients) was still higher than those of most prospective rTMS studies, which have enrolled fewer than 10 participants. Second, we applied a protocol with 900 pulses *per session* during the rTMS treatment instead of 1,200 pulses *per session*, as used in some other studies. This discrepancy in conditioning pulses may influence the modulation to the functional remodeling measured by the FC changes. Third, the recruited patients received language therapy once a week after the rTMS intervention. The rTMS might boost receptiveness to the language therapy session. To reduce this synergy effect, we have already reduced the frequency of language therapy to once a week. However, we were unable to completely eliminate this potential confound factor considering the patients' right to receive the language therapy. Fourth, a larger patient cohort may be required in the further study to confirm our findings. Finally, heterogeneity of lesions can be a critical factor in most stroke studies. The effects of lesion variability should be carefully addressed in the future studies.

Further considerations for the future studies might be proposed. In addition to nonfluent aphasia, LF-rTMS modulation on the right pars triangularis also resulted in concomitant improvement in language function in patients with Wernicke's aphasia in our experience. This observation suggests that fluent aphasia might benefit from this approach through the strengthening of the Wernicke-related circuits, even though the LF-rTMS target is not directly on the perceptive pathway (superior temporal gyrus).

CONCLUSION

In this study, we demonstrated the promising therapeutic effects of LF-rTMS on patients with chronic aphasia following stroke. The rTMS group exhibited significant improvement in the comprehension and expression of language functions compared with the sham group. Our data further indicated that the rTMS-induced functional remodeling, involving the core language cortices and supplemental modulating areas in both the

hemispheres, supported the language recovery. The engagement of the identified circuits may inspire future research on refining the rTMS protocol to improve the therapeutic effects on chronic poststroke aphasia.

DATA AVAILABILITY STATEMENT

The raw data cannot be made publicly available for ethical and legal reasons. However, researchers can submit inquiries for analyzed data to the corresponding authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local Institutional Review Board in Taipei Veterans General Hospital, Taiwan. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

C-FL and P-YT: conceptualization, funding acquisition, resources, and supervision. B-FL and C-FL: methodology and writing—original draft preparation. B-FL, C-FL, and P-YT: formal analysis and investigation. B-FL, S-CY, Y-CK, C-FL, and P-YT: writing—review and editing. 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.2022.809843/full#supplementary-material

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Serial Backward Locomotor Treadmill Training Improves Bidirectional Walking Performance in Chronic Stroke

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Awosika OO, Chan D, Rizik BA, Sucharew HJ, Boyne P, Bhattacharya A, Dunning K and Kissela BM (2022) Serial Backward Locomotor Treadmill Training Improves Bidirectional Walking Performance in Chronic Stroke. Front. Neurol. 13:800757. doi: 10.3389/fneur.2022.800757

Background and Research Question: Walking impairment remains a major limitation to functional independence after stroke. Yet, comprehensive and effective strategies to improve walking function after stroke are presently limited. Backward Locomotor Treadmill Training (BLTT) is a promising training approach for improving walking function; however, little is known about its mechanism of effect or the relationship between backward walking training and resulting overground forward walking performance. This study aims to determine the effects of serial BLTT on spatial aspects of backward and forward walking in chronic post-stroke individuals with residual walking impairment.

Methods: Thirty-nine adults (>6 months post-stroke) underwent 6 days of BLTT (3×/week) over 2 weeks. Outcome measures included PRE-POST changes in backward and forward walking speeds, paretic and non-paretic step lengths, and single-support center of pressure distances. To determine the association between BLTT and overground walking, correlation analyses comparing training-related changes in these variables were performed.

Results: We report an overall improvement in BLTT and overground walking speeds, bilateral step lengths, and single-support center of pressure distances over six training sessions. Further, there were weak positive associations between PRE-POST changes in BLTT speed, BLTT paretic step length, and overground forward walking speed.

Conclusion and Significance: Our findings suggest that individuals with chronic post-stroke walking impairment experience improvements in spatial walking measures during BLTT and overground. Therefore, BLTT may be a potential adjunctive training approach for post-stroke walking rehabilitation.

Keywords: backward locomotion, post stroke walking rehabilitation, gait rehabilitation, backward treadmill training, walking impairment

INTRODUCTION

Walking impairment resulting from stroke significantly reduces functional ambulatory independence and is a significant public health issue worldwide (1). While most post-stroke survivors have some residual walking ability, <8% have adequate walking speed and endurance to allow for normal daily functioning (e.g., work, grocery shopping) (2, 3). This insufficient recovery of walking ability is devastating because it leads to a loss of life roles, social isolation, dependency, sedentary lifestyle, and increased risk of falls, fractures, and secondary medical complications (4). It is recognized that post-stroke walking rehabilitation training should be multimodal (3) and emphasize exercises such as task-specific training (5), paretic limb weight-bearing (i.e., strengthening) (6), aerobic conditioning (7), and balance (3); yet, there are currently limited rehabilitative training strategies available that incorporate all of these rehabilitative components into one exercise. In light of the anticipated increase in the rate of post-stroke survivors with residual walking impairment (8), the development of more comprehensive and time-efficient rehabilitation approaches is needed to facilitate the rate and extent of walking recovery.

Recent studies suggest that backward walking training may be one comprehensive rehabilitative approach to enhance walking recovery (9–11). Although the mechanism of backward walking is not well-understood, past electrophysiologic studies in healthy controls and the elderly have reported that backward walking training activates trunk, hip, and knee muscles to a greater extent than forward training. In addition, backward walking training has been suggested to improve motor control by alleviating the maladaptive flexor-synergy gait pattern associated with central nervous system injury (12–14). Further, functional neuroimaging and electrocorticography studies report greater cerebral activity in the supplementary motor area, pre-central gyrus, and superior parietal lobule during backward compared to forward walking, suggesting that backward walking presents more of a challenge to the nervous system and therefore may provide greater neuronal connectivity, which may contribute to enhancing corticomotor plasticity (15–17). From a functional movement perspective, investigations spanning a wide range of individuals, including the young and neurologically intact, elderly, and neurologically impaired individuals, have reported that backward training can improve forward walking performance by promoting lower extremity strengthening (18), enhancing proprioception (10, 19), agility, and balance (11)—ultimately leading to an improvement in overground forward walking speed (20).

Specific to the post-stroke population, a limited number of pilot studies and small randomized controlled have studied backward walking training in combination with other conventional modalities with promising preliminary results. These include backward treadmill training with the use of body-weight support (BWS) (21, 22), with and without usual physical therapy (23, 24), direct overground training with standard physical therapy (25), observation (26), and mirror assisted therapy (27), and concurrent administration of botulinum toxin (28). Despite the wide variations in approaches to backward walking training, the majority of these studies have reported training-related improvements in walking speed, balance, and other spatiotemporal measures (9). Our group recently developed a training protocol termed backward locomotor treadmill training (BLTT) in light of these past studies. BLTT differs from past backward walking training studies in the post-stroke population because the entirety of the training takes place on an instrumented treadmill and does not utilize BWS. Specifically, it is postulated that the absence of body weight support inherently requires trainees to bear more weight on the paretic leg (29) while concurrently receiving a high dose of practice on a continuously moving platform (i.e., treadmill), likely providing a greater exercise than previous backward walking training approaches. Additionally, the use of an instrumented treadmill in this protocol allows for real-time adjustments and longitudinal monitoring of backward walking training speeds and other metrics (e.g., step length) and helps to highlight how these parameters change over time. For example, it is unknown whether trainees with chronic post-stroke walking impairment will overtime increase their backward walking speed or lengthen vs. shorten their step lengths—a factor that may help to understand better the mechanistic benefits of BLTT in relation to walking performance and neuromotor control (30–35). Similarly, the correlation between training-related changes during backward training and overground walking has not been reported and may provide preliminary insight into which aspects of BLTT most closely predict overground walking performance.

Our group recently performed a pilot safety, feasibility, and preliminary efficacy of BLTT and a non-invasive spinal neuromodulatory protocol (36). That study confirmed that the BLTT protocol is safe and feasible in chronic stroke survivors and found clinically meaningful improvement in walking speed lasting beyond 2 weeks post-training with BLTT that was independent of non-invasive neuromodulation. However, due to the limited scope of that study, that manuscript was unable to incorporate outcomes concerning training-related changes associated with BLTT or the relationship between those changes and overground forward walking performance. Hence, this secondary analysis manuscript utilizes data collected from that study along those from nine additional individuals subsequently enrolled into the protocol to optimize statistical power for achieving the aims of this study. As such, the objectives of this manuscript are to highlight training-related spatial changes over six sessions of BLTT in chronic post-stroke individuals, and to determine its association with overground walking performance. Knowledge gained from study may help provide key preliminary insight into the relationship between backwards treadmill training and forward walking performance, while serving as a means for sample-size determination for larger prospective studies.

METHODS

Design Overview

Setting and Participants

This study was approved by the University of Cincinnati Institutional Review and was performed in the Neurorecovery Lab from September 2017 to October 2019. Thirty-nine chronic

stroke survivors with residual walking impairment were recruited from the community and gave written informed consent prior to enrollment, in accordance with the recommendations of the Declaration of Helsinki. Inclusion and exclusion criteria as previously described elsewhere (36) were: *Inclusion:* 18–80 years of age, residual walking impairment secondary to ischemic/hemorrhagic stroke(s), >6 months post-stroke (chronic), ability to provide consent, ambulate at least 10 meters without a walker, and maintain at least a 0.13 m/s speed on the treadmill while walking in a backward direction for a duration of six consecutive minutes. In addition, all participants were asked to abstain from formal physiotherapy and botulinum toxin injections at least 2 weeks prior to study enrollment and through the entirety of training and follow-up (37). *Exclusion*: Unstable cardiovascular status precluding participation in a moderate-high intensity exercise, severe lower extremity spasticity (modified Ashworth >2/4), significant language barrier which may interfere with the ability to follow instructions during training and testing, and untreated depression [>10 on the Patient Health Questionnaire (PHQ9)] (38), see **Table 1**.

TABLE 1 | Baseline characteristics of study participants ($n = 39$).

	n	Percentage	
Gender (female)	17	44	
Stroke type (ischemic)	31	79	
Left hemispheric	19	49	
Brain stem/cerebellar	6	15	
Single point cane	4	10	
Quad cane	6	15	
Hemi-walker	1	3	
AFO	13	33	
KAFO	2	5	
	Mean	**Median**	**Range (min–max)**
Age	56.9	57.3	33.7–72.9
Time post-stroke (years)	4.18	2.40	0.70–18.6
PHQ9 score	4.38	3	0–16
MMSE score	28.1	29	18–30
Height (cm)	174	172	157–195
Gait Measures			
Backward locomotor treadmill training			
Speed (m/s)	0.29	0.27	0.13–0.69
Step length (cm) -paretic leg	25.9	25.0	10.0–61.75
Step length (cm)-non-paretic leg	24.6	23.8	10.0–64.75
Step length symmetry index (%)	94.4	96.7	82.6–100
10-meter walk test (fast)			
Speed (m/s)	0.99	1.06	0.19–2.00
Step length (cm)-paretic leg	60.0	60.0	34.8–89.6
Step length (cm)-non-paretic leg	53.5	53.5	14.3–92.1
Step Length Symmetry Index (%)	88.9	92.1	52.7–99.9
SS COP dist. (cm)- paretic leg	6.81	5.00	1.13–16.1
SS COP dist. (cm) - non-paretic leg	10.9	11.1	8.50–18.6
SS COP dist. symmetry index (%)	69.1	68.0	19.3–99.6

AFO, Ankle-Foot Orthosis; KAFO, Knee-Ankle-Foot Orthosis; MMSE, Mini-Mental State Examination; PHQ-9, Patient Health Questionnaire 9-item Depression Scale; SS COP Dist., Single Support Center of Pressure Distance. Symmetry indices range from 0 TO 100%, where 0% means complete asymmetry and 100% means perfect symmetry.

Description of Training and Outcomes

Backward Locomotor Treadmill Training

On the first visit (screening), enrolled participants were oriented to the backward locomotor treadmill task while holding one handrail for support for 3 min. All participants were expected to maintain the minimum required training speed of 0.13 m/s on the instrumented Biodex Gait Trainer^{TM} 3 motorized treadmill, per study inclusion criteria, as this speed was the minimum necessary for the treadmill sensors to detect and record walking metrics associated with training. Based on the comfort level, the belt speed was increased in increments of +0.04 m/s until a comfortable training speed was achieved, as previously described (36). Qualifying participants then underwent six sessions of training, which consisted of four 6-min blocks. All training sessions were conducted by a protocol-trained and certified physical therapist, **Figure 1**. The starting belt speed was based on the last preferred speed achieved on the previous day, with the option to increase or reduce the speed, per subject preference. For additional safety, all participants wore a safety harness (without-body weight support) and were provided 2-min rest breaks between each 6-min training block. Participants were cued to step "reach" back as far as possible with each step during the swing phase of gait while working to maintain an upright posture throughout the duration of the training period. In addition, to reduce possible confounders between training sessions, participants were instructed not to practice walking backward outside of the study protocol for the duration of the study.

Outcomes

BLTT

The outcome variables obtained during training were the change in backward walking speed and step lengths (paretic and non-paretic). Previous studies have suggested that backward walking ability decreases with age and is characterized by decreasing speeds and stride lengths and may be related to a myriad of factors such as an age-related decline in strength, neuromotor control, and biomechanical constraints (39, 40). Since stroke commonly impacts chronologically older individuals, compounded by acquired functional hemiparesis, it is likely that study participants may experience similar limitations. Hence, investigating training-related changes in these parameters may inform how BLTT may impact lower extremity strengthening and neuromotor control. These measures were acquired using built-in treadmill sensors (41) and were later exported for offline analysis. Four separate values (from each 6-min training block) were averaged to formulate a single cumulative value per training session. Of specific interest were: PRE to POST changes [Day 7 minus Day 2 (baseline)] in average walking speed and step length during BLTT.

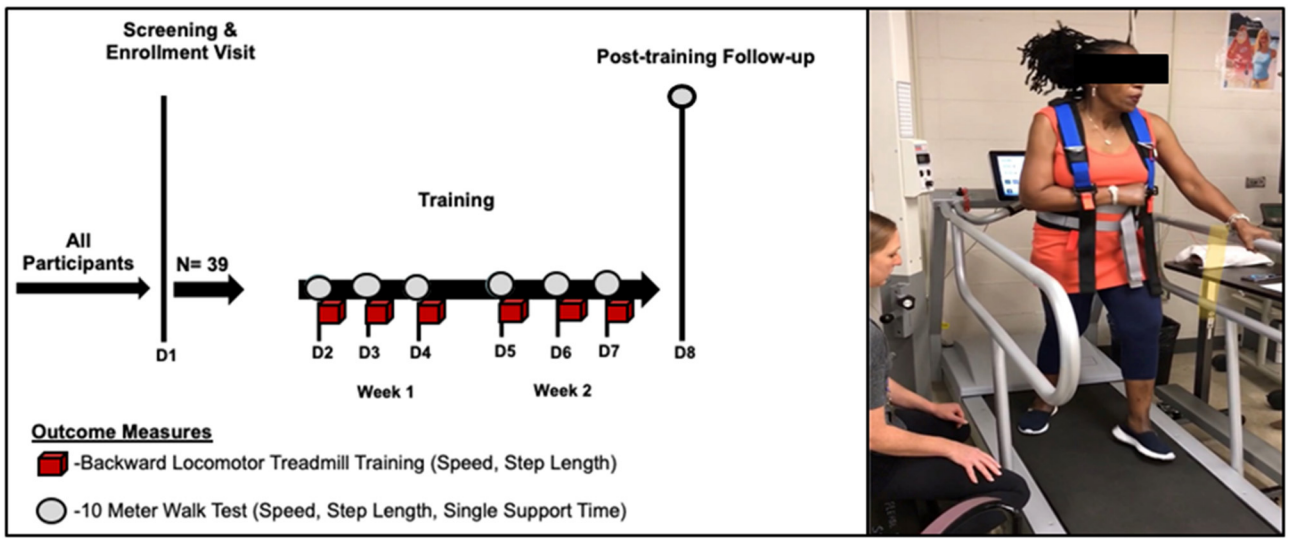


FIGURE 1 | Backward locomotor treadmill training (BLTT) protocol. Study participants underwent six, 30-min sessions of BLTT over a 2-week period (red cubes). Outcome measures were obtained prior to training at baseline (D2), subsequent training days (D3–D7), and ∼24 h following the completion of training (D8).

Overground Walking

Three measures were obtained during the 10-meter walk test (10-mWT): speed, step length (paretic and non-paretic), and single support center of pressure distance [SS COP Dist. (paretic and non-paretic)]. Walking speed has been shown to be a valid, reliable, and good predictor of functional ambulation and community independence (42) and is commonly impaired after stroke. Likewise, bilateral step length is often shorter than in healthy controls and is associated with decreased walking speed and an increased risk of falls (43, 44). The SS COP Dist. measures how body weight is progressed over the foot during single support and has been suggested to be a predictor of hemiparetic gait velocity (45, 46). As such, measurement of training-related changes in SS COP Dist. may provide information about the neuromuscular response involved in maintaining upright balance and forward progression during walking. To obtain the above measures, the 10-mWT was performed daily prior to the start of BLTT and was captured with a 20-feet Zeno Walkway gait analysis mat (Protokinetics, PA, USA) and Protokinetics Movement Analysis Software (PKMAS) (24), and were later exported for offline analysis. Of specific interest were: PRE to POST [Post-training Day 8 (∼24 h post Day 7) – Day 2 (pre-training baseline)] changes in walking speed, average step length, and SS COP Dist.

Relationship Between BLTT and Overground Walking Performance

To determine the association between BLTT and forward walking performance, correlation analyses were performed comparing PRE to POST changes between 1. ΔBLTT speed vs. Δ10-mWT speed, 2. ΔBLTT step lengths vs. Δ10-mWT speed, 3. Δ-BLTT step lengths vs. Δ-overground walking step lengths, 4. ΔBLTT speed vs. Δ10-mWT speed SS COP Dist and 5. Δ-BLTT step lengths vs. Δ-overground SS COP Dist.

Spatial Symmetry

Symmetry indices were calculated for Step Lengths (BLTT and 10-mWT) and SS COP Dist. (10-mWT), PRE to POST using the following equation: [1 - | Paretic – Non-paretic | / (Paretic + Non-paretic)] * 100%; with possible values ranging from 0–100%, where 0% means complete asymmetry and 100% means perfect symmetry.

Statistical Analysis

To address the objectives of this study, only participants that completed at least half of the six training sessions were included for BLTT analysis; therefore, one participant from the original safety and feasibility study who did not complete the first day of training was excluded. For forward walking and correlation analysis, one participant whose forward walking data was uninterpretable during forward gait analysis (due to walk-running). Two participants who did not complete the entire 6 days of the study were excluded from the correlation analysis looking at PRE to POST changes. Shapiro-Wilk tests were used to assess for deviations from normal distribution among the continuous variables, and the significance level was set at $p = 0.05$ for all measures. Paired t-tests were used to test PRE to POST changes in spatiotemporal measures on the treadmill (backward) and overground (forward). Robust regression was used to limit the impact of outliers in determining the relationship between training-associated changes during BLTT compared to changes observed with the 10-mWT (47).

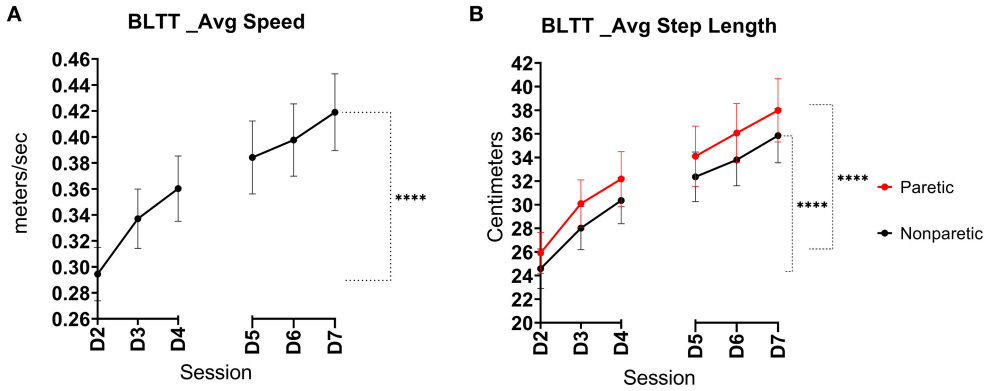


FIGURE 2 | Backward locomotor training (BLTT) speed and step length over six training sessions. Mean progression in BLTT speed **(A)** paretic and non-paretic step lengths **(B)** per training session from baseline (D2) through session 6 (D7), (error bars show standard error, ****indicates significance level <0.001).

RESULTS

BLTT: Speed

The BLTT speed was significantly greater on Day 7 (0.42 m/s ± 0.18) relative to baseline (D2) (0.30 m/s ± 0.13), ($p < 0.001$), see **Figure 2A**.

BLTT: Step Length

Both lower extremities demonstrated an improvement in step length. The non-paretic leg showed an increase in step length at Day 7 (35.9 ± 14.0 cm) compared to baseline (24.8 ± 10.7 cm), $p < 0.001$. Similarly, the change in paretic step length on Day 7 also increased (38.0 ± 16.3 cm) relative to baseline (26.1 ± 11.0 cm), $p < 0.001$, See **Figure 2B**. Interlimb BLTT step length symmetry was less on Day 7 (91.8% ± 5.92) compared to baseline (94.4% ± 4.98), $p = 0.019$.

10-mWT: Overground Walking Speed

Overground walking speed was significantly greater on *Post-training Follow-up Day 8* (1.21 m/s ± 0.60) compared to baseline walking speed (0.98 m/s ±0.49), $p < 0.001$, see **Figure 3A**. In total, 25 of 36 study participants (69%) experienced clinically meaningful improvements in walking speed (≥0.15 m/s) by the completion of training (48).

10-mWT: Step Length

Both lower extremities demonstrated an improvement in overground walking step length during overground walking. The non-paretic step length increased from 52.0 ± 17.7 cm at baseline to 56.4 ± 16.1 cm, $P < 0.001$. Likewise, the paretic step length increased from 60.3 ± 13.8 cm to 63.4 ± 14.7 cm ($p = 0.003$), see **Figure 3B**. Interlimb step length symmetry was greater on Day 8 (90.6% ± 9.48) compared to baseline (88.9% ± 10.8), $p = 0.019$.

10-mWT: SS COP Dist

The non-paretic SS COP Dist. increased from 10.9 ± 3.96 to 12.3 ± 4.45 at Post-training Follow-up Day 8, $p < 0.001$. Similarly, the paretic leg also demonstrated an increase from 6.81 ± 4.49 at baseline to 8.38 ± 5.32, $p < 0.001$, see **Figure 3C**. Interlimb SS COP Dist. symmetry was unchanged on Day 8 (72.8% ± 20.4) relative to baseline (69.1% ± 21.6), $p = 0.169$.

Correlation Analysis

There was a weak positive relationship between Δ BLTT Speed and Δ 10-mWT Speed, R2 = 0.11, β = 0.90 (0.23–1.57), $p < 0.010$, and ΔBLTT Paretic Step Length and Δ 10-mWT Speed, R2 = 0.10, β = 0.01 (0.001–0.01), $p < 0.030$, see **Figure 4**. No significant relationship was seen between all the other variables, see **Table 2**.

DISCUSSION

Our findings suggest that chronic stroke individuals with residual walking impairment experience progressive improvement in backward walking speed and bilateral step lengths with training. In addition, study participants demonstrated training-related improvement in overground forward walking speed, bilateral step lengths, and single support center of pressure distances. Furthermore, correlation analysis suggests a weakly positive association between the changes in backward walking speed, BLTT paretic step length, and change in overground forward walking speed. In addition, there was a slight improvement in overground step length symmetry following six training sessions.

Previous studies have reported that backward walking ability significantly declines with age, and hemiparesis as a result of stroke increases this likelihood, resulting in functional walking impairment and increased risk of falls (49). Therefore, the finding that our study participants showed improvement in backward walking ability with serial training is encouraging and may have several functional, safety, and quality of life implications (39, 50). Further, while the relationship between backward and forward walking is not entirely understood, previous work suggests that the two forms of locomotion may overlap, enabling one training modality to improve the other (13, 51). As such, in this study, participants demonstrated improvements in both backward and forward walking speeds and step lengths over consecutive days of training.

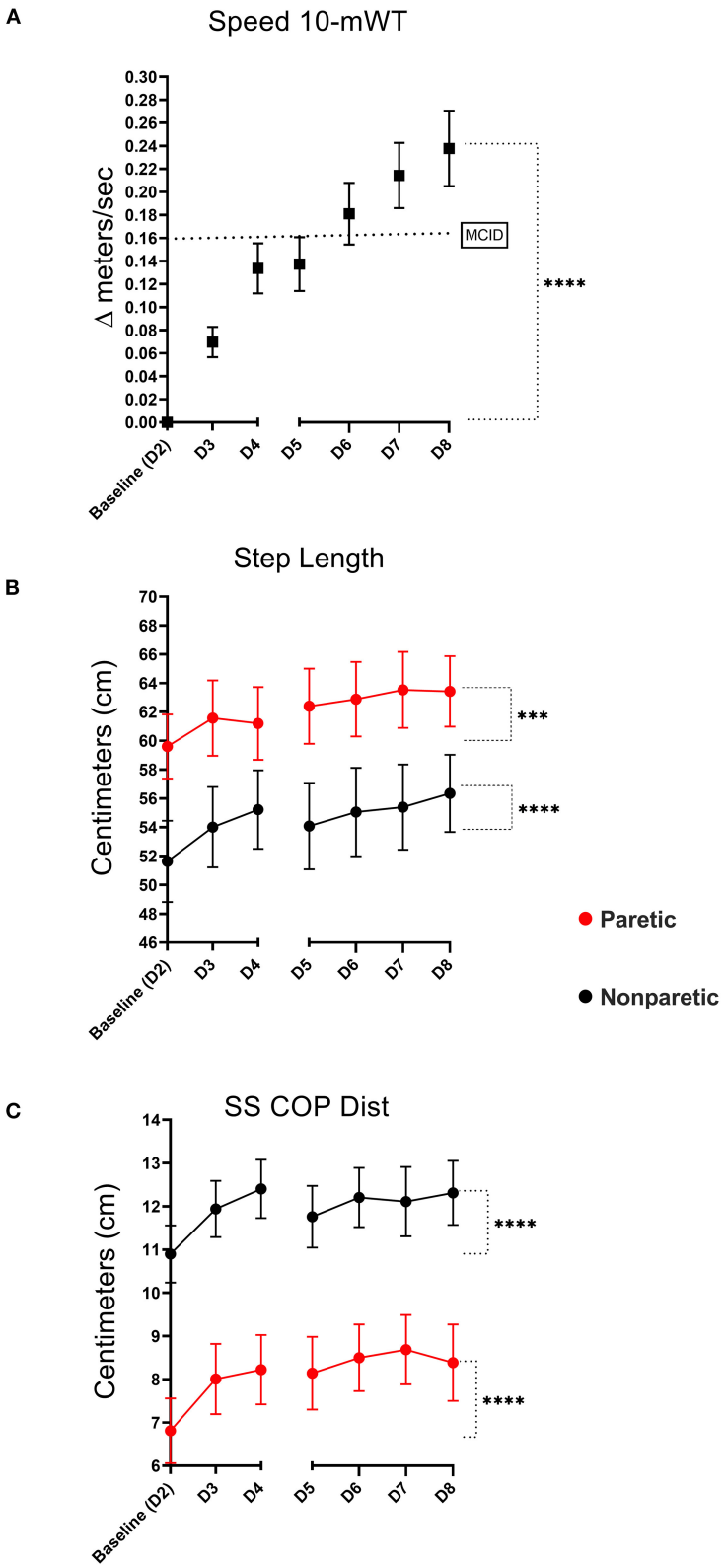
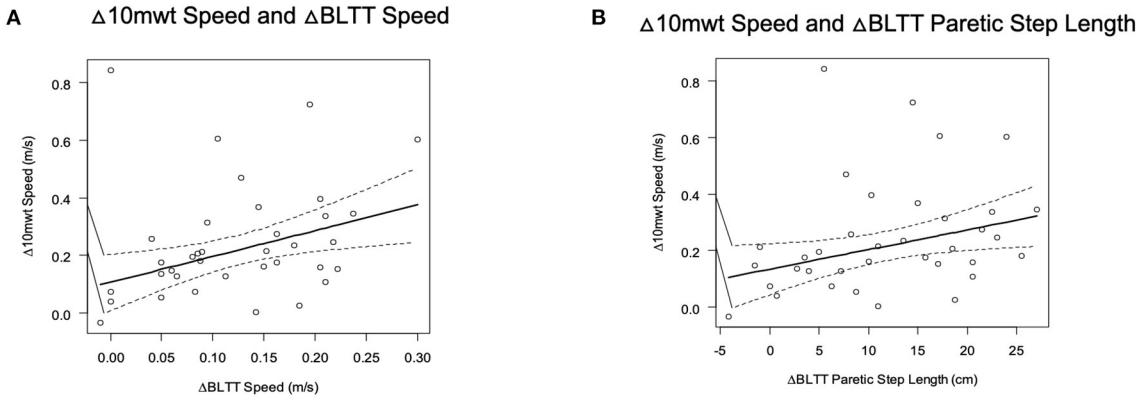


FIGURE 3 | Ten meter walk test (10-mWT). Mean change in 10-mWT speed relative to baseline [dotted line signifies the minimal clinically important difference (MCID)-≥0.15 meters/s] **(A)**. Mean training-related change in paretic and non-paretic step lengths **(B)**, and percent single support times **(C)** (error bars are standard error, ****indicates significance level <0.001, ***level <0.01).



Intercept	B (95% CI)	B p-value	R2
0.11	0.90 (0.23 to 1.57)	0.0088	0.11

Intercept	B (95% CI)	B p-value	R2
0.13	0.01 (0.001 to 0.013)	0.0286	0.10

FIGURE 4 | Correlation analysis of backward locomotor treadmill training change in BLTT speed **(A)** and paretic Step Length **(B)** and overground walking speed on the 10-meter walk test.

The mechanism of walking impairment after stroke is multifactorial and it is widely recognized that post-stroke walking rehabilitation training should be multimodal in its approach (3). While our reported findings are preliminary, we postulate that BLTT may be one such approach, as it provides task-specific training (5), facilitates aerobic conditioning (7, 52) and has been suggested to improve balance by emphasizing sensorineural integration practice (3, 25, 50, 53, 54). Moreover, BLTT likely improves walking performance by training key muscles essential for efficient biomechanics during forward walking. For example, previous backward walking exercise studies have demonstrated that the backward walking approach uniquely activates fundamental supplementary core and lower extremity muscle groups, including hip extensors, which are also important contributors to forward walking (25, 55). In addition, since BLTT requires trainees to bear a significant portion of their body weight during training, serial BLTT may improve lower extremity loading ability, resulting in greater stability, postural control, and adequate weight shifting during stance. The observed improvement in SS COP Dist. during forward walking supports the idea that training enables greater lower extremity strengthening and foot and ankle stability, enabling body weight to progress over the foot more effectively during single support (46). Another unifying association is the possibility that BLTT improves neuromotor control, as suggested by the incremental increase in overground step length and symmetry following six training sessions (56)–an attribute that has implications for the stability of gait and is decreased with aging and after brain injury (39, 57).

While improvement in backward treadmill training ability does not inherently translate to improved overground walking performance, our correlation analysis found a positive but weak association between changes in backward treadmill training speed, paretic step length, and forward walking speed. This finding suggests that several confounding variables still exist in determining the precise relationship between backward training and overground forward walking. Nevertheless, these results lay a foundation for future studies that will confirm these relationships and ultimately uncover the best predictors of walking rehabilitation training to improve walking performance.

Limitations and Future Directions

Our findings are limited by the lack of a control group (forward walking training); therefore, a determination regarding the uniqueness of our measures to BLTT cannot be made. Nevertheless, it is reassuring that previous backward walking protocols with forward walking controls report similar improvements (20). Furthermore, the generalizability of our results is limited due to the single site and exploratory nature of this study; hence future hypothesis-driven, and larger randomized controlled multisite studies are needed to validate our findings. In addition, since the factors contributing to stroke walking impairment are often heterogeneous (i.e., age, stroke size type and location, level of spasticity), larger studies would enable further subgroup analysis to determine the impact of such variables on BLTT performance and overground walking performance. In addition, this study was limited to ambulators; therefore, our findings are not generalizable to non-ambulatory stroke survivors, who BLTT is likely not feasible without the use of bodyweight support. With respect to underlying mechanisms of improvement, the instrumented treadmill used in this study was not equipped with built-in force-sensors, therefore it was not possible to obtain COP-related measures during BLTT. Therefore, future investigations are needed to capture SS COP Dist. during BLTT and empirically determine its influence on overground walking performance. To this end, our conclusion regarding muscle-strengthening and foot-ankle stability was based on observations from previous studies and indirectly from the observed improvement in SS COP Dist.

TABLE 2 | Correlation analysis of backward locomotor treadmill training and overground walking performance.

	Robust Regression			
	Intercept	**ß (95% CI)**	**ß *p*-value**	**R2**
Δ10-mwt speed				
ΔBLTT speed	0.11	0.90 (0.23–1.57)	0.01*	0.11
ΔBLTT non-paretic step length	0.14	0.01 (−0.002 to 0.01)	0.06	0.08
ΔBLTT paretic step length	0.13	0.01 (0.001–0.01)	0.03*	0.10
Δ10-mwt non-paretic step length				
ΔBLTT non-paretic step length	5.90	−0.22 (−0.48 to 0.05)	0.11	0.06
Δ10-mwt paretic step length				
ΔBLTT paretic step length	3.13	0.10 (−0.12 to 0.31)	0.38	0.02
Δ10-mwt %SST paretic				
ΔBLTT non-paretic step length	0.95	0.10 (−0.04 to 0.24)	0.18	0.03
Δ10-mwt %SST non-paretic				
ΔBLTT paretic step length	0.51	0.12 (−0.01 to 0.25)	0.08	0.06

during overground walking. Therefore, future studies should incorporate electromyography and dynamometry to empirically test changes in muscle recruitment patterns and strength associated with BLTT in the post-stroke population. Lastly, while this study was primarily focused of walking speed as the primary outcome measure, clinical measures such as balance (58) and spasticity (59) play an equally critical role in walking rehabilitation and outcome; therefore future BLTT studies should consider adding these measures in order to provide a more comprehensive view of the impact of this training approach on walking rehabilitation.

CONCLUSION

To our knowledge, this study is the first to report progressive BLTT-specific changes in the post-stroke population and highlight its association with changes in overground walking performance. Well-powered, prospective randomized control studies are needed to determine the efficacy of BLTT. Likewise, mechanistic-based studies will help determine more definitively which training metrics to target during backward walking training—an essential step in developing and optimizing future stroke rehabilitation clinical trials (60).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Cincinnati Institutional Review (IRB). 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 inv this article.

AUTHOR CONTRIBUTIONS

OA, DC, BR, HS, PB, and KD: conception and design of the study, acquisition of data, or analysis and interpretation of data. OA, HS, PB, AB, KD, and BK: drafting the article or revising it critically for important intellectual content. 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.2022.800757/full#supplementary-material

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Do Muscle Changes Contribute to the Neurological Disorder in Spastic Paresis?

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Background: At the onset of stroke-induced hemiparesis, muscle tissue is normal and motoneurones are not overactive. Muscle contracture and motoneuronal overactivity then develop. Motor command impairments are classically attributed to the neurological lesion, but the role played by muscle changes has not been investigated.

Methods: Interaction between muscle and command disorders was explored using quantified clinical methodology—the Five Step Assessment. Six key muscles of each of the lower and upper limbs in adults with chronic poststroke hemiparesis were examined by a single investigator, measuring the angle of arrest with slow muscle stretch (X_{V1}) and the maximal active range of motion against the resistance of the tested muscle (X_A). The coefficient of shortening $C_{SH} = (X_N\text{-}X_{V1})/X_N$ (X_N, normally expected amplitude) and of weakness $C_W = (X_{V1}\text{-}X_A)/X_{V1}$) were calculated to estimate the muscle and command disorders, respectively. Composite C_{SH} (CC_{SH}) and C_W (CC_W) were then derived for each limb by averaging the six corresponding coefficients. For the shortened muscles of each limb (mean $C_{SH} > 0.10$), linear regressions explored the relationships between coefficients of shortening and weakness below and above their median coefficient of shortening.

Results: A total of 80 persons with chronic hemiparesis with complete lower limb assessments [27 women, mean age 47 (SD 17), time since lesion 8.8 (7.2) years], and 32 with upper limb assessments [18 women, age 32 (15), time since lesion 6.4 (9.3) years] were identified. The composite coefficient of shortening was greater in the lower than in the upper limb (0.12 ± 0.04 vs. 0.08 ± 0.04; $p = 0.0002$, while the composite coefficient of weakness was greater in the upper limb (0.28 ± 0.12 vs. 0.15 ± 0.06, lower limb; $p < 0.0001$). In the lower limb shortened muscles, the coefficient of weakness correlated with the composite coefficient of shortening above the 0.15 median C_{SH} ($R = 0.43$, $p = 0.004$) but not below ($R = 0.14$, $p = 0.40$).

Conclusion: In chronic hemiparesis, muscle shortening affects the lower limb particularly, and, beyond a threshold of severity, may alter descending commands. The latter might occur through chronically increased intramuscular tension, and thereby increased muscle afferent firing and activity-dependent synaptic sensitization at the spinal level.

Keywords: spastic myopathy, spastic cocontraction, chronic hemiparesis, synaptic sensitization, clinical extensibility, muscle disorder, stretch-sensitive paresis, quantified assessment

INTRODUCTION

In spastic paresis, muscle changes coexist with neurologic abnormalities (1, 2) and the two have been suggested to potentiate each other (3–5). Disruption of the motor command causes immediate paresis, i.e., reduced voluntary motor unit recruitment, which, in the context of muscle hypo-mobilization, triggers a cascade of pathological changes affecting muscle tissue extensibility and motor neuronal excitability (4, 5).

In the acute stages, the common occurrence of hypo-mobilization of several paretic muscles in a shortened position (6) represents an assault on muscle tissue, causing acute transformation in molecular genetics and gene transcription (4, 5, 7–9). Within days, muscle mass is reduced and muscle extensibility decreases, in parallel with sarcomere loss (10–12); in addition, collagen tissue is modified and deposits around muscle fibers with fascial thickening (13–16). These muscle changes can be demonstrated through biomechanical and clinical measurements; they gradually worsen if hypo-mobilization is not addressed (16–21).

In the subacute stages of spastic paresis, additional plastic neural mechanisms come into play, whereby stretch-sensitive (spastic) muscle overactivity causes a third mechanism to contribute to the motor impairment, along with the agonist paresis and the muscle disorder (4, 5, 21–23). Antagonist muscle overactivity predominates in some muscles, producing agonist-antagonist imbalance around joints (5, 24, 25). Among the various types of muscle overactivity in spastic paresis, spastic co-contraction has been defined as a misdirection of the supraspinal drive that abnormally recruits antagonist motor units during agonist command, independent of any phasic stretch (5, 26, 27). This form of overactivity directly impedes and may sometimes reverse the desired voluntary movement (26). Stretch receptor recruitment in the overactive muscle aggravates this antagonistic co-contraction, hence the term *spastic* co-contraction (26–28). Finally, for the agonist muscles responsible for the movement, the responsiveness of agonist motor neurons to descending command may be negatively impacted by the stretch imposed on the antagonist, producing a *stretch-sensitive paresis* (4, 28, 29).

Decreased extensibility of the antagonist muscle in hemiparesis can be estimated clinically as reduced passive range of motion when attempting maximal slow and strong passive movement against the resistance of the tested muscle group. Here, we question whether decreased muscle extensibility might play a role in the later plastic neural events described above (spastic co-contraction and stretch-sensitive agonist paresis). The second question is whether motor function seems compromised more by the muscle disorder or the abnormal descending command. A better understanding of the respective contributions of muscle and neural disorders to functional impairment in chronic hemiparesis might then indicate where interventions should be mostly directed for individual patients. To answer these questions, we conducted a retrospective investigation of two coefficients of impairment designed as normalized, clinical estimates of the muscle and the neural components of spastic paresis. The overarching hypothesis tested here was that, beyond a threshold of muscle shortening in chronic hemiparesis, the transmission of active command to an agonist may depend, at least in part, on the severity of collagenous modifications of the antagonist, i.e., on the degree of antagonist hypo-extensibility.

METHODS

Study Design

This study was conducted in compliance with the Declaration of Helsinki (2008), Good Clinical Practice guidelines, and local regulatory requirements for the Henri Mondor University Hospital, Créteil, France. We retrospectively reviewed the charts of subjects with chronic hemiparesis that had been consecutively evaluated using at least steps 1, 2, and 4 of the Five *Step Assessment* (an expansion of the Tardieu scale, see below) (30) in the lower and/or the upper limb, by a single clinician (JMG) between January 2014 and December 2019 (**Figure 1**).

Inclusion and Exclusion Criteria

All the patient charts were included in this study if they fulfilled the following criteria: (i) adults (age $\geq$ 18 years) with chronic hemiparesis due to a single stroke that occurred $>$ 1 year before the assessment (**Figure 1**); (ii) assessment using at least Steps 1, 2, and 4 of the Five Step Assessment in soleus (SO), gastrocnemius (GN), gluteus maximus (GM), hamstrings (HS), vastus (VA) and rectus femoris (RF) for the lower limb, or shoulder extensors (SE), subscapularis (SS), pronator quadratus (PQ), elbow flexors (EF), wrist flexors (WF) and finger flexors (FF) for the upper limb, performed between January 2014 and December 2019 (iii) ability for independent ambulation (Functional Ambulation Classification score of 5–6) (31); (iv) absence of botulinum toxin injection in the evaluated muscles in the 3 months before the assessment; and (v) clinically stable condition. Exclusion criteria were: (i) recurrent strokes or other neurological or

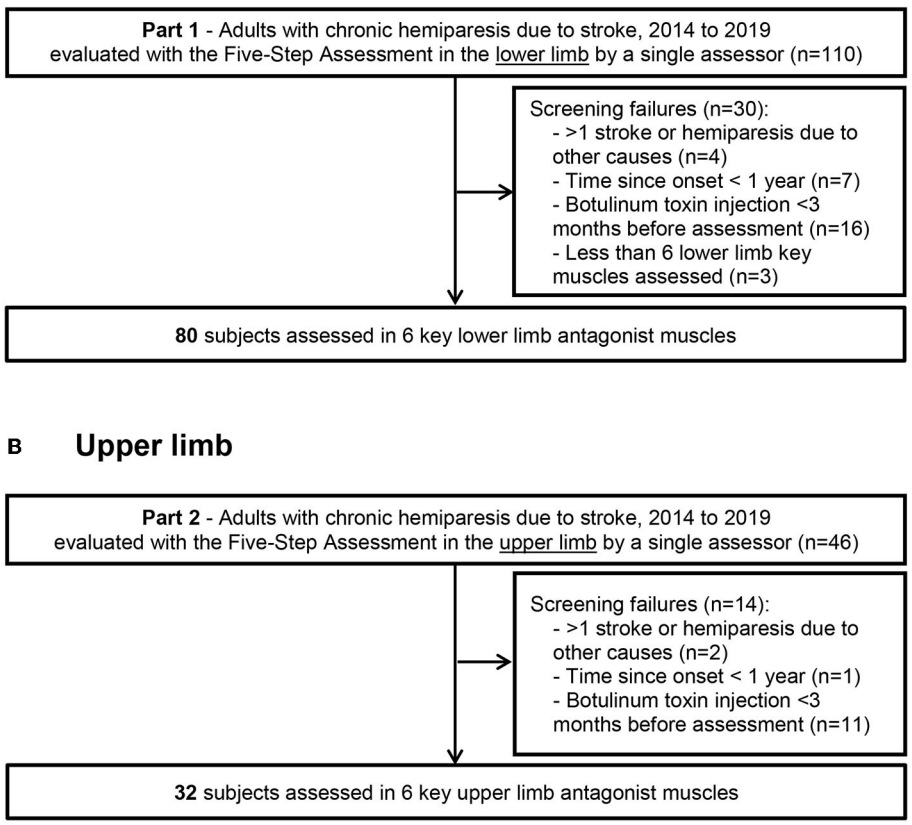

FIGURE 1 | Flow diagram Flow diagram for the lower limb **(A)** and upper limb **(B)** data collection.

orthopedic disorders affecting the evaluated muscles; (ii) severe cognitive impairment (Mini-Mental Status test score < 23 or major receptive aphasia) interfering with the ability to assess the patient; (iii) treatment with antispasticity medications that could produce synaptic depression, whether oral or intrathecal (baclofen, benzodiazepines, etc) (32, 33). In each patient chart, the first visit chronologically that met these criteria was selected for analysis.

Description of the Five Step Assessment

For each subject, the same clinician used the Five Step Assessment for the six muscles defined above in the lower limb and/or the upper limb (30). The patient was always seated for the upper limb assessments and supine for the lower limb assessments (apart from locomotion).

Step 1 of the Five Step Assessment evaluates active function. For the lower limb, this involved measurement of ambulation speed in meters/second (m/s) over 10 m (AT10) performed barefoot at maximal speed with the assessment starting and ending in a seated position (19, 30, 34). For the upper limb, the active function was measured using the Modified Frenchay Scale (MFS), and consisted of videotaping ten activities of daily living (4 uni-manual activities using the paretic hand and 6 bimanual activities, in which the paretic hand assists the other hand) and rating each of them on a ten-point visual analog scale based on video review (19, 35). In that visual analog scale, zero means no movement, 10 is the perfect achievement of the task, and 5 is a task barely accomplished (36). The 10 scores were averaged to derive the MFS score for each patient. Individual task rating on the MFS has excellent intra- and inter-reliability and the MFS has been validated against a subjective scale of perceived function (Disability Assessment Scale, DAS) as well as the Fugl–Meyer score, a classic measurement of motor impairment (19, 36–38).

Step 2 of the Five Step Assessment is the measurement of the *passive range of motion* of the tested muscle, referred to as the X_{V1} angle of the Tardieu scale (19, 30, 39), using zero as the theoretical angle of minimal stretch for each muscle (19, 30, 39). Stretch was applied slowly and strongly, up to the point where further passive stretch was not possible or would cause pain or would jeopardize joint integrity (30, 39). The stretch was performed as slowly as possible to avoid triggering a phasic stretch reflex and as strong as possible to overcome most of the spastic dystonia (30, 40). X_{V1} angle measurements were made visually, as the reliability of these angle measurements has been shown to be similar between visual or goniometric evaluations (41), except at the knee where a goniometer was used. X_{V1}

measurements have shown good to excellent intra- and inter-rater reliability in paretic adults (41–44); this measure provides information primarily about the extensibility of *muscle* tissue (45). From the X_{V1} measure, the coefficient of shortening C_{SH} was derived for each muscle (19), based on the formula $C_{SH} = (X_N\text{-}X_{V1})/X_N$ where X_N is the normally expected passive joint amplitude for each tested muscle (46). The normally expected passive amplitude X_N is also defined using zero as the theoretical angle of minimal stretch for each muscle (as in the Tardieu Scale). In this study, the normal reference X_N was considered to be 120° for the SO, 115° for GN, 150° for GM, 270° for HS (180° knee extension + 90° hip flexion), 150° for VA muscles, 240° for RF (150° knee flexion + 90° hip extension), 180° for the SE, SS, EF and WF, PQ, and 270° for FF (46, 47).

Step 4 of the Five Step Assessment is the measurement of the maximal *active range of motion* X_A, against the resistance of the evaluated antagonist muscle (30). The patient was asked to accomplish one movement of maximal amplitude against the resistance of the tested antagonist; here a goniometer was used to measure the angle (**Figure 2**). The maximal range of active movement represents the balance between the forces generated by agonist activation and those related to the passive and active resistances generated by the tested antagonist muscle group. From the X_A measure, the coefficient of weakness C_W was derived for each tested muscle, using the formula $C_W = (X_{V1}\text{-}X_A)/X_{V1}$ (19). The coefficient of weakness estimates the impairment of active command against the resistance of the tested antagonist, its maximal passive extensibility being taken into account (19). The intra- and inter-rater reliabilities of X_A and of the coefficient of weakness have been established (44).

Data Treatment

Over the period from January 2014 to December 2019, data for each (upper/lower) limb of each subject from the first visit that met the inclusion criteria were systematically collected. For each lower and upper limb muscle, we normalized its X_{V1} value to a theoretically expected value of 180°, using the formula $X_{V1normalized} = X_{V1} \times 180/X_N$. From here on, the symbol X_{V1} represents these normalized X_{V1} values. This normalization allowed a Composite X_{V1} to be derived, by averaging the normalized X_{V1} values for the six key muscle groups of each limb:

$$\begin{aligned}\text{Composite } X_{V1-LL} &= (X_{V1SO} + X_{V1GN} + X_{V1GM} \\ &\quad + X_{V1HS} + X_{V1VA} + X_{V1RF})/6; \\ \text{Composite } X_{V1-UL} &= (X_{V1SE} + X_{V1SS} + X_{V1EF} \\ &\quad + X_{V1PQ} + X_{V1WF} + X_{V1FF})/6.\end{aligned}$$

Composite X_A for each limb was calculated using the same process (48). We then calculated a *composite coefficient of shortening* as (180-Composite X_{V1})/180 and a *composite coefficient of weakness* as (Composite X_{V1}-Composite X_A)/Composite X_{V1}.

Finally, for the shortened muscle groups defined as those with a mean $C_{SH} > 0.10$, two subgroups were considered: those below and those above their median coefficient of shortening.

Statistical Analysis

Descriptive statistics were used for the parameters X_{V1} and X_A for each muscle, Composite X_{V1}, Composite X_A, coefficient of shortening and coefficient of weakness per muscle, composite, ambulation speed, and Modified Frenchay Score. *t*-tests for paired data were used to compare the coefficients of shortening between individual muscles. Univariate logistic regression analyses then explored correlations between the Composite X_{V1} and the Composite X_A (raw data) and between the coefficient of shortening and the coefficient of weakness (normalized data) for each individual muscle group, for the mean of the six muscles of each limb (composite scores) and for the most shortened muscle groups only ($C_{SH} > 0.10$). In those muscles, correlations between the coefficient of shortening and the coefficient of weakness were explored in the total sample and in the two subgroups below or above the median coefficient of shortening.

Secondarily, univariable regression analyses explored, for each muscle group of the upper and lower limb and

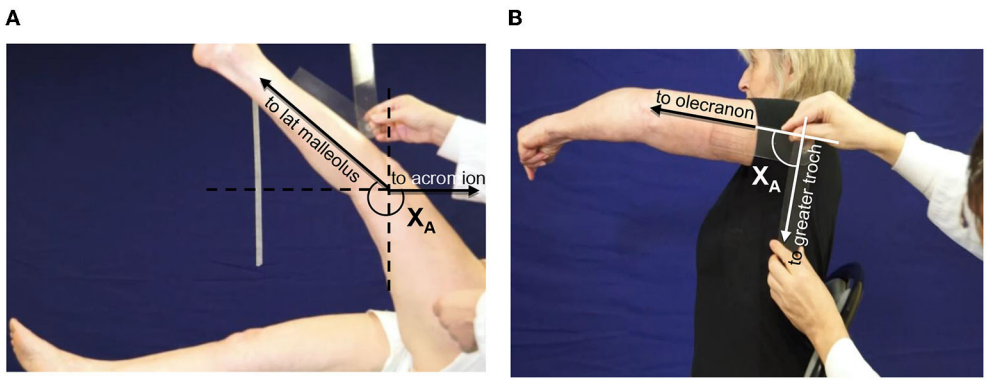

FIGURE 2 | Clinical assessment of active movement X_A. **(A)** Hamstrings: patient supine, lower limb lying straight on the table. The clinician asks for a hip flexion keeping the knee extended. Axis of rotation: lateral condyle. The angle X_A is measured between the two lines lateral condyle-external malleolus and lateral condyle-acromion (through projection, parallel to the line greater trochanter-acromion). **(B)** Shoulder extensors: patient seated, upper limb alongside the body. The clinician asks for a shoulder flexion keeping the elbow extended. Axis of rotation: acromion. The angle X_A is measured between the two lines acromion-olecranon and acromion-GT.

for the composite scores, the respective impacts of the coefficient of shortening and of the coefficient of weakness on motor function (Modified Frenchay score or maximal ambulation speed). If both the coefficient of shortening and the coefficient of weakness were predictive of motor function on univariable analyses, bivariable regression analysis was used, for each individual muscle and for the composite score. Lastly, for each limb, if the coefficients of shortening of several muscle groups were predictive of motor function in univariable analyses, multivariable regression explored which of these muscles remained important determinants of motor function once the regression coefficients were adjusted for the effects of the other predictors. Statistical significance was set at 0.01. All analyses were conducted with SPSS (18.0) software.

RESULTS

Subject Characteristics

Of 110 consecutive patients with adult-onset chronic hemiparesis in whom the lower limb was evaluated during the study period, 80 patients met the criteria for inclusion (aged 51 ± 16 years; 26 women, 54 men; 42 injured on the left hemisphere, 58 right hemisphere; 66 with ischemic stroke, time since lesion, 9 ± 8 years; **Figure 1**). For the upper limb group, 46 consecutive patients with adult-onset chronic spastic paresis were evaluated during the study period and 32 patients met the inclusion criteria (aged 39 ± 15 years; 18 women, 14 men; 19 injured on the left hemisphere, 13 on the right; 22 with ischemic stroke, time since lesion, 6 ± 9 years). In 15 of these 32 patients, investigations were performed on both the upper limb and the lower limb. At the selected visit, the Modified Frenchay score was 5.47 ± 1.09 for the upper limb cohort (normal function = 10), and the maximal ambulation speed barefoot was 0.88 ± 0.39 m/s for the lower limb cohort (normal around 1.7 m/s) (34).

Muscle Shortening and Motor Command Disorder

Overall, the coefficient of shortening (C_{SH}) was greater in the lower limb than in the upper limb [0.12, CI 95 (0.11–0.13) vs. 0.08 (0.07–0.09), upper limb; $p = 0.0002$, *t*-test; see **Figure 3A**, **Table 1**]. Conversely, the coefficient of weakness (C_W) was greater in the upper than in the lower limb [0.28 (0.24–0.32) vs. 0.15 (0.14–0.16) lower limb; $p < 0.0001$, *t*-test]. These relationships were similar in the 15 patients in whom there was documentation for both the upper and lower limbs [C_{SH} lower limb 0.11 (0.085; 0.133) vs. upper limb 0.08 (0.055; 0.097); $p = 0.03$ *t*-test; C_W upper limb 0.35 (0.277; 0.423) vs. lower limb 0.16 (0.125; 0.195); $p = 0.0015$; not illustrated].

The individual coefficients of shortening, and of weakness, for the six muscles in each limb are displayed in **Figures 3B,C**, respectively. In the lower limb, over the six evaluated muscles, GN exhibited the greatest shortening: $C_{SH-GN} = 0.17$ (0.16; 0.18). Then SO: $C_{SH-SO} = 0.15$ (0.14; 0.16), GM $C_{SH-GM} = 0.14$

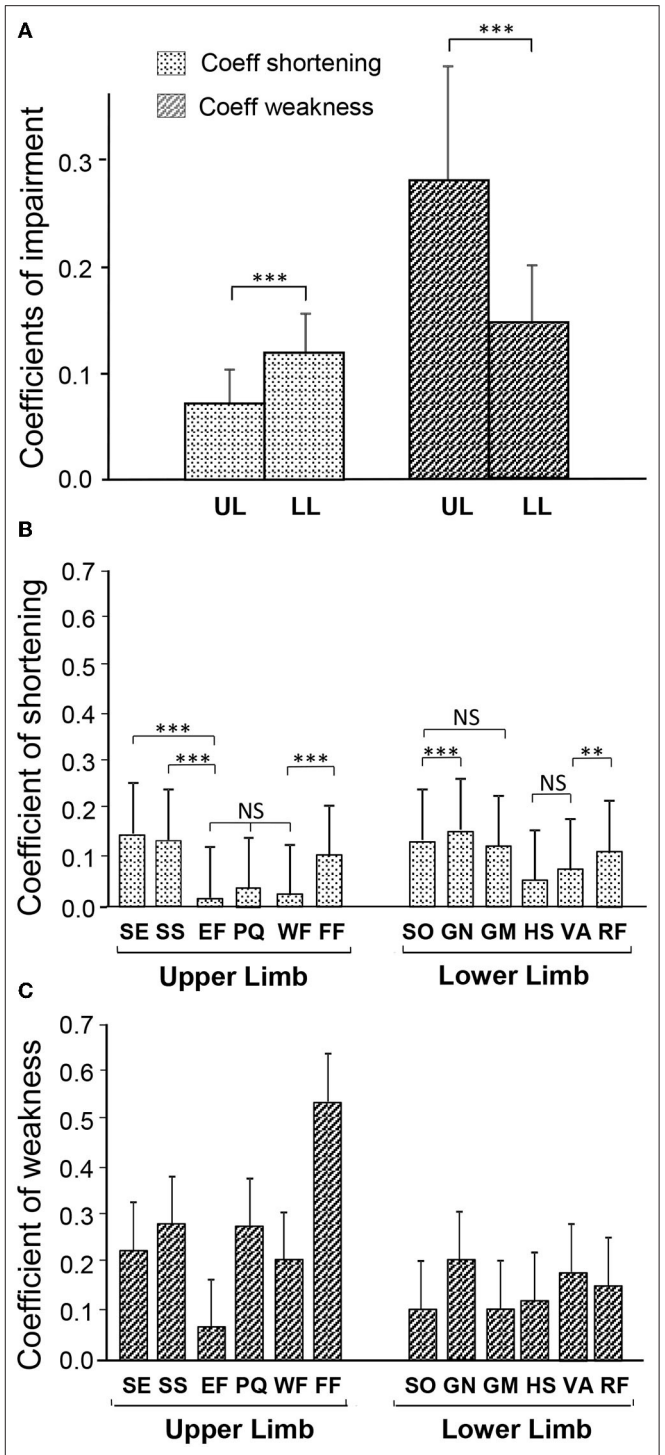

FIGURE 3 | Degree of muscle shortening and of motor command impairment in chronic hemiparesis. **(A)** Coefficients of impairment of the Composite score of the upper and lower limbs. **(B)** Coefficient of Shortening of each of the investigated muscles. **(C)** Coefficient of Weakness of each of the investigated muscles. SE, shoulder extensor; SS, subscapularis; EF, elbow flexors; PQ, pronatus quadratus; WF, wrist flexors; FF, finger flexors; SO, soleus; GN, gastrocnemius; GM, gluteus maximus; HS, hamstrings; VA, vastus; RF, rectus femoris. $^{**}p < 0.01$; $^{***}p < 0.001$.

TABLE 1 | Clinical parameters and comparison of muscle shortening.

A. Clinical parameters

Lower limb	Soleus	Gastroc	Glut Max	Hamst	Vastus	Rect Fem	Comp score
X_{V1}	102 ± 6	95 ± 4	129 ± 12	253 ± 13	137 ± 7	208 ± 16	154 ± 7
X_A	91 ± 9	76 ± 13	116 ± 16	222 ± 23	112 ± 16	176 ± 25	132 ± 13
C_{SH}	0.15 ± 0.05	0.17 ± 0.04	0.14 ± 0.08	0.06 ± 0.05	0.09 ± 0.05	0.13 ± 0.07	0.12 ± 0.04
C_W	0.10 ± 0.07	0.21 ± 0.12	0.10 ± 0.07	0.12 ± 0.08	0.18 ± 0.11	0.15 ± 0.09	0.15 ± 0.06
Ambul speed	0.88 ± 0.39						
Upper limb	**Sh Ext**	**Subscap**	**Elbow flex**	**Pron quad**	**Wrist flex**	**Finger flex**	**Comp score**
X_{V1}	150 ± 22	152 ± 23	177 ± 4	177 ± 16	175 ± 6	264 ± 13	183 ± 15
X_A	116 ± 33	111 ± 37	165 ± 13	128 ± 44	138 ± 21	121 ± 63	130 ± 11
C_{SH}	0.16 ± 0.12	0.15 ± 0.13	0.01 ± 0.02	0.04 ± 0.08	0.03 ± 0.03	0.12 ± 0.04	0.08 ± 0.04
C_W	0.23 ± 0.18	0.29 ± 0.17	0.07 ± 0.06	0.28 ± 0.23	0.21 ± 0.11	0.54 ± 0.25	0.28 ± 0.12
MFS	5.5 ± 1.1						

B. Differences between coefficients of shortening of individual muscles

	Upper Limb							Lower Limb					
	C_{SH-SE}	C_{SH-SS}	C_{SH-EF}	C_{SH-QP}	C_{SH-WF}	C_{SH-FF}		C_{SH-SOL}	C_{SH-GAS}	C_{SH-GM}	C_{SH-HS}	C_{SH-VA}	C_{SH-RF}
C_{SH-SE}							C_{SH-SOL}						
C_{SH-SS}	0.55						C_{SH-GAS}	3E-06					
C_{SH-EF}	8E-08	2E-06					C_{SH-GM}	0.011	3E-04				
C_{SH-QP}	2E-06	4E-06	0.053				C_{SH-HS}	3E-15	6E-26	1E-10			
C_{SH-WF}	9E-08	2E-06	0.03	0.31			C_{SH-VA}	2E-11	2E-19	2E-06	0.013		
C_{SH-FF}	0.11	0.17	2E-15	3E-06	4E-11		C_{SH-RF}	0.22	2E-03	6E-01	9E-07	2E-04	

X_{V1}, Maximal passive range of motion against the resistance of the investigated muscle; X_A, active range of motion against the resistance of the investigated muscle; C_{SH}, coefficient of shortening; C_W, coefficient of weakness; MFS, Modified Frenchay Scale; Ambul Speed, ambulation speed over 10 meters (AT10) at maximal speed, barefoot.
B. Comparison of muscle shortening (C_{SH}) between individual muscles within each limb.
SE, shoulder extensor; SS, subscapularis; EF, elbow flexors; PQ, pronatus quadratus; WF, wrist flexors; FF, finger flexors; SO, soleus; GN, gastrocnemius; GM, gluteus maximus; HS, hamstrings; VA, vastus muscles; RF, rectus femoris.

(0.06; 0.22) and RF $C_{SH-RF} = 0.13$ (0.06; 0.20) were shortened to about the same extent (**Table 1B**; **Figure 3B**). In the upper limb, the three most shortened muscles were SE: $C_{SH-SE} = 0.16$ (0.12; 0.20), SS: $C_{SH-SS} = 0.15$ (0.10; 0.18), and FF: $C_{SH-FF} = 0.10$ (0.06; 0.14) (**Table 1B**; **Figure 3B**). GN: $C_{W-GN} = 0.21$ (0.18; 0.24) and FF: $C_{W-FF} = 0.54$ (0.45; 0.63), were exhibiting the highest coefficient of weakness at the lower and upper limb, respectively (**Figure 3C**).

Relation Between Coefficients of Shortening and Coefficients of Weakness

In terms of raw values in the upper and lower limbs, the maximal active range of motion against the resistance of the examined muscle (Composite X_A) correlated with the angle of arrest with slow muscle stretch (Composite X_{V1}), the correlation being strong in the lower limb (upper limb, $R = 0.43$, $p = 0.017$; lower limb $R = 0.73$, $p < 0.0001$; univariable analysis; see **Figure 4**). After normalizing and taking the mean coefficients across the six muscles, the composite coefficient of weakness still correlated with the composite coefficient of shortening for the lower limb ($R = 0.36$, $p = 0.0009$). Evaluation of each muscle group individually found this dependency in the GN only ($R = 0.36$, $p < 0.0001$), with trends in the GM ($R = 0.22$, $p = 0.045$) and HS ($R = 0.21$, $p = 0.052$). In the upper limb, however, the composite coefficient of weakness did not correlate with the composite coefficient of shortening ($R = 0.19$, $p = 0.30$). A trend for this correlation was found only in SS, when examined by individual muscles ($R = 0.48$, $p = 0.016$).

Univariable analysis for the most shortened muscles of the lower limb taken together (**Figures 5A–C**) (i.e., those muscles with $C_{SH} > 0.10$, which was the case for SO (**Figures 5D–F**) GN, GM, and RF), showed that C_{SH} correlated with the coefficient of weakness for patients with values above the median (**Figure 5B**), but not for patients with coefficients of shortening below the median (**Figure 5C**). This was also true for the SO (**Figures 5E,F**) and GN (not shown), taken individually.

Relationships of the Coefficients of Shortening and Weakness With Motor Function

In univariable analyses for the lower limb, each of the composite coefficients of shortening (strongly) and of weakness predicted motor function ($R = -0.62$, $p <$

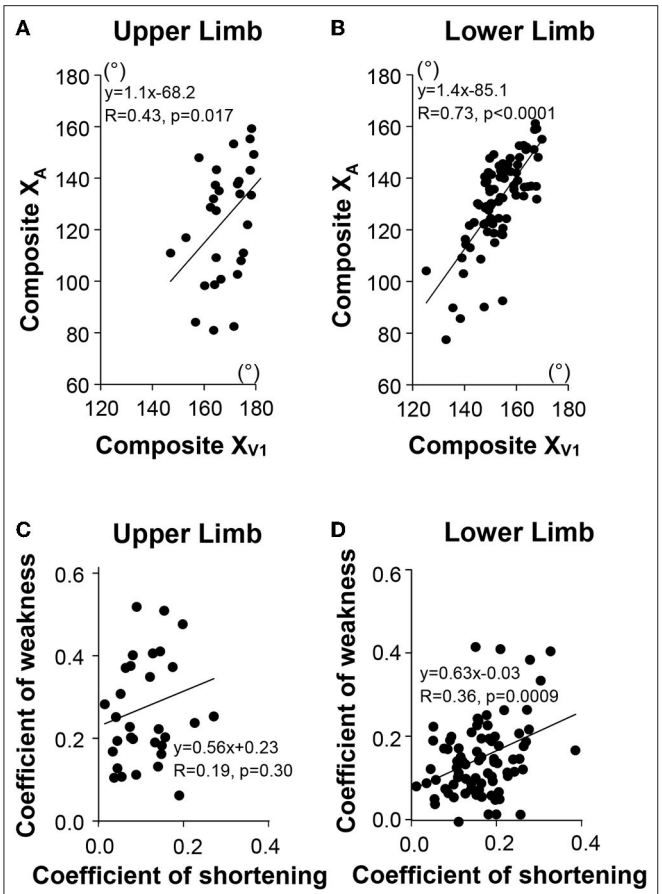

FIGURE 4 | Relationship between passive (X_{V1}) and active movements (X_A) for the upper limb **(A)**, for the lower limb **(B)**. Composite X_{V1}, mean X_{V1} of the six investigated muscles; Composite X_A, mean X_A of the six investigated muscles. Relationship between the mean Coefficient of Shortening and the mean Coefficient of Weakness (Composite Scores) in the upper limb **(C)**, in the lower limb **(D)**, respectively.

0.0001; $R = -0.48$, $p < 0.0001$, respectively, **Table 2A**). When exploring the impact of the extensibility loss in each of the six lower limb muscles taken individually, ambulation speed depended on the coefficient of shortening primarily (**Table 2A**). In the upper limb, the Modified Frenchay score depended on coefficients of weakness only (**Figure 6B**, **Table 2A**).

In the bivariable analysis for the lower limb, the composite coefficient of shortening and the composite coefficient of weakness remained both predictors of maximal ambulation speed once the regression coefficients were adjusted for the effect of the other predictor, although the coefficient of shortening remained a stronger predictor (composite coefficient of shortening $\beta = -0.51$, $p < 0.0001$; coefficient of weakness $\beta = -0.29$; $p = 0.003$; **Figure 6A**, **Table 2B**). In multivariable analysis, none of the six evaluated lower limb muscles remained a sole predictor of maximal ambulation speed once the regression coefficients were adjusted for the effects of the other muscles.

DISCUSSION

The present findings suggest that, in chronic hemiparesis, abnormal muscle properties reach greater severity and contribute more to disability in the lower limb than in the upper limb, while in contrast, the upper limb is affected more by the severity of the impairment of the descending command. In the more shortened lower limb muscles (SO, GN, RF, and GM), the coefficient of weakness correlated with the coefficient of muscle shortening above the median coefficient of shortening only. In the upper limb, a trend for such correlation was present for SS only, one of the most shortened upper limb muscles. In chronic spastic paresis, a tipping point may exist where, past a certain threshold of severity, muscle shortening starts worsening the disordered descending command.

Value of a Clinical Methodology Such as the Five Step Assessment to Draw Inferences Into Actual Muscle Shortening and Actual Impairment of the Descending Command

The Five Step Assessment represents a clinical attempt to distinguish between the muscle disorder and the neurological disorder of spastic paresis, using specific coefficients of impairment (19, 30). However, there is a "double nature" in coefficients of shortening and of weakness, both combining muscular and neural components, that should be discussed.

As for passive X_{V1} measurements (passive range of motion against the tested muscle), when stretching a muscle slowly in a patient at rest, one faces the classic impossibility to safely distinguish between residual spastic dystonia (a neural component of stiffness) and true, passive muscle hypo-extensibility (muscular component) at the end of the passive range (40). Yet, it is commonly accepted by the clinical community that the limitations encountered during maximal passive movements are, for the most part, linked to muscle shortening rather than to residual dystonia. Indeed, except possibly for very large muscles (GM), it is likely that the hand of the examiner typically manages to overcome most of the muscle activation due to residual dystonia. On the other hand, the examiner's hand is bound to fail to overcome all of the passive resistance, as that resistance to passive movement is known to increase exponentially with the amount of stretch in a resting muscle; therefore, passive resisting force is bound to become greater than the maximal force developed by the examiner (49, 50). Thus, while the respective contributions of passive and active resistance at the end of the available range are difficult to clinically quantify, passive phenomena constitute the primary source of range limitation, as demonstrated through X_{V1} measurements after lidocaine blocks that still remain far from the expected physiological values (X_N) (51).

Reciprocally, active X_A measurements also partially depend on the passive resistance that the agonist has to overcome along the way. Yet, the agonist muscle is rarely able to achieve the amplitude reached by the hand of the examiner, therefore X_A is almost invariably lower than X_{V1}, and frequently far

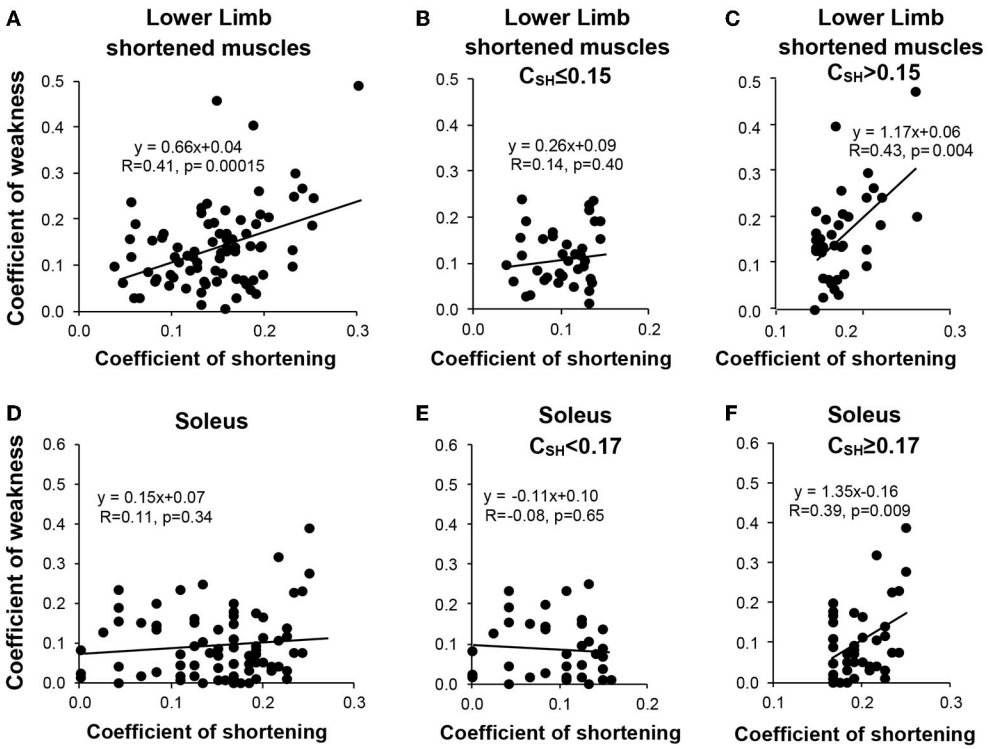

FIGURE 5 | Relationship between the muscular (shortening) and the neurological (weakness) disorders for the shortened muscle groups of the lower limb (sample of the muscle groups with mean CSH > 0.10, i.e., soleus, gastrocnemius, gluteus maximus, and rectus femoris) **(A–C)** and for the soleus muscle **(D–F)**. Left, the entire sample **(A,D)**; middle, coefficients of shortening below the median **(B,E)**; right, coefficients of shortening beyond the median **(C,F)**.

lower (52). This means that the agonist recruitment-induced torque cannot make the limb segment reach the maximal passive range that would be allowed by the antagonist, so that X_A often finds itself far below "exponential" levels of passive antagonist resistance. Therefore, it is likely—even though difficult to clinically demonstrate, except by the marked increase in active range motion observed after lidocaine blocks (51)—that once arrived at that "submaximal" X_A level, the agonist recruitment is mostly limited by active antagonist co-contractions more than by passive antagonist hypo-extensibility.

Overall, once it is accepted that C_{SH} and C_W represent substantially passive vs. active phenomena through these X_{V1} and X_A clinical estimates, why would the relationship between them vary depending on X_{V1} or on the limb (upper vs. lower) from which one selects muscles? In other words, if both X_{V1} (maximal passive movements) and X_A (maximal active movements) manoeuvers were to be hindered in constant proportions by passive and active components, the correlation between the coefficients of shortening and the coefficients of weakness would be constant, whichever the values of X_{V1}. The fact that the correlation emerges only beyond a certain threshold value of X_{V1} is a strong suggestion—if not a demonstration—that muscle shortening itself is associated with further deterioration of the quality of the descending command (e.g., by causing increased co-contraction).

Causal Relationship or "Casual" Association Between Muscle Shortening and Weakness of Motor Command

Although the correlations do not prove causality by themselves, the respective time courses between the muscle disorder and motoneuronal overactivity, the strength of the correlations above a certain threshold and physiological plausibility suggest a causal relationship, as developed below. Interestingly, it has already been demonstrated that ameliorating the changes in the properties of muscle and soft tissue that constitute the "spastic myopathy" (19) is accompanied by gains in function in the lower limb (53).

Chronology: The Muscle Disorder Precedes Motoneuronal Overactivity

A substantial body of biological and histological evidence from animal models with limb immobilization demonstrates very early qualitative and quantitative changes in muscle protein synthesis, measured within hours of immobilization, long before any detectable muscle overactivity (7, 8, 11). This chronology has been confirmed in patients with severe hemiparesis from biomechanical measurements, where the onset of passive tissue stiffness of WF was detected long before true neural reflexive stiffness (21).

TABLE 2 | Respective contribution of the muscular and the neurological disorders to functional impairments.

A. Univariable analyses: for C_{SH} and C_W, respectively

Lower limb	Pred Fact	Soleus		Gastroc		Glut Max		Hamst		Vastus		Rect Fem		Comp score	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Max ambul Speed	C_{SH}	−0.33	0.004	−0.39	<0.001	−0.50	<0.001	−0.58	<0.001	−0.51	<0.001	−0.45	<0.001	−0.62	<0.001
	C_W	−0.37	<0.001	−0.48	<0.001	−0.31	0.006	−0.30	0.008	−0.41	<0.001	−0.16	0.17	−0.48	<0.001
Upper Limb	**Pred Fact**	**Sh Ext**		**Subscap**		**Elbow Flex**		**Pron Quad**		**I: Wrist Fex**		**I: Finger Fex**		**Comp score**	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
MFS (Frenchay)	C_{SH}	−0.32	0.08	−0.31	0.12	0.30	0.10	−0.11	0.54	0.01	0.95	0.18	0.26	−0.22	0.21
	C_W	−0.48	0.008	−0.27	0.20	−0.37	0.04	−0.48	0.006	−0.53	0.002	−0.69	<0.001	−0.43	0.013

B. Bivariable analyses: impact of C_{SH} and C_W (taken together) on motor function when for a given muscle, each of the two coefficients (C_{SH} and C_W) was individually correlated to motor function

Lower limb	Pred Fact	Soleus		Gastroc		Glut Max		Hamst		Vastus		Rect Fem		Comp score	
		β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Max ambul Speed	C_{SH}	−0.33	0.002	−0.22	0.045	−0.45	<0.001	−0.54	<0.001	−0.49	<0.001	–	–	−0.51	<0.001
	C_W	−0.37	<0.001	−0.39	<0.00	−0.20	0.047	−0.19	0.049	−0.38	<0.001	-	–	−0.29	0.003
Upper Limb	**Pred Fact**	**Sh Ext**		**Subscap**		**Elbow Flex**		**Pron Quad**		**I: Wrist Fex**		**I: Finger Fex**		**Comp score**	
		β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
	C_{SH}	−0.34	0.03	–	–	–	–	–	–	–	–	–	–	–	–
	C_W	−0.46	0.008	–	–	–	–	–	–	–	–	–	–	–	–

C_{SH}, coefficient of shortening; C_W, coefficient of weakness; MFS, Modified Frenchay Scale; Max Ambul Speed, ambulation speed over 10 meters (AT10) at maximal speed, barefoot.

Physiological Plausibility: Can Muscle Shortening Aggravate the Abnormal Motor Command?

In models of muscle immobilization in a shortened position in *healthy* animals, muscle spindle firing pathologically increases as shortening of the muscle develops (54–56). These findings were not evident from human microneurography data in spastic paresis, but those studies had insufficient numbers to reach such conclusions (57) or recorded from muscles that were not immobilized in a shortened position [elbow and wrist extensors in Wilson et al. (58) and ankle dorsiflexors in Macefield et al. (59)]. More recently, neuromusculoskeletal models in individuals with chronic stroke-induced hemiparesis suggest that absolute muscle fiber length plays a significant role in the spastic reflex response to imposed movements (60–63). Accordingly, stretch reflex hypersensitivity may be occurring partly through muscle length and extensibility changes, as the pulling force is transmitted more readily to spindles through stiffer hyperelastic structures (4, 5, 54, 56, 64).

A greater muscle afferent input could lead to activity-dependent synaptic plasticity at the spinal level. In chronic hemiparesis, a permanent increase in muscle afferent feedback from the shortened muscle (54, 56) could lead to chronic synaptic sensitization at homonymous α-motoneurons (64–66), decreasing the firing thresholds of these target α-motoneurons. For the antagonist motoneuron pool, a reciprocal situation may occur where activity-dependent synaptic plasticity (66) could sensitize inhibitory synapses in the reciprocal inhibitory pathway, and this would in turn result in increased inhibition of that antagonist motor neuron (and thereby stretch-sensitive paresis). For both the agonist and antagonist motoneuron pools, such facilitatory, respiratory inhibitory, influence from peripheral afferents, might be unleashed by the potentially decreased presynaptic inhibition linked to disengaging supraspinal control after central lesions (67–70). Interestingly, it has been found in animals that remobilization through step-training may restore reciprocal presynaptic inhibition (71).

Threshold of Effect: Level of Severity Beyond Which Muscle Shortening Might Worsen the Abnormal Motor Command

A relationship between the clinical estimates of shortening and of weakness was observed in the more shortened lower limb muscles, beyond the median value of the composite coefficients of shortening only. The same relationship was not found below the median value of the composite coefficients of shortening in the lower limb or in the upper limb, except for a trend noted for the SS muscle. The low level of muscle shortening (8%) in the upper limb may have been insufficient to create significant muscle afferent firing and synaptic sensitization at the spinal level. On the other hand, the mean shortening found in the lower

limb (12%) may be sufficient to reveal this relationship with the clinical tools used here. When looking at individual examples, several muscles fit with this hypothesis: the EF and the WF were characterized by only 2 and 4% of extensibility loss, respectively, and we did not observe any dependence of the neural command on their shortening. In contrast, the extensibility loss was 15% in SS and data did suggest this relationship for this muscle.

Impact of Passive Mechanical Properties on Active Function

This study confirmed that, in each of the six investigated muscles of the lower limb, the loss of muscle extensibility and impairment of the motor command both affect motor function in spastic paresis. Considering the composite scores of the lower limb, muscle shortening correlated with ambulation speed more strongly than did the estimated neural command component, with a steeper slope, explaining 26% of the variance of walking speed. Furthermore, individual correlations between each of the six coefficients of muscle shortening in the lower limb and motor function in multivariable analysis indicate the need to consider *all* of these six antagonist muscles to swing phase for assessment, and potentially for treatment. None of the lower limb antagonists alone predicted lower limb function once the regression coefficients were adjusted for the effects of the other predictors.

This strong dependence of motor function on mechanical impairment in the lower limb corroborates previous results. For example, passive resistance of the plantar flexors significantly affects active dorsiflexion amplitude during the swing phase in subjects with hemiparesis (1, 72). Similarly, in adults with cerebral palsy muscle shortening starts in early life, is more severe than in acquired paresis and correlates with walking speed, stair ascent, and descent speeds (73–76). In the upper limb, even though the composite coefficient of shortening did not correlate with motor function in this study, ultrasound measured average fascicle length in EF correlated with impairment level in the upper limb of stroke subjects in recent reports (77, 78).

The Predominance of Muscle Shortening in the Lower Limb and of Primary Motor Command Impairment in the Upper Limb

Muscle shortening was 50% more severe in the lower than in the upper limb. In contrast, the composite coefficient of weakness in the upper limb was almost double that in the lower limb.

The overall mild coefficients of shortening found in the upper limb muscle groups confirm previous results obtained in large international studies also using the Five Step Assessment (46, 52, 79). In the lower limb, GN had the highest coefficient of shortening in this study, similar to values found in previous large studies (80, 81). Such findings reflect the dramatic changes in muscle structure known from previous biomechanical investigations in the hemiparetic lower limb, including reduced pennation angle, shorter fascicle length, decreased passive dorsiflexion, and increased ankle stiffness (82–87).

Greater impairment of the motor command occurred in the upper limb even though there was less muscle shortening.

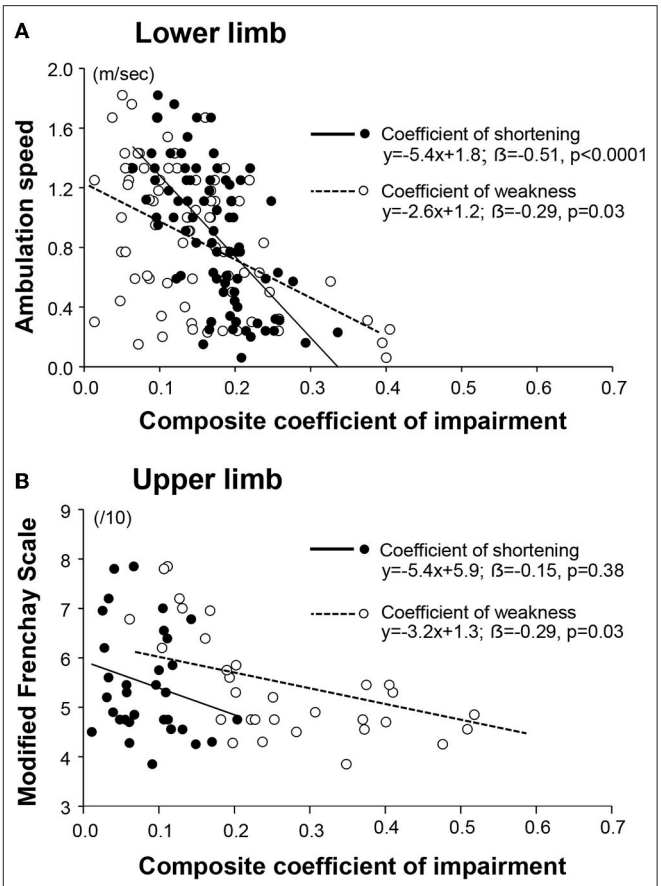

FIGURE 6 | Respective contribution of the muscular and the neurological disorders to functional impairments. The coefficient of impairment refers to the coefficient of shortening or the coefficient of weakness, as indicated in the legend. The composite coefficient is the mean of the individual coefficients for each of the six muscles of the lower limb **(A)**; and of the upper limb **(B)**.

This may indicate that muscle shortening may be only one determinant of the disorder of descending command, obvious other factors being the location and size of the lesion, and the amount of limb disuse since the lesion. Specifically, there is likely to be more severe disuse of the paretic upper limb (also called "functional motor amnesia" or "learned non-use") (88–90), than of the lower limb. Walking represents a critical daily activity necessarily involving both legs while the use of one upper limb might be partly offset when the other functions normally.

Clinical Implications

The understanding of the role of the muscle disorder on the neural command and on motor function should encourage therapists to consider the muscle disorder as a nosologic entity in hemiparesis and to implement meaningful therapeutic interventions specifically on this target (21, 91). Descriptive results found in this study will help to direct these interventions, addressing particularly the plantar flexors, GM and RF in the lower limb, and the shoulder muscles and FF in the upper limb. Besides the central nervous system, skeletal muscle is another

plastic tissue with response to changes in stimulation and in the environment (18, 91–93). Spastic myopathy should be treated with an appropriate physical treatment, using techniques such as prolonged daily self-stretch postures at high load (53), active stretching (94), short wave and ultrasound therapies (95), as it is known that botulinum toxin injections alone will not allow any long-term meaningful muscle lengthening (52, 96, 97). To minimize muscle damage from the acute stages, vibrations (98), stretching postures through positioning (99, 100) and specific splinting (101), or Leucine and vitamin D (102, 103) might also be helpful.

Study Limitations

As considered above in the first section of this discussion, the main limitation of this study lies in the clinical nature of its methodology, which comes short of physiologically assessing "true" descending command and "true" passive muscle extensibility. In addition, the weight of the limb segment to lift up against gravity could have impacted the measure of X_A particularly against the resistance of three of the investigated muscles (SE, GM, and HS). In addition, brain imaging and the role of lesion locations were not analyzed in this study. Lesion locations may have factored into the observed discrepancy between upper and lower limb features. Also, patients were supposed to be affected by purely singular strokes, but some of them, through a long post-stroke state, might have acquired additional subclinical strokes.

In conclusion, increased attention should be directed toward abnormal muscle properties in chronic hemiparesis, particularly in the lower limb in which muscle shortening is severe and harmful to ambulation. Beyond a threshold of severity, the passive biomechanical and structural abnormalities of the most affected muscles may make a significant contribution to the neural command disorder and to functional disability.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

J-MG and MP were involved in the conception and design of the study, in the acquisition and analysis of data, and the draft of the manuscript and figures. CM, DB, JV, BB, NB, EH, and MG participated in the analysis of data, the draft of the manuscript, and checked the final draft of the manuscript. All authors read and approved the final manuscript.

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Therapeutic Effect of Repetitive Transcranial Magnetic Stimulation for Post-stroke Vascular Cognitive Impairment: A Prospective Pilot Study

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Objective: Post-stroke cognitive impairment (PSCI) is resistant to treatment. Recent studies have widely applied repetitive transcranial magnetic stimulation (rTMS) to treat various brain dysfunctions, such as post-stroke syndromes. Nonetheless, a protocol for PSCI has not been established. Therefore, this study is aimed to evaluate the therapeutic effect of our high-frequency rTMS protocol for PSCI during the chronic phase of stroke.

Methods: In this prospective study, ten patients with PSCI were enrolled and received high-frequency rTMS on the ipsilesional dorsolateral prefrontal cortex (DLPFC) for 10 sessions (5 days per week for 2 weeks). Cognitive and affective abilities were assessed at baseline and 2 and 14 weeks after rTMS initiation. To investigate the therapeutic mechanism of rTMS, the mRNA levels of pro-inflammatory cytokines (interleukin (IL)-6, IL-1β, transforming growth factor beta [TGF-β], and tumor necrosis factor alpha [TNF-α]) in peripheral blood samples were quantified using reverse transcription polymerase chain reaction, and cognitive functional magnetic resonance imaging (fMRI) was conducted at baseline and 14 weeks in two randomly selected patients after rTMS treatment.

Results: The scores of several cognitive evaluations, i.e., the Intelligence Quotient (IQ) of Wechsler Adult Intelligence Scale, auditory verbal learning test (AVLT), and complex figure copy test (CFT), were increased after completion of the rTMS session. After 3 months, these improvements were sustained, and scores on the Mini-Mental Status Examination and Montreal Cognitive Assessment (MoCA) were also increased ($p < 0.05$). While the Geriatric Depression Scale (GeDS) did not show change among all patients, those with moderate-to-severe depression showed amelioration of the score, with marginal significance. Expression of pro-inflammatory cytokines was decreased immediately after the ten treatment sessions, among which, IL-1β remained at a lower level after 3 months. Furthermore, strong correlations between the decrease in IL-6 and increments in AVLT ($r = 0.928$) and CFT ($r = 0.886$) were found immediately after the rTMS treatment

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($p < 0.05$). Follow-up fMRI revealed significant activation in several brain regions, such as the medial frontal lobe, hippocampus, and angular area.

Conclusions: High-frequency rTMS on the ipsilesional DLPFC may exert immediate efficacy on cognition with the anti-inflammatory response and changes in brain network in PSCI, lasting at least 3 months.

Keywords: chronic stroke, post-stroke vascular cognitive impairment, depression, repetitive transcranial magnetic stimulation, ipsilesional dorsolateral prefrontal cortex

INTRODUCTION

The global lifetime risk of stroke is increasing (1). Despite treatment, stroke patients often remain disabled due to neurological damage. It has been reported that 30–40% of stroke survivors suffer cognitive decline, and these impairments cause disabilities in performing daily living activities and lower quality of life (2). Rehabilitation for stroke patients includes cognitive training based on their implicated domains and severity. Depression after stroke is also known to hinder rehabilitation and worsen outcomes (3). The efficacy of therapeutic interventions for cognition and depression during the acute and subacute phases has been reported (4, 5). However, during the chronic stage, post-stroke cognitive impairment (PSCI) is unlikely to be ameliorated by conventional therapy (6–8). Therefore, new therapeutic measures have been developed for patients with chronic disabilities.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technology that exerts neuromodulating effects and has been applied to treat the cerebral dysfunction caused by various diseases (9, 10). Clinical trials of rTMS for stroke patients have been conducted, reporting therapeutic effects that include recovery from motor weakness, aphasia, and dysphagia (11–13). However, most of these patients were in the acute or subacute phases. Moreover, rTMS has been used to enhance the cognitive function in patients with Alzheimer's dementia and Parkinson's disease (14, 15). However, research on the effect of rTMS treatment on established cognitive impairment after stroke during the chronic phase is insufficient (16).

Above all, rTMS is used worldwide for its apparent effect in major depression. The effect of a protocol applying high-frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) region is gaining popularity (17), and rTMS' therapeutic effect on post-stroke depression is becoming an established fact. Most of the protocols used involved the administration of a high frequency of 5 Hz or more to the left DLPFC region (18, 19). Nevertheless, there is no definitive protocol for the use of rTMS to enhance cognition in post-stroke patients (20). Our clinical research team established a treatment protocol with high-frequency rTMS over the ipsilesional DLPFC according to our clinical experiences with positive results by retrospective analyses (21). In this study, we aimed to determine whether high-frequency rTMS on the ipsilesional DLPFC had a therapeutic effect in patients with PSCI during the chronic phase of stroke who also exhibited depressive symptoms. As a prospective study, the therapeutic effects were determined *via* psychological and neurobehavioral evaluations.

Despite the widespread application of rTMS in many clinical trials, the mechanisms underlying its therapeutic effects are poorly understood. Recent experimental studies have revealed that rTMS treatment inhibits inflammation and apoptotic cell death while improving the functional recovery in a rat model of focal cerebral ischemia. Among the different mechanisms involved, inflammation is one of the possible targets of rTMS effects, but detailed experimental studies are lacking. To investigate the mechanism of the therapeutic effect of rTMS, the inflammatory status was assessed using peripheral blood samples according to previous findings of augmented inflammatory status in stroke patients (22, 23). Moreover, cognitive functional magnetic resonance imaging (fMRI) findings were obtained from two randomly selected patients to visualize the changes after rTMS treatment in the brain network.

Additionally, to enable comparisons with control stroke patients, a historical control group that had not received rTMS and with available results of follow-up psychological tests was enrolled for retrospective comparative analyses.

MATERIALS AND METHODS

Participants

This prospective clinical trial was approved by the Institutional Review Board (IRB file no: 2018-07-001-015) of the study hospital. The inclusion criteria were as follows: 1) age $\geq$ 20 years, 2) cognitive impairment developed with stroke despite adequate rehabilitation, and duration of PSCI $\geq$6 months. In this study, adequate rehabilitation was defined as at least 3 months of intensive rehabilitation consisting of twice of 30 min duration occupational therapy, which essentially includes tailored cognitive and perceptual training. To screen for cognitive impairment, an Mini-Mental State Examination (MMSE) score of 26 (sensitivity, 71%) was selected as the cutoff (24). PSCI was determined based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and Erkinjuntti imaging criteria (see **Supplementary Material 1**), 3) depression developed after stroke, as determined by a Geriatric Depression Scale (GeDS) score $\geq$ of 10 or clinical symptoms judged by a medical doctor. Additionally, the complaints of patients and their families regarding disturbances in their quality of life due to PSCI were considered for inclusion. Exclusion criteria were 1) those suspected of other causes of cognitive decline, such as Alzheimer's dementia, 2) those who had previously

TABLE 1 | Demographic characteristics of the patients.

Characteristic	Values
Treatment group (*N* = 10)	
Age, years	53.8 ± 8.2 (41–73)*
Gender (Male/Female) (n)	8/2
Education. years	10.4 ± 3.8 (6–16)*
Etiology (n)	10
Cerebral infarction/intracerebral hemorrhage	6/4
Lesion (n)[a]	
Right hemisphere	3
- MCA territory, parietal lobe[b]	1
- Basal ganglia and paramedian pons	1
- Internal capsule, posterior limb	1
Left hemisphere	7
- Basal ganglia	2
- Basal ganglia, frontal lobe and thalamus	1
- Basal ganglia, posterior limb of internal capsule and thalamus	1
- Frontal lobe extending to lateral ventricle	1
- ACA territory, corpus callosum genu and parietooccipital lobes	1
- MCA territory, parietofrontotemporal lobes	1
Post-stroke duration, months	29.5 ± 49.5 (6–169)*
Geriatric depression scale (0–30)	16.9 ± 7.1 (7–29)*
Mini-mental state examination (0–30)	22.2 ± 4.7 (12–26)*
Montreal cognitive assessment (0–30)	16.1 ± 5.6 (8–24)*
Intelligence quotient (40–160)	77.6 ± 14.2 (65–100)*
Auditory verbal learning test	60.6 ± 25.3 (31–100)*
Complex figure test	28.7 ± 9.0 (15–41)*
Memory quotient	88.9 ± 19.8 (68–118)*
Global deterioration scale (1–7)	3.9 ± 0.8 (3–5)*
Clinical dementia rating (0–5)	1.0 ± 0.7 (0.5–2)*
Seoul-instrumental activities of daily living (0–45)	25.3 ± 9.1 (15–42)*
Functional ambulation categories (0–5)	3.8 ± 1.6 (1–5)*
Control group (*N* = 11)	
Age, years	61.8 ± 9.7 (52–80)*
Gender (Male/Female) (n)	8/3
Education. years[c]	12.2 ± 2.3 (9–16)*
Etiology (n)	11
Cerebral infarction/intracerebral hemorrhage	3/8
Lesion (n)[a]	
Right hemisphere	4
- MCA territory, frontoparietoocipital and insula lobe and basal ganglia	1
- Superior frontal lobe	1
- Insula - frontotemporal lobe	1
- Temporal lobe	1
Left hemisphere	6
- External capsule	1
- MCA territory	2
- Basal ganglia	2
- Thalamus	1
Subarachnoid hemorrhage	1
Post-stroke duration, months	18.3 ± 24.6 (6–91)*
Mini-mental state examination (0–30)	21.8 ± 7.7 (4–30)*

Values are given as mean ± SD (range) except for numbers of patients in etiology and lesion. ACA, anterior cerebral artery; MCA, middle cerebral artery; [a]Brain MRI axial view was attached to the **Supplementary Material S5** for each patient. [b]This patient had infarction, which progressed to multifocal hemorrhagic transformations. [c]There is no information on the educational level of one patient in the chart review, so the results are for 10 patients.*

received rTMS treatment within the preceding 6 months, 3) those suspected of having systemic infections at the time of screening, and 4) contraindications for rTMS (e.g., pacemaker, pregnant, metallic implants such as deep brain stimulation electrode, and cerebral aneurysm clip). Ten patients were recruited from November 2018 to January 2019, and their baseline characteristics are shown in **Table 1**. Four of these patients had received continuous rehabilitation therapy before the start of treatment, whereas six had not received hospital-based rehabilitation. The treatment settings did not change throughout the study period. All patients were educated on how to perform the cognitive training on their own during the study period.

rTMS Procedure

Each patient received a total of 10 days of rTMS, on 5 weekdays per week, for 2 consecutive weeks, using a 70 mm figure-8 coil stimulation device (ALTMS®, Remed Co., Korea). The coil was placed over the ipsilesional DLPFC. The intensity of stimuli was 100% of the patient's resting motor threshold (20 Hz, 5-s train duration, and 55-s intertrain interval) for 20 min (2,000 pulses per session). The resting motor threshold was determined as the minimal intensity required to elicit a potential of $> 50\ \mu V$ peak-to-peak amplitude in the contralateral abductor pollicis brevis muscle at least five out of 10 times. Before the intervention, the resting motor threshold was measured for each patient (see **Supplementary Material S2**). The protocol was established based on studies of rTMS treatment for depression or cognitive decline, which involved stimulating the DLPFC that transduces an excitatory stimulus with high-frequency ($\geq$5 Hz) stimulation of the cerebral cortex (18, 25). rTMS was administered by trained medical doctors.

Assessment of Outcomes

The participants underwent baseline psychological tests within 4 weeks before initiation of the rTMS treatment and follow-up tests with the same items 2 and 14 weeks after rTMS initiation. Psychological tests, such as the MMSE (26), Montreal Cognitive Assessment (MoCA) (27), Intelligence Quotient (IQ) from the Wechsler Adult Intelligence Scale Fourth Edition (28), auditory verbal learning test (AVLT), complex figure test (CFT), and memory quotient (MQ), which were derived from the AVLT and CFT performances (29), Global Deterioration Scale (30) and Clinical Dementia Rating – Sum of Boxes (CDR-SB) (31) were used to evaluate cognitive status. The GeDS (32) was also used to assess patients' depressive mood. Two expert clinical psychologists performed cognition and mood evaluations using the authorized nationality-specific versions of the tests.

Several tests for evaluating the motor function, such as the Berg Balance Scale (BBS) (33), trunk impairment scale (34), manual function test (MFT) (35), and Fugl-Meyer Assessment (36), were also conducted by each rehabilitation professional. Additionally, the Stroke Specific Quality of Life Scale (37) was assessed to evaluate satisfaction with the quality of life. The Seoul-Instrumental Activities of Daily Living (38), Modified Barthel Index (39), and Functional Ambulation Categories (40) were used as scales to evaluate daily activities.

Clinical improvement was determined by the significance of the score change as the enrolled patients were diagnosed with chronic PSCI status, where expecting meaningful recovery was difficult (41, 42).

Although the present study was prospectively designed without a control, a retrospective analysis comparing the outcomes in the historical control group was additionally performed using serial MMSE records in the study clinic. All the available data of chronic stroke patients who had received either inpatient or outpatient rehabilitation therapy, from January 2015 to December 2020 with the same criteria as this study enrollment, were collected. A total of 22 patients underwent an MMSE follow-up evaluation with >3 months of interval. Among them, five patients received rTMS treatment around the MMSE evaluation dates, five had participated in another study, and one was in a minimally conscious state. Therefore, these patients were excluded from the additional analyses, and data from 11 patients were used.

Blood Sampling and Assay for Inflammatory Gene Expression

Morning fasting venous blood for inflammatory cytokine analysis was collected within 4 weeks before (baseline), 2 weeks, and 14 weeks after initiation of the rTMS treatment (immediately after and 12 weeks after completion of the rTMS treatment). The gene expression of inflammatory cytokines, tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, transforming growth factor beta (TGF-β), and IL-6, was further assessed. Procedures to quantify the mRNA levels of inflammatory cytokines are described in **Supplementary Material S3**.

Furthermore, to determine whether the patient's basic hematologic status was affected by rTMS treatment, blood samples at baseline and 14 weeks after treatment were compared using the Wilcoxon signed-rank test. Comparisons of nine complete blood count indices (white and red blood cell counts, hemoglobin and hematocrit levels, mean corpuscular volume, mean corpuscular hemoglobin level, red blood cell distribution width, platelet count, and mean platelet volume) and eight chemical analysis indices (sodium, potassium, glucose, chloride, and aspartate transaminase, alanine transaminase, total cholesterol, and triglyceride) were performed (see **Supplementary Material S4**).

Acquisition, Processing, and Analysis of fMRI

Data Acquisition

Twice fMRI was performed within 4 weeks before the initiation of rTMS and 12 weeks after completion of the treatment. Two randomly selected patients out of the 10 underwent fMRI. For cognition fMRI, the "language sentence completion" task was given, which involves finding appropriate words by showing a sentence with a blank space (for example, "If you go to the mountain, there are ___." Participants had to generate a word such as "trees" to complete the sentence in mind and not out of mouth). A total of 24 sentences were presented at 5-s intervals, and a 40-s interval was provided for every four sentences.

Scans were obtained using a GE SIGMA 3.0T (General Electric, Milwaukee, Wisconsin). The fMRI sequence parameters were as follows: slice thickness, 4 mm; repetition time [TR], 2,000 ms; echo time [TE], 30 ms; flip angle = 90, matrix = 64 (frequency) × 64 (phase); number of excitations [NEX] = 1, Freq. field of view [FOV] = 24 cm; and phase FOV = 1.0.

Data Preprocessing

We corrected the differences in timing across the slices, followed by realigned head movements. We subsequently used images from echo planar imaging for normalization instead of the damaged T1-weighted images (43). The images were smoothed with an isotropic Gaussian kernel (8 mm full width at half maximum). fMRI analysis for significant changes from baseline to 12 weeks after completion of rTMS was conducted using SPM12.

General Linear Model

We constructed a general linear model in a task fMRI language sentence completion test. In the patient-level analysis, we used "active condition > rest" as the contrast of interest. Multiple comparison correction was performed using a cluster-extent method with a cluster-forming (uncorrected) p threshold of < 0.005.

Safety Assessment

The patients were monitored from the time of enrollment until completion of the study for any adverse events defined in the Common Terms Criteria for Adverse Events (CTCAE) version 5.0. Reports of adverse events that might be related to the intervention were also available after the study.

Statistical Analysis

SPSS (IBM, version 21) was used for the data analysis. Using the Wilcoxon signed-rank test, the score from each functional evaluation immediately after rTMS session completion and at 12 weeks after session completion was compared with the baseline score. Statistical significance was set at $p < 0.05$. The changes in MMSE scores of the rTMS treatment group and the historical control group were compared using the Mann-Whitney test.

Changes in cytokine levels after treatment were analyzed using the Wilcoxon signed-rank test, and Spearman correlation analysis was performed to assess the relationship between decrements in the gene expression of each inflammatory cytokine and gains in the score representing cognitive outcome immediately after and after 14 weeks of treatment from the baseline values.

RESULTS

Demographic and Clinical Characteristics

The demographic characteristics of the 10 patients (8 men and 2 women) are summarized in **Table 1**. The mean post-stroke period until enrollment in the study was 29.5 months (ranging from 6 and 169 months), which corresponds to the state where the recovery of function has reached a plateau after stroke. There were 6 cases of cerebral infarction and 4 cases of intracerebral hemorrhage. Lesions were located in

the right cerebral hemisphere in three patients and in the left hemisphere in seven. Nine of them received 6 months and one received 3 months of intensive rehabilitation that include cognitive training after acute care of stroke. After the stage, all of them received 10 min duration guidelines for cognitive training at home on every 2–3 months interval outpatient visit. Three patients had diabetes and were taking medication, and one was diagnosed with diabetes at the baseline. Further, three patients with hypertriglyceridemia were reported in the initial evaluation, and all were taking medications to reduce the risk of recurrent stroke before rTMS treatment.

Unfortunately, the clinical psychologist performing the MMSE, MoCA, IQ, MQ, and CDR-SB screening and efficacy evaluations suddenly died due to an emergent disease. For this reason, some data were omitted that include three patients' baseline efficacy evaluations. To compensate for the lost data, the medical records were reviewed, and the evaluation results acquired during routine medical care within the assessment window period were filled with the values. The evaluations were conducted by doctors who passed evaluation training courses, and through this, it was possible to supplement some of the MMSE, GeDS, MoCA, CDR-SB, and Global Deterioration Scale data.

The baseline cognitive score of the patients evaluated through the MMSE was 22.2, and the average ambulatory ability, as seen through the Functional Ambulation Categories score, was 3.8. Among them, 8 patients were evaluated as having the ability to walk on flat ground without aid from other people, with a score of 3 or higher, and the other two patients were evaluated as 1 point.

All patients were diagnosed with depression either by psychological assessments or clinical judgment prior to rTMS intervention, and seven were taking antidepressants. Of the 10 patients with depression, seven were evaluated as mild and three as severe.

In the assessment immediately after completion of the rTMS treatment session, IQ, MQ, AVLT, CFT, SSQoL, and MFT scores were significantly higher than those at baseline ($p < 0.05$). In the assessment conducted 14 weeks after baseline, improvement in cognition seemed obvious, showing sustained increased scores of AVLT, CFT, and MQ, which were increased immediately after completing rTMS treatment ($p < 0.05$). Moreover, MMSE and MoCA scores, which were not increased at 2 weeks after initiation of rTMS, were increased at 14 weeks ($p < 0.05$). CDR-SB showed a significant decrease at the last evaluation ($p < 0.05$). Moreover, MFT scores that were increased immediately after the treatment from baseline also showed a sustained improvement in hand function at the last evaluation along with other motor ability scores, BBS, and trunk impairment scale, which were not increased immediately after treatment ($p < 0.05$; **Table 2**).

While the GeDS scores did not show significant change among all patients, those with moderate-to-severe depression (GeDS $\geq$ 20) showed amelioration of the score with marginal significance after the treatment ($p = 0.057$). Analyses regarding antidepressant medication status and brain lesion side did not reveal any significance in the affective outcomes of the patients.

A comparison analysis with the historical control group and 11 patients with PSCI (eight men and three women) were conducted. Their mean age was 53.8 $\pm$ 8.2 (between 41 and 73), and the mean post-stroke duration was 18.3 $\pm$ 24.6 months (between 6 and 91 months) at the time of baseline MMSE assessment (**Table 1**). The average follow-up evaluation of the control group was 13.7 $\pm$ 9.8 months (between 5 and 35 months). The mean baseline MMSE score was 21.8 $\pm$ 7.70, which was not different from the patients enrolled in this study. The follow-up score of the historical control group was 22.5 $\pm$ 7.57, which did not change during the interval ($p = 0.356$). Although there was no difference in comparison of the changed scores between the control group (0.73 $\pm$ 3.90 SD) and the treatment group in this study (2.20 $\pm$ 2.04 SD), the patients in the present study showed a significant increment only in the MMSE score 3 months after treatment ($p < 0.05$).

Changes in fMRI

We found brain areas showing greater task-evoked activation after rTMS. More specifically, the right angular gyrus of both participants was activated during the language sentence completion task. Additionally, other brain areas showed greater activation: the right medial frontal gyrus for patient no. 6 ($p = 0.039$); the left supplementary motor area, right hippocampus, right postcentral, left medial frontal, and left postcentral showed greater activation after rTMS for patient no. 3 ($p = 0.063$; **Figure 1** and **Supplementary Material S6**).

Downregulation of Inflammatory Cytokines and Correlation With Cognitive Improvement

Reverse transcription polymerase chain reaction (PCR) results from the blood drawn just after the rTMS treatment session indicated downregulated expression of IL-1β, IL-6, TNF-α, and TGF-β mRNA when compared to those before the treatment ($p < 0.05$). Peripheral blood samples drawn 12 weeks after completion of the treatment revealed a sustained reduction in gene expression of IL-1β ($p < 0.05$; **Figure 2**), while there was no change in C-reactive protein (CRP) level ($p = 0.838$).

We examined whether the decrease in the expression of each cytokine correlated with changes in cognitive function, depression index, or motor function. The amount of reduction in the mRNA level of IL-6 immediately after the rTMS treatment session from the baseline was highly correlated with increments in AVLT ($r = 0.928$) and CFT ($r = 0.886$), respectively ($p < 0.05$; **Figure 3**).

Safety

In the blood test, total cholesterol was slightly higher than the normal range in one patient initially but decreased to the normal range after rTMS treatment. There were no reports of serious adverse events, but some mild (grades 1 and 2) adverse events were observed. Hyperglycemia was reported in two patients without prior diabetes at 14 weeks after initiation of treatment, but they showed improvement at clinical follow-up and did not meet the diagnostic criteria for diabetes. There was an increment of aspartate and alanine aminotransferase in one patient corresponding to CTCAE grade 1 before rTMS

TABLE 2 | Changes in scores of functional evaluation after rTMS.

	Baseline	2 weeks	14 weeks	*P*-value (*n*)	
				0–2 week	0–14 week
MMSE	23.0 (17–26)	24.7 (18–28)	25.3 (19–30)	0.062 (7)	0.041* (7)
MoCA	18.3 (11–24)	19.8 (11–24)	20.3 (11–25)	0.059 (6)	0.042* (6)
IQ	79.7 (66–100)	88.2 (72–109)	83.7 (74–99)	0.046* (6)	0.058 (6)
AVLT	65.5 (34–100)	81.5 (49–117)	87.2 (62–112)	0.042* (6)	0.028* (6)
CFT	29.2 (15–41)	35.5 (16–47)	35.2 (18–50)	0.028* (6)	0.028* (6)
MQ	92.3 (69–118)	104.7 (71–137)	110.7 (87–137)	0.028* (6)	0.028* (6)
GIDS	3.5 (3–4)		3.0 (2–4)		0.083 (6)
CDR-SB	5.5 (1–12)		3.75 (0.5–9)		0.018* (8)
BBS	47.4 (20–56)	49.4 (22–56)	49.5 (22–56)	0.066 (10)	0.042* (10)
TIS	16.5 (7–21)	17.1 (8–21)	17.7 (9–23)	0.109 (10)	0.026* (10)
MFT	63.8 (0–96.88)	67.5 (0–96.88)	67.8 (0–96.88)	0.027* (10)	0.027* (10)
FMA	48.4 (4–66)	50.4 (4–66)	49.9 (4–66)	0.068 (10)	0.066 (10)
MBI	74.1 (21–98)	76.5 (33–100)	76.4 (33–100)	0.068 (10)	0.168 (10)
FAC	3.8 (1–5)	3.9 (1–5)	3.9 (1–5)	0.317 (10)	0.317 (10)
S-IADL	25.3 (15–42)	23 (15–42)	25 (15–42)	0.285 (10)	0.440 (10)
SS-QoL	137.1 (61–210)	150.7 (62–245)	149 (62–209)	0.043* (10)	0.182 (10)
GeDS	18.7 (12–29)	16.7 (3–30)	14.2 (6–29)	0.399 (6)	0.136 (6)

*All values are presented a mean (range). *p < 0.05, Wilcoxon signed-rank test was performed at each follow-up time point compared to the baseline, except for patients who missed even one outcome. GeDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; IQ, Intelligence Quotient; AVLT, auditory verbal learning test; CFT, complex figure test; GIDS, Global Deterioration Scale; CDR-SB, Clinical Dementia Rating – Sum of Boxes; S-IADL, Seoul Instrumental Activities of Daily Living; MMT, Manual Muscle Test; BBS, Berg Balance Scale; TIS, trunk impairment scale; MBI, Modified Barthel Index; SS-QoL, Stroke Specific Quality of Life Scale; MFT, manual function test; FMA, Fugl-Meyer Assessment; FAC, Functional Ambulation Categories. Two weeks indicate immediately after 2-week treatment and 14 weeks indicate 12 weeks after completion of 2-week treatment. (n) means the patient number that was analyzed for change of score from baseline evaluation at each time point.*

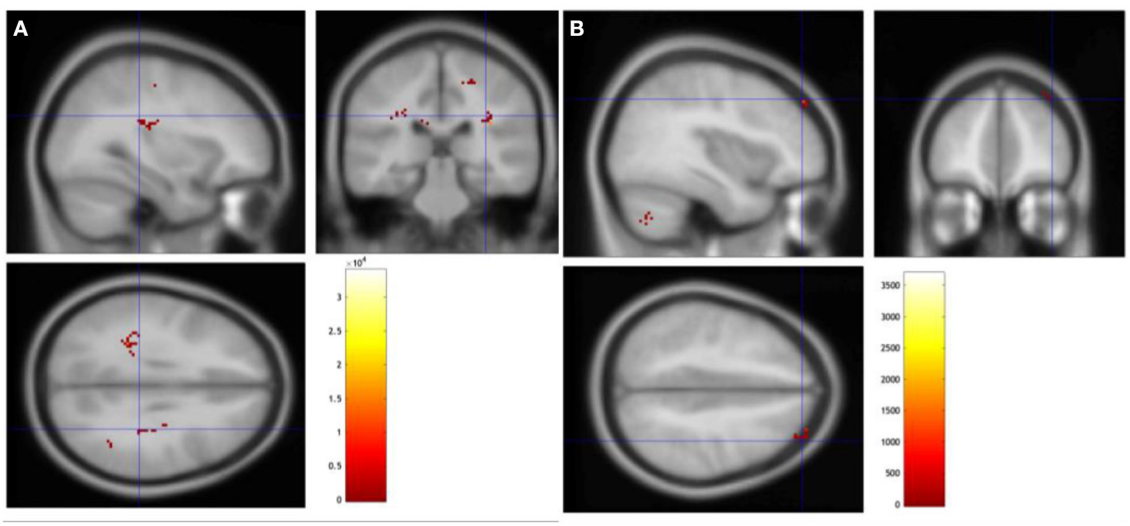

FIGURE 1 | Changes in fMRI during language sentence completion task. **(A)** Change in patient no. 3. **(B)** Change in patient no. 6.

treatment, but this was normalized after approximately 1 week of medication.

Moreover, two patients reported constipation symptoms, and one patient each reported vitreal floaters and headaches during the study period. All patients were classified as CTCAE grade 1, which was not directly related to rTMS treatment. Another patient who reported headache had complained of intermittent headache before enrollment in the study. Additionally, one patient reported the appearance of a spider web in her left vision after rTMS. The corresponding ophthalmologist diagnosed a vitreal floater that seemed to have existed before rTMS treatment, without any sign of retinal problems (44, 45), indicating that the

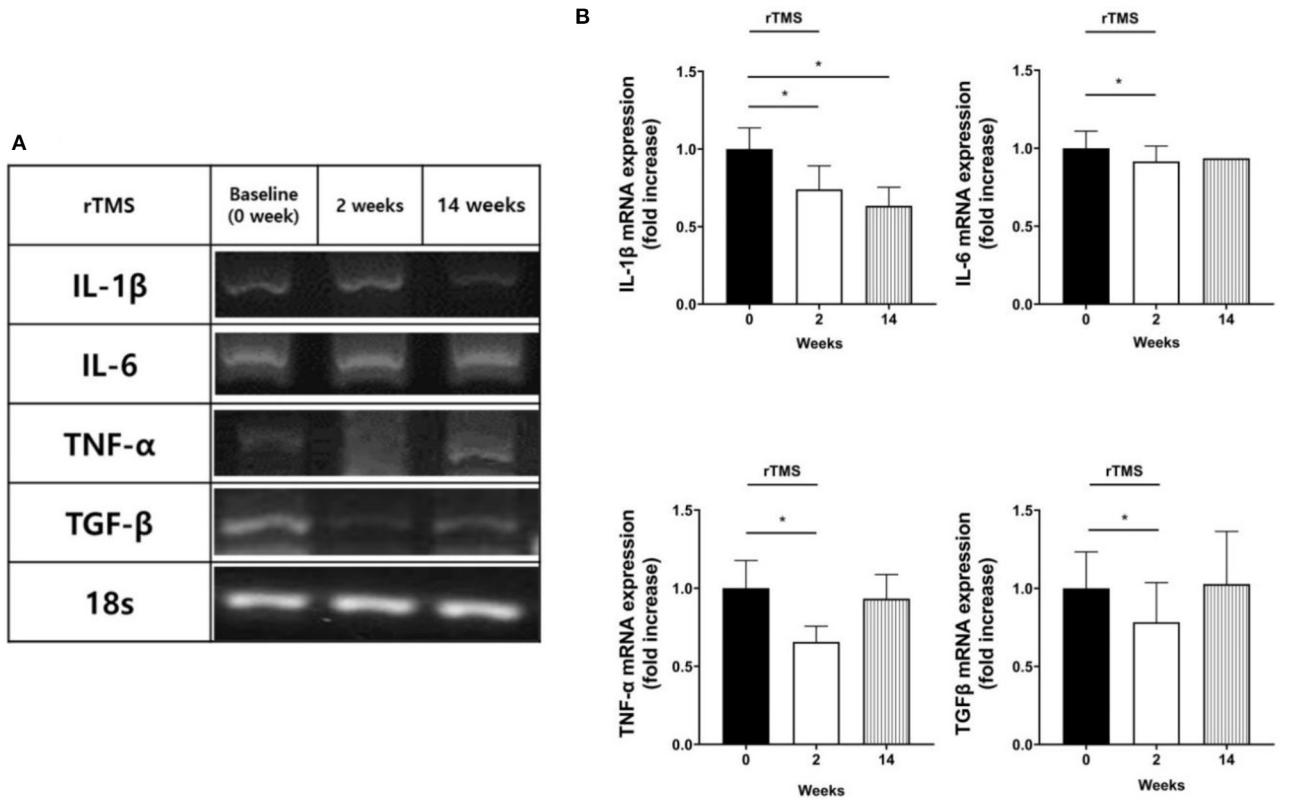

FIGURE 2 | mRNA expression results. Reverse transcription polymerase chain reaction (PCR) products of target mRNAs (IL-1β, IL-6, TNF-α, and TGF-β). **(A)** Representative agarose gel electrophoresis of PCR products on cDNA from human peripheral blood mononuclear cells. **(B)** The relative levels of target mRNA expression. The amount of mRNA expression was quantified by densitometry of bands in comparison to 18s. Densitometry of mRNA band was quantified by three independent scans presented as mean ± standard error (SE) of the mean for ten patients. $^*p < 0.05$; Wilcoxon signed-rank test was used for each follow-up point compared to the baseline.

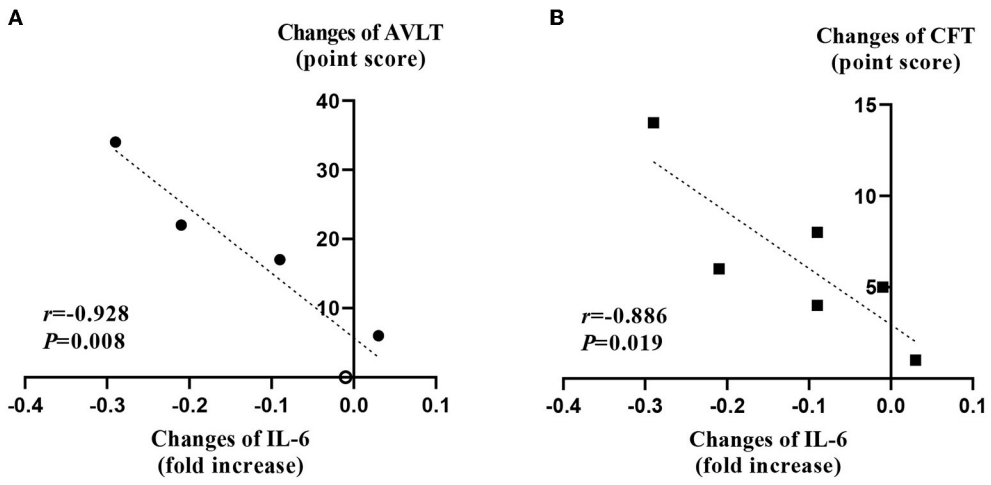

FIGURE 3 | Correlation analysis between changes of interleukin-6 and cognitive function test. **(A)** The change of the IL-6 negatively correlated with the change of the score of AVLT test after 2 weeks of rTMS treatments. The empty circle indicates an overlapped value from two different patients. **(B)** The change of the IL-6 negatively correlated with the change of the score of CFT test after 2 weeks of rTMS treatments. These figures depict results of 6 patients. IL-6, interleukin-6; AVLT, auditory verbal learning test; CFT, complex figure test.

patient was able to sense a vitreal floater that was not perceived before treatment.

DISCUSSION

This study was conducted to determine the possibility of inducing cognitive recovery by using rTMS treatment for patients with PSCI that persisted for more than 6 months, despite intensive rehabilitation treatment for cognition. The results indicated a cognition-enhancing effect in the patients *via* increments in the IQ, AVLT, CFT, and MQ scores just after 2 weeks of rTMS completion. After 3 months, the increments in the AVLT, CFT, and MQ scores were sustained ($p < 0.05$), and the IQ was increased with marginal significance ($p = 0.058$). Moreover, the MMSE and MoCA scores, which did not show changes 2 weeks after the rTMS, were also increased at this time. Furthermore, considering the prevalent knowledge of resistance to treatments in patients with PSCI and that the result also did not show a positive change in the MMSE score in the historical control group, the outcomes in the treatment group seem to be meaningful. According to the changed CDR-SB scores at 3 months after treatment completion, the dementia-ameliorating effect of rTMS seems remarkable. CDR-SB has been acknowledged as a sensitive method for detecting the progression of cognitive impairment (46). The Global Deterioration Scale scores showed only a trend toward ameliorated cognitive dysfunction, and this weak result might have been caused by the sparse rating score system.

With regard to depression, the overall mean scores of the GeDS did not show a significant change in all patients. However, the score decreased in those with severe depression, although with marginal significance. As the efficacy of rTMS treatment has been previously revealed in patients with major depression who do not respond to conventional treatment due to their severe degree of depression, the Food and Drug Administration (FDA) has approved this intervention for such patients (47). Previous studies have also revealed that rTMS monotherapy has a greater antidepressant effect than rTMS add-on therapy (48). Because the total number of participants and non-medicated depressed patients ($n = 3$) was small, the effect on depression could not be fully addressed in this study. Further, the characteristics of patients with substantial cerebral injury could have affected the results.

The BBS, trunk impairment scale, and MFT scores indicating motor function also showed significant improvements after 3 months of treatment completion. Preparation for movement involves the complex and extensive regulation of multiple brain centers (49). The DLPFC plays a crucial role in linking cognition and motor function, and its connections can reportedly reach the primary motor cortex and transfer important information for motor execution (50). Therefore, it can be inferred that the application of rTMS to the DLPFC affected the motor cortex and led to improved motor function.

Regarding the cognition-recovering effect of rTMS in patients with PSCI, the stimulation protocol could be of importance. In the present trial, rTMS was administered to stimulate the DLPFC in the ipsilesional hemisphere at 20 Hz for 10 days. The DLPFC plays an important role in various cognitive processes, such as working memory, planning, banning, and abstract reasoning (11, 51, 52). To date, rTMS studies on cognition have mostly been applied to the left DLPFC, and recent clinical research has reported improvements in the immediate and delayed recall by high-frequency rTMS over the left DLPFC in patients with left hemispheric stroke (53). Although reports on the cognition-enhancing effects of rTMS on the left DLPFC outnumber those of the right side stimulation, as there has been a report of cognitive improvement by rTMS in the right inferior frontal gyrus of patients with Alzheimer's disease or mild cognitive impairment, the application site of rTMS remains controversial (54). Moreover, animal experiments using the ischemic stroke model revealed the efficacy of rTMS at reducing ipsilesional apoptosis, which involves post-stroke neuronal deterioration (55, 56). Along with the abovementioned results, considering that positive effects appeared with increased scores in the cognitive assessments of MMSE, MoCA, IQ, AVLT, CFT, and MQ in this study, high-frequency rTMS on the ipsilesional DLPFC could be a usable protocol for PSCI patients.

Although our sample size was small, the present study provided an understanding of the therapeutic mechanism of rTMS for PSCI. First, an anti-inflammatory effect that spread to the systemic circulation was observed with the decreased gene expression of pro-inflammatory cytokines. Immediately after the rTMS session, the IL-1β, IL-6, TNF-α, and TGF-β levels were decreased, and the depletion of IL-1β was retained 3 months after rTMS. These findings conform with those of previous studies. In a clinical study on elderly patients with refractory depression, serum levels of IL-1β and TNF-α were decreased after rTMS treatment (57). Another study on cerebral infarction also revealed lowered serum levels of IL-6 and TNF-α following rTMS treatment (58). In animal experiments using a brain injury mouse model, rTMS exerted a neurological deficit-ameliorating effect by inhibiting the activity of the TGF-β pathway (59). In the present study, the reduction in the IL-6 gene expression showed a strong correlation with the increments in AVLT ($r = 0.928$) and CFT ($r = 0.886$) scores immediately after the rTMS treatment. This result might be significant in understanding the impact of rTMS on inflammation and the role of rTMS in cognitive impairment in a clinical study that revealed greater cognitive decline at higher IL-6 levels (60). Besides the cytokines we investigated, a previous study showed the possibility of ischemia-induced amyloid beta and tau pathology involvement in the pathogenesis of PSCI (61). Moreover, the impact of inflammatory change in the brain of Alzheimer's dementia has been reported *vice versa* (62). Therefore, investigation of the therapeutic mechanism of rTMS targeting PSCI may adopt biomarkers of Alzheimer's disease in the following research.

Second, according to the fMRI findings, both patients showed increased activity of the right angular gyrus, which is a brain region involved in high-level cognitive functions, such as visuospatial attention, decision-making, solving familiar problems, and reorienting attention to important stimuli (63, 64). Additionally, some activation areas differed between the two patients, which may be due to the differences

in the ratio of the functional networks preserved in both hemispheres and the left and right positions of the lesion (65). A previous study reported a decrease in the functional connectivity of the medial prefrontal cortex, left temporal lobe, and hippocampus in patients with PSCI (66, 67). The result suggests that the activation of the right hippocampus and left medial frontal lobe of patient 3 and the right medial frontal area of patient 6 was due to the rTMS treatment. However, this study did not include electroencephalography or other neurophysiological assessment, understanding of baseline mechanism regard to the neural network, such as spike-time dependent plasticity, has not fully been achieved (68). By enlightening the role of neural network in each cognitive function, stimulation of different sites could exert more effect in future research.

In terms of safety, blood chemistry indices reported as abnormal were temporary and could not be regarded as a side effect of rTMS. Instead, the decreasing pattern of total cholesterol was consistent with previous studies showing that rTMS lowers the total cholesterol by altering the lipid metabolism (69). Therefore, chemical confirmation through a large population study is required to confirm these adverse reactions. Consequently, considering the present study along with previous reports, rTMS treatment can be considered a safe treatment technique.

This study had some limitations. First, the sample size was small, with only 10 participants, and the study was conducted without a randomized control group. Furthermore, a learning effect through repeated measurements could not be ruled out. However, other studies have also used MMSE as a short-term cognitive function follow-up assessment tool (70). Repeatable Battery for the Assessment of Neuropsychological Status is known as a tool to exclude content practice effect (71), but since this test is difficult to apply to patients with low cognitive function, other appropriate psychological tests need to be developed and used for short-term evaluation studies. Nevertheless, differential results at 2 and 14 weeks after the initiation of rTMS, such as the significantly increased MMSE and MoCA scores at the last examination and not immediately after the treatment, suggest a real improvement in cognition.

Studies with larger sample sizes with matched control groups and using cognitive evaluation tools to avoid learning effects should be conducted.

CONCLUSIONS

In summary, we have obtained significant results that suggest that high-frequency rTMS treatment for ipsilateral DLPFC may exert beneficial effects on the short- and long-term improvement of cognitive function in chronic PSCI patients by reducing inflammation in the brain and altering the functional connectivity of several brain regions.

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 IRB file No: 2018-07-001-015. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK designed the study and performed critical revision of the article. BC conducted clinical research and drafted the manuscript. JK and JMK involved in the statistical analysis. J-WC and JCho have quantified pro-inflammatory cytokines using reverse transcription polymerase chain reaction. KK and JCha analyzed fMRI and describe the corresponding results. 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.2022.813597/full#supplementary-material

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Virtuous and Vicious Cycles of Arm Use and Function Post-stroke

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Large doses of movement practice have been shown to restore upper extremities' motor function in a significant subset of individuals post-stroke. However, such large doses are both difficult to implement in the clinic and highly inefficient. In addition, an important reduction in upper extremity function and use is commonly seen following rehabilitation-induced gains, resulting in "rehabilitation in vain". For those with mild to moderate sensorimotor impairment, the limited spontaneous use of the more affected limb during activities of daily living has been previously proposed to cause a decline of motor function, initiating a vicious cycle of recovery, in which non-use and poor performance reinforce each other. Here, we review computational, experimental, and clinical studies that support the view that if arm use is raised above an effective threshold, one enters a virtuous cycle in which arm use and function can reinforce each other via self-practice in the wild. If not, one enters a vicious cycle of declining arm use and function. In turn, and in line with best practice therapy recommendations, this virtuous/vicious cycle model advocates for a paradigm shift in neurorehabilitation whereby rehabilitation be embedded in activities of daily living such that self-practice with the aid of wearable technology that reminds and motivates can enhance paretic limb use of those who possess adequate residual sensorimotor capacity. Altogether, this model points to a user-centered approach to recovery post-stroke that is tailored to the participant's level of arm use and designed to motivate and engage in self-practice through progressive success in accomplishing meaningful activities in the wild.

Keywords: stroke, neurorehabilitation, learned non-use, computational neurorehabilitation, decision-making, compensatory movement, wearable sensors

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INTRODUCTION

Current rehabilitation of upper extremities (UEs) in clinical settings often fails to improve the quality of life of people who have had a stroke for two main reasons. First, whereas principle-based (1) rehabilitation focused on improving UE function or on reducing impairment requires very large doses of intensive movement practice (2–5), such doses are far from being the norm in clinical settings, at least in the US (6) and in Europe (7). Second, rehabilitation is often "in vain", as an important reduction in function and use is commonly seen subsequent to rehabilitation-induced gains. For example, it has been shown that patients experience functional deterioration during the 4 years following hospital discharge, which puts them back to where they were just 2 months post-stroke (8). Similarly, in a re-analysis of UE use of the immediate treatment group of the EXCITE trial, one-quarter of the participants showed a marked decrease in use in the 2 years following treatment (9).

Here, we propose for mild to moderately impaired stroke survivors that increasing daily use of the more affected UE following motor therapy can solve the two above problems: if goal-directed UE movements in daily activities are seen as a single practice movement, such "self-practice" could potentially provide the large dose of movements and sensorimotor feedback needed to improve performance. The improvement in performance could then counteract the deteriorations in use by engaging the patients in a virtuous cycle of recovery, in which high levels of use and function reinforce each other (10) (**Figure 1A**). In contrast, a low level of use below a threshold may initiate a vicious cycle in which non-use and poor performance reinforce each other (**Figure 1B**) (10–12), leading to progressive deterioration in motor function and a further reduction in use.

In the following, we review earlier work that has led to the concept of virtuous and vicious cycles and more recent mechanistic models that yield such cycles. We then review experimental and clinical studies supporting such a "use it and improve it or lose it" phenomenon and the existence of an effective threshold in use and function separating the virtuous and vicious cycles. We next review recent work that aims at enhancing UE use in daily activities, including our recent work using ecological momentary assessment (EMA), and propose how to further develop the efficacy of embedding rehabilitation in the wild for those who possess enough residual sensorimotor capacity to benefit from more practice with motivational reminders to use the paretic limb.

ACQUIRED NON-USE AND THE ORIGIN OF THE VIRTUOUS/VICIOUS CYCLES OF RECOVERY POST-STROKE

The human motor system is highly redundant, offering multiple possible behavioral solutions to achieve a goal. When the behavior deviates from that observed in neurotypical individuals, we refer to the behavior as "compensatory" (13). For instance, individuals post-stroke frequently use their less affected hand to perform reaching movements. Because of the often large motor and sensory deficits immediately following stroke, the initial compensation is "mandatory". However, as performance improves due to spontaneous recovery or rehabilitation, or both, the movements with the more affected arm are now possible but often not performed spontaneously (14, 15). Such "a non-use", which is measured by the difference between what the patient can do when instructed and what the patient does when given a choice (16–18), was originally described as a learning process according to which preference for the less affected arm due to past unsuccessful repeated attempts to use the more affected UE (12, 19).[1] It was also proposed that acquired non-use subsequently causes a loss of motor function leading to the acquisition of compensatory behaviors (12, 19, 21). Note that besides the loss of function, there may be other factors originating and perpetuating these compensatory behaviors, such as higher effort requirements associated with using the more affected limb (22, 23) and sensory perception and attention deficits after stroke. A re-analysis of baseline data from the EXCITE trial (24) shown in **Figure 2A** illustrates the often-considerable extent (and variability) of such acquired non-use in the chronic stroke population.

Acquired non-use has long been recognized to be a major issue facing patients post-stroke, but only recently has there been an attempt to operationalize this complex phenomenon where multiple physiological (e.g., sensorimotor impairment, lesion load), behavioral (e.g., expected success and effort), and psychological factors (e.g., self-efficacy, perceived effort) intersect (20, 28, 29). Although little is known about how these multiple factors interact to create acquired non-use, interventions that aim at reducing non-use have been developed. In particular, constraint-induced movement therapy (CIMT), which forces the use of the more affected by restraining the less affected limb with a mitt, while intensively training the use of the more affected arm, has been shown to reduce non-use (11, 24, 30, 31). However, CIMT is indicated for only ∼15% of all stroke cases (e.g., being able to voluntarily extend the wrist and at least two fingers through a specified range of motion) (32). In addition, the mitt can only be worn by a few patients, requires supervision, and is often disliked. Importantly, the mitt prevents bimanual tasks, which make up the majority of daily arm and hand activities (33, 34). Furthermore, the common factor in CIMT and its variants is the delivery of a high number of repetitions. Besides compromising treatment adherence (35), large doses of practice are difficult to implement in the clinic, and, as we recently showed, highly inefficient (i.e., with low gain in outcome per hour of practice) (26).

VIRTUOUS AND VICIOUS CYCLES ARISE FROM PLASTIC INTERACTIONS BETWEEN MOTOR AND DECISION-MAKING SYSTEMS: INSIGHTS FROM A COMPUTATIONAL MODEL

Inspired by Taub's ideas, Han et al. proposed a computational model of brain plasticity and motor learning to unmask non-linear interactions between arm use and functional motor recovery (10). The model contains two main plastic neural processes: (1) A bilateral model of the motor cortex/cerebellum

[1]The original term "learned non-use" (LNU) was developed from studies in a monkey deafferentation model that is not the same as a stroke model. In spite of these different models, Taub et al. perpetuated the use of the term in their human stroke model work. However, there is no consensus as to what extent the observed non-use post-stroke is acquired through operant conditioning of early attempts to use the paretic limb that failed/negative reinforcement, or due to other factors such as diminished attention from reduced sensory perception, etc. Therefore, instead of the term LNU, we use "acquired non-use" to acknowledge the discrepancy between the deafferentation and stroke models. In our empirical and modeling work (10, 17, 20), we have developed an objective measure of "acquired non-use" using a paradigm first introduced by Sterr et al. (16) where we take the difference in the tasks or targets attempted in a "free" (spontaneous) condition in which the participant can choose either arm to capture the target, to that in a "forced" condition in which the participant must use the paretic limb to capture the target. The degree to which the "forced" condition is greater than the "free" condition captures the magnitude of spontaneous non-use and is consistent with the Andrews and Stewart article (14), "He can, but does he." Our objective measure highlights the action selection process in arm use that precedes the actual behavior and that is of great interest to rehabilitation scientists who seek to develop interventions to promote the selection of the paretic limb spontaneously in the natural environment.

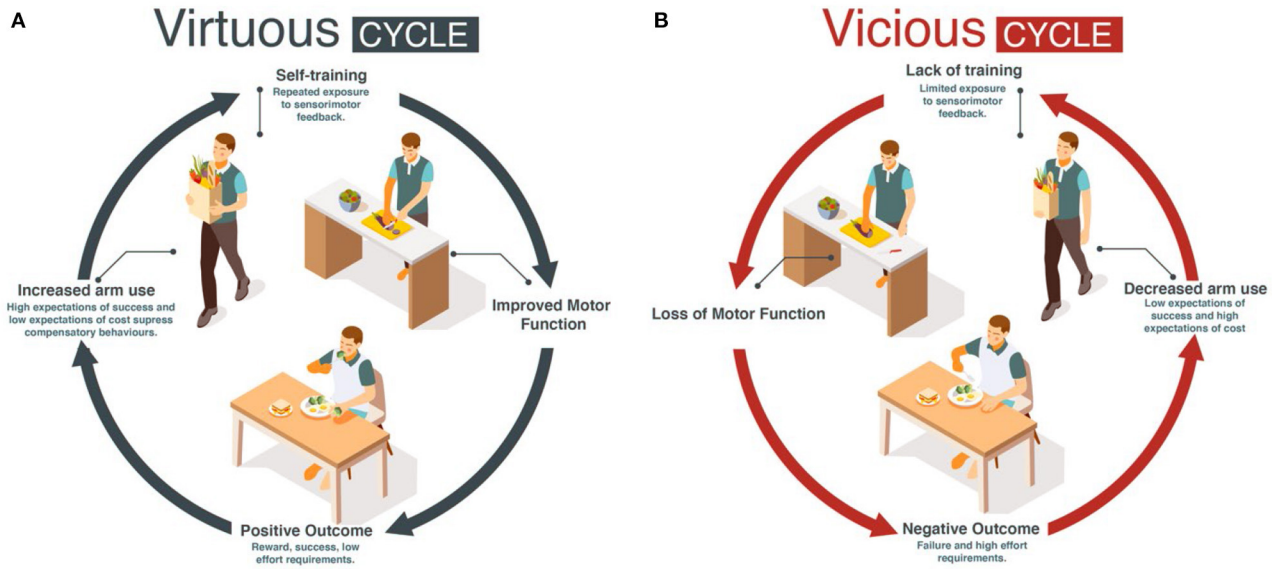

FIGURE 1 | Conceptual model: the virtuous **(A)** and vicious **(B)** recovery cycles.

networks that generate reaching movements and that is (unilaterally) lesioned by stroke, and (2) a decision-making process, loosely based on the basal ganglia, that selects the arm to reach a given target. Motor performance is updated via plastic processes in the motor networks that reduce both errors and variability in movements. Motor decisions to choose one arm or the other depend on the between-arm comparison of expected future rewards, or "action values", which are updated via plastic processes that aim at reducing reward prediction errors. Such choice mechanism is in line with studies showing that reinforcement modulates hand selection (36) and that effort plays a role in motor decisions (37–40). We confirmed since that arm selection depends on a context-dependent linear combination of the expected success and the anticipated cost for both arms in both neuro-typical (23) and post-stroke (20) individuals.

The Han et al. model predicted that if stroke suddenly decreases motor performance, the value of the more affected UE is down-regulated because of reach failures, leading to acquired non-use and compensatory choice of the less affected arm (10). In addition, the model predicted that recovery is bistable: following treatment, performance is either improving (recovery) or deteriorating. (Simulated) patients who use the affected arm above a threshold experience improved performance via "self-practice". In turn, the amelioration of impaired performance increases use. The patients thus enter a chain of events in which improved performance leads to increase in use, which further improves performance and so on, resulting in a continuous process of improvement. Such a chain of events is called a "virtuous cycle" (Merriam Webster dictionary, 2022; **Figure 1A**). In contrast, (Simulated) patients who do not use the affected arm above this threshold enter a chain of events in which deteriorated performance leads to decrease in use, which further deteriorates performance, and so on, resulting in a continuous process of deterioration. Such a chain of events is called a "vicious cycle" (Merriam Webster dictionary, 2022; **Figure 1B**), with rehabilitation becoming "in vain".

RECENT EVIDENCE FOR THE VIRTUOUS AND VICIOUS CYCLES AND THE THRESHOLD

Determining the threshold in use and function separating the virtuous and vicious cycles would allow for evidence-based decision-making of treatment schedules, preventing "rehabilitation in vain" and improving clinical outcomes. Recent work has been pursued toward the determination of such a threshold at the group level. In an animal study with rats who received focal ischemia, MacLellan et al., following the threshold hypothesis of the Han et al. model, theorized that functional benefit occurs only if a threshold of rehabilitation intensity is achieved (41). Skilled reaching improved in rats with unlimited access to the reaching apparatus in the dark but not when reaching was restricted. In addition, an enriched environment did not benefit the restricted group. This study showed that a critical threshold of rehabilitation intensity was required to obtain functional benefit.

Following the threshold prediction in the Han et al. model, we (42) performed a retrospective analysis of data from the EXCITE trial (24). We compared use of the paretic UE (assessed via the subjective Motor Activity Log Amount of Use scale) 1 week after therapy to use a year later. The paretic UE function (assessed via the Wolf Motor Function Test Functional Ability Scale-FAS) measured immediately after therapy predicted, on average, long-term changes of arm use: for about two-thirds of participants with function above a threshold (3.5/5.0 FAS), use improved.

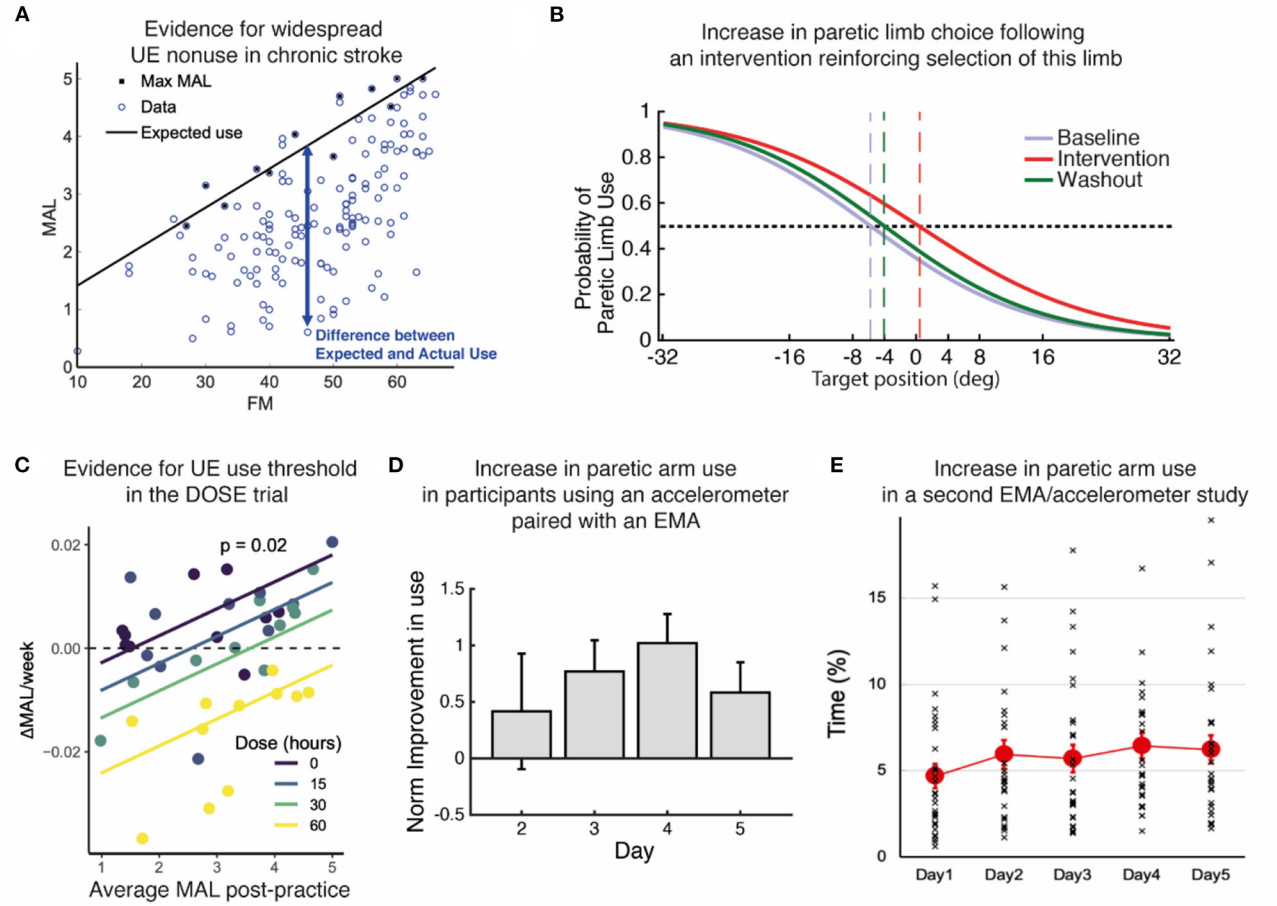

FIGURE 2 | Summary of evidence. **(A)** Re-analysis of baseline data from the EXCITE trial (24) shows prevalent UE non-use beyond what is expected from impairment levels. Motor Activity Log Amount of Use sub-scale (MAL) as a function of the Upper Extremity Fugl Meyer (FM). We estimated the maximal use *MaxMAL* given impairment by the maximum MAL in each bin of 2 FM points (black line: $MaxMAL = 0.067 \times FM + 0.74$). **(B)** Increase in paretic arm choice following an intervention that focuses on reinforcing the selection of this limb (25). Logistic fit of all subject's probabilities of paretic limb choice against target direction before (baseline), during, and after (washout) the intervention. Vertical dashed lines indicate targets with an equal probability of being reached with either arm. **(C)** Evidence for a threshold following practice in the DOSE study (26). The average weekly change in Motor Activity Log-Quality of Movement (MAL) following supervised practice is positively modulated by the average MAL post-practice for each dose. The intersections of the regression lines with the horizontal dashed line show the thresholds for each dose. Colored lines: retention rates as a function of average post-practice MAL for different doses; dots: individual retention rates. **(D)** Increase in paretic arm use in our first study using an accelerometer-embedded bracelet device paired with an EMA (25). Mean change in the activity of the paretic limb estimated by the wearable system across participants with respect to day 1 across days of intervention in which patients received haptic feedback and arm activity reports (days 2–4), and immediately after (day 5). **(E)** Small but statistically significant increase in paretic arm use over 5 days in our second study with an EMA / accelerometer combination (27). Solid color circles: daily average duration of unimanual right (paretic) arm/hand movements. Error bars, standard errors. Cross (×): individual use duration as a % of accelerometer wearing time.

Below this threshold, use decreased. In a second re-analysis of the EXCITE trial data, this time using all repeated measures of UE use (assessed via the Motor Activity Log Amount of Use Scale) and function in the 2 years following treatment, we studied putative non-linear interactions between UE function and use (9). For this purpose, we largely simplified the Han et al. model via first-order non-linear dynamical models of change in use and function, which were fitted to the EXCITE data using a Bayesian regression framework. A model with reciprocal interactions between arm function and use was the best fitting model and accounted for the virtuous and vicious cycles. Furthermore, we found that therapy increased the parameter that modulated the effect of UE function on use. Simulations showed that increasing this parameter, which can be thought of as the confidence to use the arm for a given level of function (i.e., self-efficacy for paretic limb use), led to an increase in spontaneous use and the development of a virtuous cycle by decreasing the threshold.

In the recent DOSE clinical trial (4), in which participants were randomized into groups that varied in the duration of scheduled therapy (i.e., 0, 15, 30, or 60 h), we observed a dose response for the Motor Activity Log-Quality of Movement. In a later analysis of UE use in the 6 months following training (26), we modeled the change in use during and following task practice. Analysis of the model's retention rates in terms of UE use (i.e.,

Motor Activity Log Quality of Movement scale) demonstrated that when use was relatively high and above a threshold, it kept increasing. Interestingly, such an effect was more pronounced in the lower dosage groups because retention following task practice was worse in the higher dosage groups (see **Figure 2C**).

Whereas, the above studies from our group tested the threshold hypothesis with self-reported UE use at home, a recent study with stroke survivors in the subacute stage (43) tested the threshold hypothesis using data from a wearable device, the *Manumeter,* which has been shown to measure the amount of arm and hand movements (44). As predicted, spontaneous paretic hand use measured at home did not increase until the participants reached a certain level of function captured by a standardized clinical scale of motor dexterity (i.e., Box and Blocks Test). Recently, Chen et al. (27) monitored in the wild paretic limb use both alone (unimanual) and with the less affected limb (bimanual) over 5 days in a group of chronic stroke survivors with a wide range of FM motor scores (i.e., 20–66) and found in a subsequent analysis (45) that it was only in 16 out of 30 participants who had FM score $>$ 50 that average unimanual paretic use time (% accelerometer wearing time) increased from 5 to ∼15% as FM score increased to 66. In contrast, bimanual arm use linearly increased from 10 to 40% as FM score increased from 20 to 66. Thus, the paretic arm is being used to a greater extent in those with FM $<$ 50, if it is embedded in the context of bimanual activities of daily living than when it is required to function alone. This suggests that there is a different impairment threshold for bimanual upper extremity activity that is much lower than that for unimanual paretic limb use. It also justifies our initial premise that those who are mild to moderately impaired (not exclusively those with mild impairment) are the ones who stand to benefit from this approach.

TOWARD A PARADIGM SHIFT: EMBEDDING REHABILITATION IN ACTIVITIES OF DAILY LIVING WITH THE AID OF WEARABLE TECHNOLOGY THAT ENHANCES PARETIC LIMB USE

The Han et al. model and the supporting evidence reviewed above suggest that increasing daily use (unimanual and bimanual) of the more affected UE following motor therapy can offer a solution to the problem of low dose of therapy observed in clinical settings and that of rehabilitation in vain. Because neurotypical and adults post-stroke make thousands of purposeful UE movements in daily activities (46), and such movements, via the feedback provided by the environment, could each be seen as single practice movements, increasing such self-practice could provide the large dose of movements needed to improve performance and then use.

In line with this vision, we explored a new method to promote arm use in stroke patients by boosting their confidence in more affected UE function. Participants with hemiparesis were exposed to reduced errors while performing arm shooting movements in a non-immersive virtual-reality system (25). Unaware of the manipulations, participants reported making internal attributions of the success they experienced through training and showed a higher probability of using their more affected arm (**Figure 2B**). We obtained similar results in a pilot study evaluating the effect of using an accelerometer-embedded bracelet device paired with ecological momentary assessment ("EMA" delivered on a smartphone) to monitor the amount of arm use and provide knowledge of progress in chronic stroke survivors (47). Participants received hourly haptic feedback and visual activity reports indicating the change from baseline in paretic arm use. The results showed a general increase in use of the more affected arm, and this increase was retained after feedback suppression (**Figure 2D**). Recently, we showed the feasibility of such EMA and sensor combination with thirty mild-severely motor-impaired stroke survivors (27). We found that the simple act of probing about arm use produced a small but significant increase (∼10 min) in paretic arm use over 5 days (**Figure 2E**). In the same study, an analysis of EMA responses along with the quantitative accelerometer data revealed that social context (i.e., not alone) and self-efficacy for paretic arm/hand use complement an individual's motor capability (i.e., FM score) and play essential roles in paretic arm/hand use behavior in the natural environment (45, 48). Previous work from one of us showed that including social interaction in stroke VR-based motor rehabilitation enhances performance (49). Altogether, these studies illustrate the importance of social context, confidence, and reinforcement in restoring non-pathological hand selection patterns in stroke survivors. Future studies should shed light on which specific disability profiles would benefit the most from this type of intervention, as well as investigate whether this improvement in spontaneous use transfers to the participant's activities and increases independence.

For maximum effectiveness, the above studies suggest a personalized schedule of practice based on an individualized determination of use thresholds (unimanual and bimanual) via wearable sensors. When the different thresholds are estimated to be reached, supervised practice via EMA could be phased out, as UE use for daily activities would continue to increase. For individuals with UE use below these thresholds, strategies to overcome barriers to use in the natural environment would be needed to foster more effective engagement in self-practice (e.g., beginning with primarily bimanual tasks and then transitioning to more difficult unimanual paretic limb tasks). Thus, the next step is to determine this threshold for each individual patient. Repeated measurement of UE use in daily activities via sensors between bouts of therapy could yield precise threshold information. However, a difficulty is to monitor (via the sensors) and promote (via EMA) daily tasks that are at the "just right challenge" to maximize plastic processes involved in motor recovery. One solution is to use EMA + sensors (27) in conjunction with EMI (ecological momentary intervention) to design the optimal intervention strategy (48). As clearly shown by an early monkey study (50), not all repetitions yield plastic changes in the motor system: only the precision grasps, which had to be learned, and not the power grasps, were associated with motor cortical map plasticity. Thus, intelligent EMAs with sophisticated sensors that can monitor both arm and

hand movements (e.g., bimanual and unimanual), such as the *Manumeter,* would need to promote a set of challenging tasks to practice, with this set varying during recovery to maintain challenge. Methods to define challenging task sets based on impairment levels have been proposed, e.g., (51). Note that in this scheme, the neurorehabilitation clinicians play an important role, as they need to assess whether or not particular movements, task components, and whole tasks are assigned so that real-world practice is engaging and productive.

In conclusion, the computational, experimental, and clinical studies reviewed above point to a user-centered approach to recovery post-stroke: besides the more traditional role of neurorehabilitation in enhancing motor function, and in line with standard therapy recommendations, we suggest that embedding rehabilitation in activities of daily living could largely improve long-term outcomes of stroke survivors. The development and validation of wearable devices for objective longitudinal monitoring and promotion of paretic arm/hand use both unimanually and bimanually may be key for implementing this rehabilitation approach that supports large doses of self-practice.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Figure 2A presents results from a re-analysis of data from the EXCITE trial [(24), JAMA]. The trial was approved by the respective institutional review boards of each participating site of the EXCITE trial. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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The MMT of Elbow Flexion and the AFE Predict Impairment and Disability at 3 Weeks in Patients With Acute Stroke

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Objective: This study aimed to investigate whether upper extremity motor function assessment within 72 h from stroke onset can predict the functional outcomes of the upper extremity.

Design: This was a prospective, cohort study of patients with a first unilateral hemispheric stroke between May 2018 and March 2020. The motor arm item of the National Institutes of Health Stroke Scale, manual muscle testing of the elbow and forearm, and active finger extension scale were assessed within 72 h after stroke onset. The Fugl-Meyer assessment upper extremity motor score and action research arm test were assessed at discharge from the acute hospital. Multiple regression analysis was used to study predictors of upper extremity motor function at discharge from the acute hospital. The adjustment variables included age, sex, thumb localizing test, and visuospatial function.

Results: Sixty acute stroke patients were recruited. The model with the highest coefficient of determination for the Fugl-Meyer assessment upper extremity motor score at discharge was the elbow flexion model ($R^2 = 0.76$), followed by the active finger extension model ($R^2 = 0.69$). For the action research arm test, the highest model was the active finger extension model ($R^2 = 0.64$), followed by the elbow flexion model ($R^2 = 0.63$).

Conclusion: The manual muscle testing of elbow flexion and the active finger extension may be useful for predicting impairment and disability at 3 weeks in patients with acute stroke.

Keywords: rehabilitation, cerebrovascular disease, upper extremity, impairment, prediction

INTRODUCTION

Upper extremity weakness is the most common impairment of stroke patients (1). Impairment of upper extremity motor function leads to activity limitations, participation restrictions, and reduced independence in daily life (2).

There are many assessments for upper extremity motor function such as the Fugl-Meyer assessment of upper extremity motor function (FMA-UE) (3), the National Institutes of Health Stroke Scale (NIHSS) motor arm item (4), manual muscle testing (MMT) (5, 6), and the active finger extension scale (AFE) (7). Recovery of hemiparesis was seen remarkably within 1 month after stroke onset (8). It is necessary to predict the functional outcome in the very early acute phase of stroke.

A meta-analysis for predicting upper extremity function in stroke reported that early upper extremity function is the most influential prognostic factor compared to other clinical factors and imaging factors (9). The FMA-UE is one of the good predictors of upper extremity motor function (10). The FMA-UE is assessed with the patient in the sitting position. It is, therefore, often difficult to assess the FMA-UE in the very early acute phase of stroke.

It has been reported that AFE, shoulder abduction, and grip strength within 72 h are useful for predicting upper extremity function (11, 12). It is very difficult to assess shoulder abduction and grip strength in patients with severe acute stroke because they have some difficulties in activities and seating posture.

TABLE 1 | The method of MMT in the supine position.

	Grade	Evaluator	Patient
MMT elbow flexion	0–2	Hold the patient's upper arm and wrist and assist the movement so that it is level with the floor	The shoulder joint should be in internal rotation Flex the elbow joint so that the forearm passes in front of the body.
	3–5		The shoulder joint in the middle position of internal and external rotation
MMT elbow extension	0–2	Hold the patient's upper arm and wrist and assist the movement so that it is level with the floor	The shoulder joint should be internally rotated Extend the elbow joint so that the forearm passes in front of the body
	3–5	Hold the patient's shoulder joint in 90 degrees of flexion	Extent the elbow joint toward the ceiling
MMT forearm pronation	0–5		The elbow joint flexion 90°
MMT forearm supination	0–5		The elbow joint flexion 90°

MMT, Manual Muscle Testing.

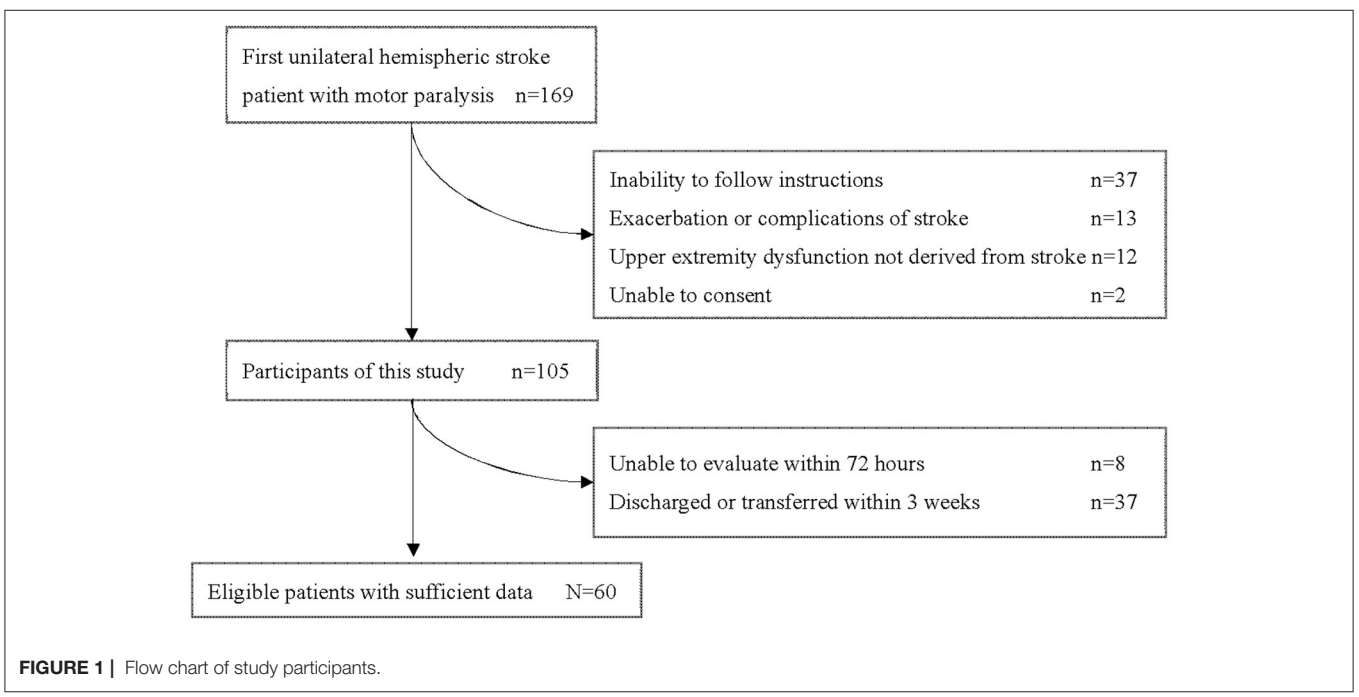

FIGURE 1 | Flow chart of study participants.

Simple tests, which can be assessed with the patient in the supine position, are needed to evaluate and predict upper extremity motor function in the very early acute phase of stroke. The AFE, NIHSS motor arm item, and some items of MMT can be performed in the supine position and can be used for clinical assessment of upper limb function in stroke. However, the connection and validity of the NIHSS motor arm, MMT, AFE, and clinical assessments (FMA-UE and ARAT) are unclear.

The purpose of this study was to investigate the early predictors of upper extremity motor function, which can be applied for very early acute stroke patients in bed in the resting supine position.

MATERIALS AND METHODS

Participants

This prospective, cohort study included a convenience sample of patients with acute ischemic stroke and hemorrhagic stroke admitted to Juntendo University Urayasu Hospital. Data were collected from May 2018 to March 2020. Patients meeting the following criteria were included: older than 18 years of age; admitted with first unilateral hemispheric stroke; and written, informed consent was provided by the patient or family. Ischemic stroke and hemorrhagic stroke were defined according to the World Health Organization criteria. The type and localization of stroke were determined using computed tomography or magnetic resonance imaging. Exclusion criteria were inability to follow instructions, exacerbation or complications of stroke during hospitalization, limited upper extremity movement due to neurological conditions other than stroke (orthopedic disease, pain, or psychological problems), unable to evaluate within 72 h, and discharged or transferred <3 weeks after onset. Approval for this study was obtained from the institutional review board of Juntendo University Urayasu Hospital, and written, informed consent was obtained from all participants.

Procedure

On the initial day of occupational therapy, the NIHSS motor arm item, MMT of the elbow and forearm, AFE, the thumb localizing test (13) for proprioception, and the visuospatial item of the Stroke Impairment Assessment Set (SIAS) (14) were measured. One week after onset, FMA-UE was measured. Three weeks after stroke onset, in addition to the above tests, FMA-UE and the action research arm test (ARAT) (15) were assessed.

Assessment

National Institutes of Health Stroke Scale Motor Arm Item

The NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke (4). The NIHSS motor arm item examines the ability to hold the paralyzed upper extremity in space. The shoulder was flexed 45 degrees in the supine position. The score ranges from 4 (no movement) to 0 (holding for 10 s without drooping) (16).

TABLE 2 | Participant Characteristics.

Participant characteristics		
Number of participants (male/female)	60 (36/24)	
Age (years old, median, IQR)	68.0 (58.25–77.75)	
Lesion type of stroke (infarction/hemorrhage)	36/24	
Lesion side of stroke (left/right)	23/37	
Days from stroke to start of OT (median days, IQR)	1(1–2)	
Daysfrom stroke to start of sitting (range)	2 (2–4)	
Length of hospital stay (medina days, IQR)	29.5 (25–38.25)	
Measurement	Baseline	3 Weeks
NIHSS motor arm	3 (1–4)	2 (0–4)
MMT elbow flexion	2 (0–4)	3 (1–4.75)
Elbow extension	2 (0–4)	3 (1–5)
Forearm pronation	1.5 (0–4)	3 (1–5)
Forearm supination	1.5 (0–4)	3 (0–4.75)
AFE	1 (0–3)	1.5 (0–4)
Thumb localizing test	2 (1–3)	1 (0–2)
Visuospatial	2 (1.25–3)	3 (3–3)
FMA-UE	1week from onset 12.5 (4–52)	31.5 (8.25–59.5)
ARAT		4 (0–34)

IQR, Interquartile range; OT, Occupational therapy; NIHSS, National Institutes of Health Stroke Scale; MMT, Manual Muscle Testing; AFE, Active Finger Extension; FMA-UE, Fugl-Meyer Assessment Upper Extremity; ARAT, Action Research Arm Test.

Manual Muscle Testing

MMT is the most commonly used method for documenting impairments in muscle strength (5). Each muscle is tested manually and scored from 0 (no muscle contraction) to 5 (complete range of motion against gravity with full resistance). In this study, MMT of elbow flexion, elbow extension, forearm supination, and forearm pronation were performed. The method of MMT in the supine position is summarized in the **Table 1**. As for manual resistance, we carefully observed the patient's condition and performed it within the range that did not involve large fluctuations in blood pressure and pulse.

Active Finger Extension Scale

The AFE was developed by Smania et al. The patient was asked to actively extend all affected fingers except the first simultaneously, with the score ranging from 0 (absence of muscle contraction) to 5 (normal muscle power) (7).

Thumb Localizing Test

The thumb of the affected upper limb is held in space by the examiner. The patient is asked to grasp the thumb of the affected hand with the thumb and index finger of the unaffected upper limb. The deviation is scored from 3 (the patient is unable to find

his thumb and does not climb up the affected arm to locate it) to 0 (the patient can locate the affected thumb accurately) (17).

Visuospatial Function

This is a screening test for unilateral spatial neglect included in SIAS. The examinee points to the center of a 50-cm tape measure, which is held by the examiner in front of the examinee. The deviation from the center is scored from 0 (more than 15 cm deviation from the central point) to 3 (<2 cm deviation from the central point) (14).

Fugl-Meyer Assessment Upper Extremity Motor Score

The Fugl-Meyer Assessment is a stroke-specific assessment scale based on the recovery process of hemiplegic stroke patients (3). The upper extremity motor score (33 items with a maximum score of 66 points) was used in this study. The FMA-UE is the most commonly used outcome measure of upper extremity impairment in prognostic studies (9).

Action Research arm Test

The ARAT consists of 19 items that are grouped into the following 4 subtests: grasp, grip, pinch, and gross movement. A maximum score of 57 was given based on the degree of completion and time for each action (15). ARAT is the most commonly used outcome measure of upper extremity function or functional movement in prognostic studies (9).

Statistical Analysis

First, the correlations between age and measurements on the initial day of occupational therapy (NIHSS motor arm item, MMT of the elbow and forearm, AFE, thumb localizing test, and visuospatial item) were confirmed using Spearman's rank correlation coefficient. Then, the correlations among age, the measurements at 3 weeks (NIHSS motor arm, MMT of the elbow and forearm, AFE, thumb localizing test, and visuospatial item), FMA-UE at 3 weeks, and ARAT at 3 weeks were confirmed using Spearman's rank correlation coefficient. Finally, multiple regression analysis was performed to identify predictors of FMA-UE at 3 weeks using the stepwise method. Age, sex, thumb localizing test, and the visuospatial item were used as adjustment variables, and one of the NIHSS motor arm item, MMT of the elbow and forearm, or AFE was selected and entered as the independent variable. The FMA-UE at 3 weeks was assigned as the dependent variable. Then, the adjusted R^2 for each model was compared. A similar test was conducted for ARAT at 3 weeks. Also, To compare our data with previous reports, we also split the sample into two groups based on FMA-UE 1 week > 10 and FMA-UE 1 week < 11, given that the 70% rule was originally and subsequently shown to be upheld when FMA-UE 1 week > 10, but not when FMA-UE 1 week < 11 (18, 19). All predictors were entered into the stepwise model, with $p < 0.05$ to enter and $p > 0.10$ to leave. We determined the goodness of fit adjusted R^2, β coefficients, p, and analysis of variance (ANOVA; F, p) for each regression model. The significance level was set at 5%. All analyses were conducted using statistical software, SPSS 24.0 for Windows.

TABLE 3 | Spearman's rank correlation coefficient between assessments at 3 weeks.

	NIHSS motor arm	Elbow flexion	Elbow extension	Forearm pronation	Forearm supination	AFE	Thumb localizing test	Visuospatial
NIHSS motor arm		−0.91**	−0.93**	−0.94**	−0.92**	−0.89**	0.52**	−0.38**
MMT elbow flexion	−0.91**		0.94**	0.94**	0.93**	0.92**	−0.57**	0.30*
MMT elbow extension	−0.93**	0.94**		0.94**	0.92**	0.87**	−0.58**	0.33*
MMT forearm pronation	−0.94**	0.94**	0.94**		0.95**	0.91**	−0.56**	0.33*
MMT forearm supination	−0.92**	0.93**	0.92**	0.95**		0.92**	−0.53**	0.30*
AFE	−0.89**	0.92**	0.87**	0.91**	0.92**		−0.51**	0.31*
Thumb localizing test	0.52**	−0.57**	−0.58**	−0.56**	−0.53**	−0.51**		−0.39**
Visuospatial	−0.38**	0.30*	0.33*	0.33*	0.30*	0.31*	−0.39**	
FMA-UE	−0.92**	0.93**	0.95**	0.94**	0.93**	0.92**	−0.59**	0.33*
ARAT	−0.94**	0.92	0.93**	0.93**	0.92**	0.91**	−0.53**	0.38*

**P < 0.01.
*P < 0.05.
NIHSS, National Institutes of Health Stroke Scale; MMT, Manual Muscle Testing; AFE, Active Finger Extension.

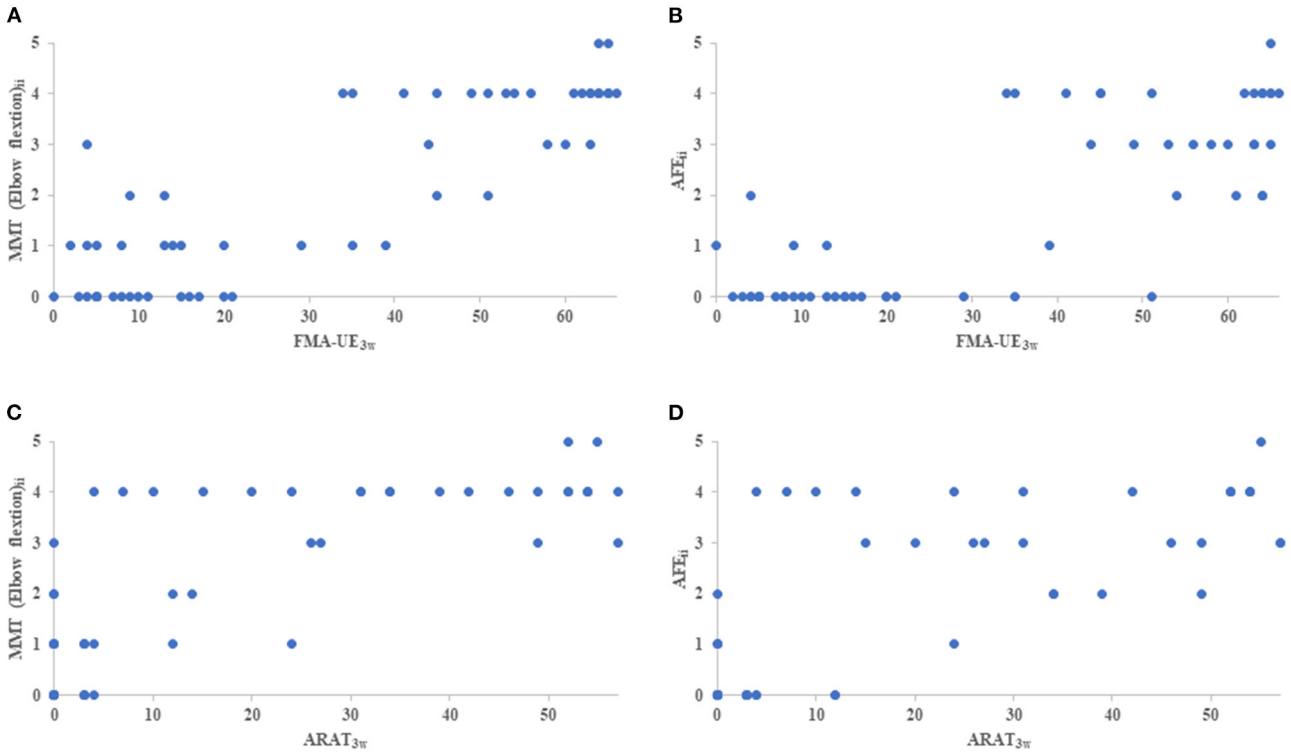

FIGURE 2 | The correlation plot between initial impairment and clinical assessment of 3 weeks. **(A)** indicates MMT elbow flexion initial impairment (MMT elbow flexion$_{ii}$) vs FMA-UE$_{3w,}$ **(B)** indicates AFE initial impairment (AFE$_{ii}$) vs FMA-UE$_{3w,}$ **(C)** indicates MMT elbow flexion$_{ii}$ vs ARAT, and **(D)** indicates AFE$_{ii}$ vs ARAT. MMT, Manual Muscle Testing; AFE, Active Finger Extension; FMA-UE$_{3w}$, Fugl-Meyer Assessment Upper Extremity at 3 weeks; ARAT$_{3w}$, Action Research Arm Test at 3 weeks.

RESULTS

During this study period, 169 patients aged 18 years or older were admitted to our hospital with a first unilateral hemispheric stroke and had motor paresis. Sixty patients (36 men, 24 women) with a median age of 68.0 (IQR 58.25–77.25) years who met the criteria were included in this study **(Figure 1)**. Participants' characteristics are described in **Table 2**. There were 36 patients with cerebral infarction and 24 with cerebral hemorrhage. Of the 36 patients with cerebral infarction, one patient received both tissue plasminogen activator and endovascular therapy, eight patients received only tissue plasminogen activator. Craniotomy hematoma removal was performed for six of the 24 patients with cerebral hemorrhage. The median (IQR) number of days from stroke to start of occupational therapy was 1 (1, 2), and the median (IQR) number of days from stroke to the start of sitting was 2 (2–4). Thirty percent (18 of 60) of the patients were unable to receive FMA-UE within 72 h after stroke. The median (IQR) number of days of stay in our hospital was 29.5 (25–38.25). Fifty-six patients were transferred to inpatient rehabilitation facilities, two patients to home, and two patients to a chronic care facility.

On the initial day of occupational therapy, the correlation coefficients of the NIHSS motor arm item, MMT of the elbow and forearm, and AFE showed strong correlations ($r \geq 0.88$) with each other. The correlation coefficients of the NIHSS motor arm item, MMT of the elbow and forearm, and AFE at 3 weeks also showed strong correlations ($r \geq 0.87$) with each other, and the correlation coefficients between these assessments and FMA-UE and ARAT were also very strong, with $r > 0.90$ **(Table 3)**. The MMT elbow flexion initial impairment vs. FMA-UE at 3 weeks is shown in the correlation plot; ARAT is shown as well **(Figure 2)**.

Multiple regression analysis to predict FMA-UE at 3 weeks showed that the model with the highest coefficient of determination was the elbow flexion model with an adjusted $R^2 = 0.76$, followed by the AFE model with an adjusted $R^2 = 0.69$. In the fitter group, the model with the highest coefficient of determination was MMT elbow flexion model with an adjusted $R^2 = 0.45$, followed by MMT forearm pronation model with an adjusted $R^2 = 0.42$. In the non-fitter group, there were no independent variables to be adopted in all models **(Table 4)**. Multiple regression analysis was performed on the ARAT at 3 weeks, and the model with the highest coefficient of determination was the AFE model with an adjusted $R^2 = 0.64$, followed by the elbow flexion model with an adjusted $R^2 = 0.63$. In the fitter group, the model with the highest coefficient of determination was MMT elbow flexion model with an adjusted $R^2 = 0.37$, followed by MMT forearm pronation model with an adjusted $R^2 = 0.35$. In the non-fitter group, there were no independent variables to be adopted in all models **(Table 5).**

TABLE 4 | Linear Regression Statistics for Predictors of FMA-UE at 3 weeks.

Total	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	***B***	***p***
$N = 60$	NIHSS motor arm	0.67	121.6	<0.001	NIHSS motor arm	−0.823	<0.001
	MMT elbow flexion	0.76	183.8	<0.001	MMT elbow flexion	0.872	<0.001
	MMT elbow extension	0.62	97.1	<0.001	MMT elbow extension	0.791	<0.001
	MMT forearm pronation	0.67	120.9	<0.001	MMT forearm pronation	0.822	<0.001
	MMT forearm supination	0.65	108.1	<0.001	MMT forearm supination	0.807	<0.001
	AFE	0.69	66.4	<0.001	AFE	0.699	<0.001
					Thumb localizing test	−0.205	0.027
Fitter	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	**β**	***P***
$N = 33$	NIHSS motor arm	0.35	18.3	<0.001	NIHSS motor arm	−0.610	<0.001
	MMT elbow flexion	0.45	27.4	<0.001	MMT elbow flexion	0.685	<0.001
	MMT elbow extension	0.31	15.0	<0.001	MMT elbow extension	0.571	0.001
	MMT forearm pronation	0.42	12.8	<0.001	MMT forearm pronation	0.689	<0.001
					Age	−0.291	0.044
	MMT forearm supination	0.27	12.9	<0.001	MMT forearm supination	0.542	<0.001
	AFE	0.25	11.4	<0.001	AFE	0.519	<0.001
Non-fitter	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	**β**	***p***
$N = 27$	All				Nothing		

FMA-UE, Fugl-Meyer Assessment upper extremity; NIHSS, National Institutes of Health Stroke Scale; MMT, Manual Muscle Testing; AFE, Active Finger Extension.

DISCUSSION

In this study, the median (IQR) number of days from stroke to starting sitting was 3 (3–5). Many patients are forced to stay on bed rest in the acute phase of stroke. Thirty percent (18 of 60) of the patients were unable to receive FMA-UE within 72 h after stroke. Although the study included patients with cerebral hemorrhage and postoperative stroke, many patients with cerebral infarction were also unable to receive FMA-UE. Previous studies that focus on patients within 72 h may have led to participant selection. Therefore, simple tests, which can be performed with the patient in the supine position, are needed to evaluate and predict upper extremity motor function in the very early acute phase of stroke. The NIHSS motor arm item, MMT of the elbow and forearm, and AFE could be assessed easily and safely in the supine position. Multiple regression analysis showed that MMT of elbow flexion and AFE were more predictive of upper extremity impairment and disability than the other assessments. The use of MMT of elbow flexion and AFE imposes minimal burden on the patient.

The decrease in adjusted R^2 in the prediction for the fitter group may be partly the result of the halving of the number of cases. For the non-fitter group, we were not able to create a prediction model. This result supports a previous study (19), and the non-fitter group may include imperfections in the corticospinal tract. TMS assessment was not used in this study. We did not use TMS assessment in this study because we considered it difficult from the viewpoint of feasibility because of the inclusion of postoperative cases.

The AFE, shoulder abduction, and grip strength have been reported as simple prognostic evaluations (13, 14). Shoulder abduction and grip strength were excluded from the evaluation in the present study because of the difficulty of measuring them in the supine position. Since patients with unstable general conditions in the early stage of the disease, such as those in the postoperative period, were included in the study, we decided to exclude grip strength, which always requires maximal muscle exertion, from the viewpoint of clinical feasibility. The results of the present study showed that AFE and elbow flexion were more useful than the other assessments. It has been reported that AFE within 72 h is useful for predicting the prognosis of patients with upper extremity dysfunction (11, 12). The results of the present study were consistent with prior research. On the other hand, there have been few reports of the usefulness of elbow flexion alone. Malmut et al. (20) reported that Rapid bedside assessment of shoulder abduction, elbow flexion, and pinch grip using the arm subscore of the Motricity Index can predict upper limb recovery after stroke according to the ARAT. The MMT of elbow flexion may be useful in predicting upper extremity impairment and disability in the acute stroke rehabilitation setting.

In this study, detailed signs of spasticity are not known because assessment measures such as the Modified Ashworth Scale were not performed. Sixty participants in this study were able to be evaluated and measured with little effect of spasticity. The delay between acute neurological insult (trauma or stroke) and the appearance of spasticity (21) may be relevant. If the evaluation results are likely to be affected by spasticity, Repeated measures ought to be incorporated to examine reliability within a trial that includes participants with a hypertonic hand (22).

The present study showed that MMT of elbow flexion and AFE could be used to safely assess upper extremity function in patients with severe acute stroke. In this study, the outcome is 3 weeks after onset is that the average length of stay in

TABLE 5 | Linear regression statistics for predictors of ARAT at 3 weeks.

Total	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	**β**	***p***
$N = 60$	NIHSS motor arm	0.59	87.2	<0.001	NIHSS motor arm	0.775	<0.001
	MMT elbow flexion	0.63	101.3	<0.001	MMT elbow flexion	0.797	<0.001
	MMT elbow extension	0.55	72.6	<0.001	MMT elbow extension	0.746	<0.001
	MMT forearm pronation	0.61	46.5	<0.001	MMT forearm pronation	0.802	<0.001
					Age	−0.175	0.039
	MMT forearm supination	0.57	77.6	<0.001	MMT forearm supination	0.757	<0.001
	AFE	0.64	36.4	<0.001	AFE	0.681	<0.001
					Age	−0.193	0.019
					Thumb localizing test	−0.220	0.026
Fitter	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	**β**	***P***
$N = 33$	NIHSS motor arm	0.34	9.1	<0.001	NIHSS motor arm	−0.601	<0.001
					Age	−0.313	0.042
	MMT elbow flexion	0.37	10.6	<0.001	MMT elbow flexion	0.626	<0.001
					Age	−0..291	0.049
	MMT elbow extension	0.33	8.9	<0.001	MMT elbow extension	0.600	<0.001
					Age	−0.328	0.036
	MMT forearm pronation	0.35	9.6	<0.001	MMT forearm pronation	0.616	<0.001
					Age	−0.334	0.031
	MMT forearm supination	0.21	9.5	<0.001	MMT forearm supination	0.484	0.004
	AFE	0.31	8.2	<0.001	AFE	0.591	0.001
					Age	−0.356	0.028
Non-fitter	**Model**	**Adjusted R^2**	***F*-value**	***p***	**Predictor**	**β**	***p***
$N = 27$	All				Nothing		

ARAT, Action Research Arm Test; NIHSS, National Institutes of Health Stroke Scale; MMT, Manual Muscle Testing; AFE, Active Finger Extension.

acute care hospitals in Japan is around 3 weeks (median for both cerebral infarction 19.0 days and cerebral hemorrhage 27.0 days from All Japan Hospital Association FY2019 data) (23). Therefore, early prediction of the prognosis in the first 3 weeks after the onset of stroke is important when considering the subsequent rehabilitation plan and transfer to a rehabilitation hospital. Further work is needed to examine long-term outcomes by extending the prediction period. It is also desirable to identify simple and easy-to-understand assessments for patients with severe aphasia.

LIMITATIONS

The present study has some limitations. The first is the shortness of the prediction period. Previous studies have often set a predictive period of 3–6 months after stroke (9). This study was limited to the acute phase of recovery. Second, the evaluation items were limited. Considering the patient's durability and comprehension, it is practically difficult to cover the entire upper extremity functional assessment. In addition, it is difficult to make distinctions between the NIHSS motor arm item and MMT of elbow and forearm because the measure and level of difficulty of the assessments are different. The third is the reliability of MMT in the supine position. Gravity assists the motion when the elbow flexion is more than 90 degrees, and gravity has little effect on MMT forearm pronation/supination test. It may be less reliable/valid than conventional MMT.There are AHA/ASA Guideline (24) recommendations for the use of MMT in stroke and its use as an outcome (25). However, as with shoulder abduction and AFE, intra- and inter-rater reliability of the test has not been demonstrated. Further work is needed. The fourth is the effect of multicollinearity in multivariate analysis and the small number of patients; considering the effect of multicollinearity in multivariate analysis, it is difficult to enter many variables in the evaluation of upper extremity function at the same time. The small number of cases in this study also limits the number of independent variables that can be assigned. The fifth is the bias of the participants. There was a difference in the number of participants on the lesion side because patients with symptoms of aphasia of left hemisphere stroke tended to be excluded. It was particularly difficult for them to understand the thumb localizing test and the visuospatial item. For this reason, the lesion side was not used for adjustment variables in the present multiple regression analysis. Considering these research limitations, it is difficult to generalize to all upper extremity dysfunctions.

CONCLUSIONS

The NIHSS motor arm item, MMT of the elbow and forearm, and AFE can be assessed with the patient in the supine position in patients with severe acute stroke. The MMT of elbow flexion

and AFE may be useful for predicting impairment and disability at 3 weeks in patients with acute stroke.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

SU and TF developed the study, prepared and analyzed the data, interpreted the results, and wrote the manuscript. HA, YY, and AN recruited the participants, collected the data, collaborated in the data preparation, and reviewed the manuscript. YH worked on the data processing, data preparation, and reviewed the manuscript. KHo, AT, TT, AK, KHa, and AH developed the study, interpreted the results, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Post-stroke Dysphagia: Prognosis and Treatment–A Systematic Review of RCT on Interventional Treatments for Dysphagia Following Subacute Stroke

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Purpose: Post-stroke dysphagia is an underdiagnosed but relevant complication, associated with worse outcome, dependency and quality of life of stroke survivors. Detailed mechanisms of post-stroke dysphagia are not very well understood, but established therapeutic concepts are needed. Different interventional studies have been published dealing with post-stroke dysphagia. This systematic review wants to collect and give an overview over the published evidence.

Methods: PubMed, Embase, Cochrane, CINAHL were searched for relevant interventional studies on post-stroke dysphagia in the (sub-)acute setting (within 3 months of stroke onset). The search has been filtered for randomized trials with an inactive control and the relevant data extracted.

Results: After initially finding 2,863 trials, finally 41 trials have been included. Seven different therapeutic concepts have been evaluated (Acupuncture, behavioral/physical therapy, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, transcranial direct current stimulation and repetitive transcranial magnetic stimulation). Studies of all modalities have shown some effect on post-stroke dysphagia with several studies raising concerns about the potential bias.

Conclusion: The amount and quality of studies are not enough to suggest certain therapies. Some therapeutical concepts (intensive physical therapy, transcranial magnetic stimulation, drug therapy) seem to be good potential therapeutic options, but further research is needed.

Keywords: swallowing, cerebrovascular, nutrition, therapy, ischemia, deglutition

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INTRODUCTION

The prevalence of dysphagia in stroke patients differs with the diagnostic method in the acute phase: 51–55% with clinical testing and 64–78% with instrumental examinations (1, 2). Impairment of swallowing still persists in up to 50% of the cases in the following course (1) and complications frequently arise. In about 40% of stroke survivors dysphagia is persistent. Patients with dysphagia have an increased risk for pneumonia which is probably linked with the severity of dysphagia since

the risk is even much greater in patients with aspiration (2) and even more in patients with silent aspiration (3). Other common complications include malnutrition and dehydration, especially in the long-term (4). Malnourished and/or dehydrated stroke patients have a relevant risk of further complications and an elevated rate of mortality and dependency (5, 6). The detailed mechanisms of post-stroke dysphagia are not well understood.

Neuroanatomically different localisations of brain lesions, infra- and supratentorial, can cause dysphagia. As to frequency, brain stem lesions more often cause dysphagia compared to hemispheric strokes. Combined lesions have the highest risk for developing oropharyngeal dysphagia (7). Infratentorial lesions usually cause dysphagia through motor deficits whereas in supratentorial stroke dysphagia is usually caused by sensory-afferent deficits (8). Sensory deficits are more pronounced in dysphagic patients with aspiration.

Early recognition of the problem is linked with a better outcome. The Predictive Swallowing Score (PRESS) (9) has been developed to identify patients who are at risk for persistent dysphagia, so that treatment and potentially the placement of a percutanous enteral tube can be initiated at an early stage. Although clinical screening of dysphagia after stroke has been established routinely in several countries, instrumental screening is restricted in most. The latter has a higher diagnostic accuracy and allows a more detailed evaluation of the swallowing function, so that the problem and potentially the treatment can be adapted more specifically. FEES (10) (Flexible endoscopic evaluation of swallowing) and VFS (11) (Videofluoroscopy) are different in the procedure and in the results they provide, but allow an elaborated view of the deglutition function.

Therapeutic options comprise dietary and nutritional interventions, behavioral treatments, oral care, pharmacological- and neuro-stimulation.

Treatment guidelines contain different physical therapies and preventive measures to avoid dysphagia-associated complications, but lack medical or electrophysiological interventions to enhance dysphagia recovery after stroke in the acute or subacute setting.

The aim of this systematic review is to search the literature for published data on interventions for post-stroke dysphagia in the acute and subacute setting and to identify potential interventions and targets for further scientific research.

METHODS

The PRISMA statement (12) (Preferred Reporting Items in Systematic reviews and Meta-Analyses) has been followed throughout the process.

Search Strategy and Selection Criteria

A systematic review of the literature was conducted to indentify all randomized cotrolled trials which assess the effect of therapeutic interventions of post-stroke dysphagia in the acute and subacute setting. The following databases were searched: Pubmed/MEDLINE, Embase, CENTRAL/Cochrane Library and The Cumulative Index to Nursing and Allied Health Literature (CINAHL). Search dates in all database were during August 2021 and consisted of the following searched terms: (*stroke* OR cerebrovascular* OR "brain ischemia") AND (dysphagia* OR "deglutition disorder" OR "impaired swallowing" OR "swallowing disorder" OR "swallowing impairment") AND (RCT OR placebo OR "randomized controlled trial" OR double-bIind OR placebo OR "controlled clinical trial"). If possible in the database, the search was filtered using "human" and "English language".

The reference lists of the screened articles were searched for articles which have not been included in the original search.

Inclusions and Exclusions

All studies were included who were interventional trials about post-stroke dysphagia with a randomized controlled design. After the above-mentioned literature search duplicates were removed and titles and abstracts screened for the eligibility criteria. Here, the PICO concept has been followed. The control arm had to be an inactive comparator with all possible interventions (medication, electrical stimulation, physical therapy, etc.) included, while usual care or standard therapy were counted as eligible for this review. Dysphagia had to be assessed clinically or instrumentally prior to the start of treatment.

The treatment had to be started within 3 months after ischemic stroke. Inclusion was restricted to studies examining interventions aiming to improve mechanisms of the impaired swallowing function are examined, so that trials assessing preventive measures i.e., prophylactic antibiotic treatment or measures trying to prevent dysphagia associated complications were not included here.

Only original data/publications have been included. Comments, case series, reviews etc. were excluded, latest at full-text-screening. Literature dealing with dysphagia due to other cause than stroke or healthy individuals and their swallowing function were not included. Full-text articles in English had to be available to be included in this review.

If treatment was started after 3 months after stroke or this relevant information is missing in the data, the publication was not included. Outcome or safety outcome parameters were not part of the inclusion criteria, although publications were excluded if they did not provide dysphagia- or swallowing-specific outcomes, whereas the methodology of obtaining those (clinical, instrumental/paraclinical) was not of interest at that stage of the process. A scaling of the global swallowing function had to be provided as any outcome parameter, where all scores (already established or explained in the publication) were accepted. Studies dealing only with parts of the swallowing act i.e., only the oral transit time, were not included.

Data Extraction

One reviewer (PB) performed the database search while two reviewers (PB, RZ) performed the screening. After removal of duplications, a title and abstract assessment was performed in a first step which was followed by a full-text screening. In case of divergent assessments, a consensus was found.

Data of the included papers were extracted into a pre-formed electronic sheet and then the trials were assessed by two reviewers

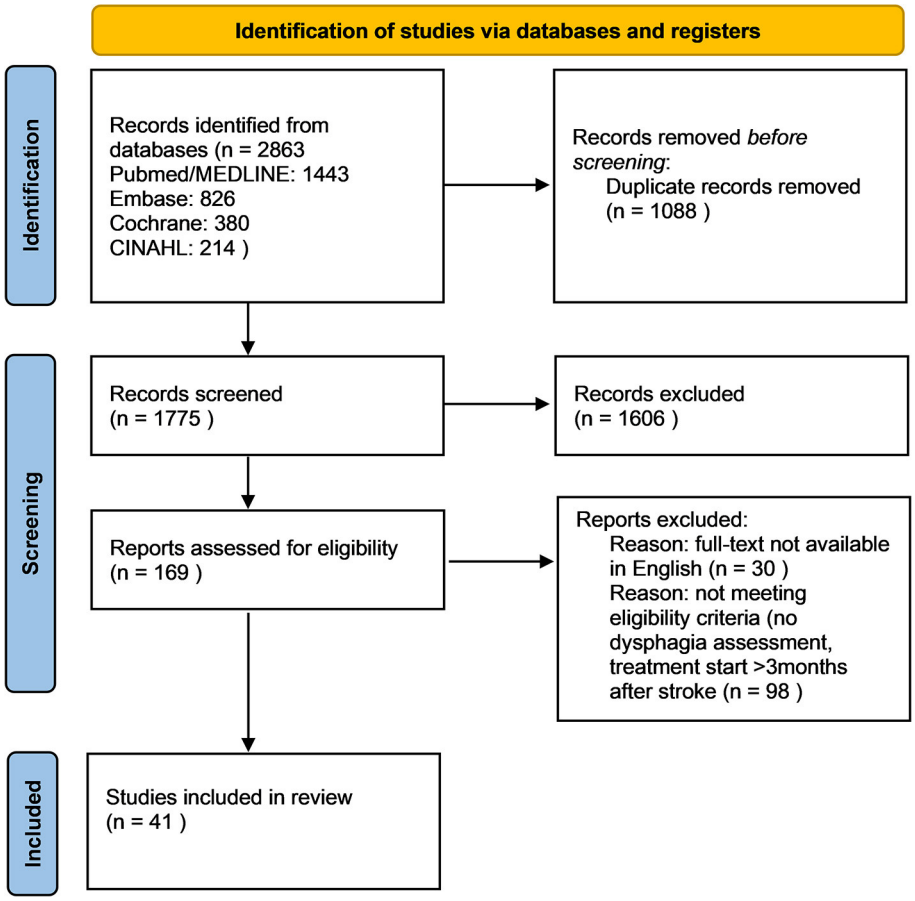

FIGURE 1 | Flow diagram on literature retrieval.

(PB, SC). The data extraction followed the PICO approach: (1) Participants–stroke patients with dysphagia, (2) Interventions–any active intervention/therapy with or without the combination of conventional routine therapy, (3) Comparison–any inactive control/placebo, (4) Outcome–swallowing functions, measured instrumentally and clinically, and complications (if available). The risk of bias of every trial included was assessed according the Cochrane's Handbook with the RoB-2-tool (13). The tool was used according to the guidelines. Risk grades were high risk (+), low risk (-) and unclear risk or some concern were put together (o). The overall assessment was performed according to RoB-2-algorithm.

In case of conflicting results, a consensus was found.

RESULTS

Literature Retrieved

The search strategy was applied and resulted in 1,367 hits with 479 duplicates, leaving 888 citations. After screening the title and abstracts 169 publications seemed eligible. After exclusion of 30 papers, which were not available in English and full-text screening for the above-mentioned eligibility criteria 41 trials were included in the review. The reasons for exclusion are mentioned after grouping in **Figure 1**.

Interventions

Seven different interventional modalities have been evaluated in the trials: acupuncture in two trials, behavioral/physical therapy in 13, drug therapy in five, neuromuscular electrical stimulation (NMES) in nine, pharyngeal electrical stimulation (PES) in four, transcranial direct current stimulation (tDCS) in four and six studies assessed repetitive transcranial magnetic stimulation (two studies assessed two modalities in a three-arm design).

The start of the interventions complied with our eligibility criteria and was started within 3 months after stroke onset.

Outcome Measures

All of the included trials had a swallowing assessment as an outcome parameter, as mentioned in the eligibility criteria. Thirty-three trials used instrumental evaluations of dysphagia as outcome assessments. For the instrumental assessments, the flexible endoscopic evaluation of swallowing (FEES) was performed in three trials, whereas videofluoroscopy (VFS) was used in 30. During both procedures different scores and scales were obtained to assess the swallowing function. Twenty-three

of the included studies had clinical examinations as outcome assessments of dysphagia with different scores and scales used for the evaluation.

Summary of Results

Forty-one trials dealing with seven different therapeutic concepts were included in this review and provided results on their effect on dysphagia recovery after stroke with a total of 2,166 participants included in these studies. **Table 1** shows the study characteristics from extracted data and its findings of the single studies (Further information can be found in the **Supplementary Material**).

Acupuncture

Two studies (14, 15) were included which compared Acupuncture vs. no specific therapy or standard care. In one study (14), patients with hemiplegic stroke were included with swallowing outcome on instrumental testing (videofluoroscopy) as a secondary endpoint, so that only a subgroup of the initial sample size was included. Acupuncture showed some effect on post stroke dysphagia within the first 7 weeks after stroke onset. In the other trial (15), the intervention showed some effect, but only in the later course of the trial, which lasted only 4 weeks.

Behavioral/Physical Therapies

Thirteen trials (16–28) have been included which assess the impact physical training and/or the intensity (15, 19) of physical therapy on dysphagia recovery. Three studies (17, 18, 24) evaluated forced respiratory muscle training against resistance and its effect on post-stroke dysphagia, where all could show enhanced dysphagia recovery. Among the other trials, two of them assess jaw opening exercises (22, 27), while the other concepts had similar aspects, but different maneuvers used in their studies (for details see **Table 1**, or **Supplementary Material**). The assessments differed within the studies, so that three trials (16, 23, 25) only used clinical measurements for dysphagia evaluation. In total, nine trials showed positive impact of the therapies on dysphagia recovery, whereas two (19, 27) did not show any difference and two other (21, 22) showed mixed results in different dysphagia assessments. Out of the nine studies showing positive impact, two (20, 26) only had impact on the oral phase of the swallowing act.

Drug Therapy

Four different medication classes have been assessed as to their effect on dysphagia rehabilitation. Caspaicin was used in two trials (29, 33), nifedipine (32), lisinopril (31) and tongyan spray (30) in one each. All studies except lisinopril showed significant differences as to recovery of the swallowing function.

Neuromuscular Electrical Stimulation

In the big majority of included trials (18, 34–41), a therapeutical effect on post-stroke dysphagia could have been shown, with one (35) having mixed results and one (38) showing no difference, though. Five of the studies (18, 34, 35, 40, 41) assessed the addition of NMES to standard or physical therapy. The combination of NMES and standard therapy has been shown to be more effective than NMES alone in the comparative studies. Whereas, most studies used stimulation of hyoid muscles, two (38, 39) used different stimulation locations. The stimulation of faucial pillars (38) failed to show a significant improvement over standard therapy. The sensory-level stimulation of the masseter muscle (39) seems to have a bigger benefit over standard care on dysphagia recovery.

Pharyngeal Electrical Stimulation

Of the four studies (42–45) in this review, two (43, 44) reached the study goal and showed a positive effect on post-stroke dysphagia. One study (43) included was in a further specified study population with stroke survivors needing tracheotomy.

Transcranial Direct Current Stimulation

In this modality group, all trials (46–49) used instrumental dysphagia assessments, but not structured clinical scales. All of them used sham procedures as control groups, but had different concepts of stimulation. Two studies (46, 48) implemented anodal tDCS over the unaffected hemisphere, one study (49) used anodal tDCS over the affected motor cortex and all achieved to show a positive effect. The other trial (47) had a dual concept with anodal stimulation over the lesioned and cathodal over the contralesional side. This failed to show an enhanced dysphagia rehabilitation.

Repetitive Transcranial Magnetic Stimulation

All of the six included trials (37, 50–54) showed at least some therapeutic effect of rTMS on post-stroke dysphagia. The concept of applying the stimulation over the affected motor cortex using the hotspotting technique was similar in the included trials. The frequency varied between 1 Hz up to 10 Hz. Tarameshlu (52) used three groups with one rTMS alone, rTMS and standard therapy combined and standard therapy only as the control, where only the combined therapy showed a significant effect. Park (54) compared bi- and unilateral TMS to a sham procedure where only the bilateral stimulation showed a significant effect.

Risk of Bias

Every trial was evaluated for risk of bias applying the RoB-2-tool. The results can be found in **Table 2** grouped by interventions performed in the trials. Since mentioned in the inclusion criteria, all studies were randomized and were compared to an inactive control group.

Overall, in several studies data for the assessment of bias was missing, so that the risk of bias could not be assessed properly (graded as 0 = some concerns / unclear bias). Other studies were evaluated as high risk (+) of bias which was majorly in the blinding (of the therapy and the outcome assessments) as well as the allocation or randomization process. Some studies were missing relevant outcome data. No relevant concerns were raised as to the reporting bias. Overall bias was performed according to the RoB-2-algorithms with an overall high risk with one domain being at high risk and low risk with all domains being at low risk. Results in between were evaluated according to the assessors' judgement.

All of the studies assessing behavioral or physical therapy and NMES were assessed overall as at least "some concerns",

TABLE 1 | Summary of results.

References	Intervention *Control*	Sample size (n =)	Dysphagia assessments (Scores/Techniques)	Summary of results
Acupuncture				
Chen (14)	Acupuncture *no treatment*	250	• Bedside swallowing test • VFS	Enhanced recovery
Xia (15)	Acupuncture + usual care *Usual care*	124	• SSA • DOSS	Enhanced recovery (in the later course of follow-up)
Behavioral/physical therapy				
Carnaby (16)	Physical therapy in different intensity levels *usual care*	306	Paramatta Hospital's assessment of dysphagia	Intensity-level dependent Enhanced recovery
Eom (17)	Expiratory muscle strength training *Sham*	33	• VDS • PAS	Enhanced recovery
Guillen-Sola (18)*	Respiratory muscle strength training *Usual care (and vs. NMES)*	42 (60 in total w/ NMES)	• FOIS • PAS • DOSS	Enhance recovery (both interventional groups)
Heo (19)	Kinesio taping *No taping*	44	FDS	No difference
Hwang (20)	Tongue stretching exercises *usual care*	25	VFS	Enhanced recovery
Kim (21)	Tongue-to-palate-resistance-training	35	• VFS/DS • PAS	Improvement on VFS, but not PAS
Koyama (22)	Jaw opening exercise *isometric sham*	16	• VFS • FOIS	No difference in clinical evaluation, mixed results for instrumental scales
Li (23)	Extended and standardized behavioral and physical training (partly including acupuncture and electrical stimulation) *usual care*	40	Kubota water swallowing test	Enhanced recovery
Moon (24)	Expiratory muscle strength training *usual care*	18	• PAS • FDS	Enhanced recovery
Moon (25)	Tongue pressure strength and accuracy training *usual care*	16	MASA	Enhanced recovery
Park (26)	Effortful swallowing training *usual care*	24	VDS	Enhanced recovery
Park (27)	Jaw opening exercise *sham*	40	• PAS • FOIS	No difference
Park (28)	Chin tuck against resistance exercise *usual care*	22	• FDS • PAS	Enhanced recovery
Drug therapy				
Cui (29)	Oral capsaicin + ice stimulation *usual care*	92	• WST • SSA	Enhanced recovery
Feng (30)	Tongyan spray *placebo*	122	SSA	Enhanced recovery
Lee (31)	Lisinopril *placebo*	93	Royal Brisbane Hospital Outcome Measure for Swallowing	No difference
Perez (32)	Nifedipine *placebo*	17	• VFS • Clinical assessment (not specified)	Enhanced recovery
Wang (33)	Capsaicin *placebo*	69	• Volume-Viscosity Swallow Test • SSA • WST	Enhanced recovery
Neuromuscular electrical stimulation (NMES)				
Carnaby (34)	McNeill Dysphagia Therapy + neuromuscular electrical stimulation *McNeill Dysphagia Therapy and usual care*	53	• MASA • FOIS	Dysphagia improvement from physical therapy and NMES
Guillen-Sola (18)*	NMES *Usual care (and vs. respiratory muscle training)*	41 (60 in total w/ NMES)	• FOIS • PAS • DOSS	Enhance recovery (both interventional groups)

(Continued)

TABLE 1 | Continued

References	Intervention *Control*	Sample size (n =)	Dysphagia assessments (Scores/Techniques)	Summary of results
Huang (35)	NMES or NMES + usual care *usual care*	29	• FOIS • PAS • VDS	Mixed results without clear significant effect
Konecny (36)	NMES hyoid *usual care*	108	• VFS	Enhanced recovery
Lim (37)*	NMES *usual care (and vs. rTMS)*	33 (47 total w/ rTMS)	• PAS • FDS • ASHA NOMS	Enhanced recovery with limitations: only first follow-up, liquids and instrumental scores
Power (38)	Faucial pillar stimulation *Usual care*	16	• PAS	No difference
Umay (39)	Sensory-level electric stimulation of masseter *sham*	98	• MASA • Fiberoptic Endoscopic Dysphagia Severity Scale	Enhanced recovery
Xia (40)	NMES or NMES + usual care *usual care*	120	• VFS • SSA	Only dysphagia improvement in NMES + usual care
Lee (41)	NMES + usual care *usual care*	57	• FOIS • VFS	Enhanced recovery
Pharyngeal electrical stimulation (PES)				
Bath (42)	PES *sham*	162	• VFS • PAS	No difference
Dziewas (43)	PES *sham* in tracheotomized patients	69	• FEES • FOIS • dysphagia severity rating scale	Dysphagia improvement, more decannulations
Jayasekeran (44)	PES *Sham*	28	• VFS/PAS	Enhanced recovery
Vasant (45)	PES *sham*	36	• Dysphagia severity rating scale • PAS	No difference
Transcranial direct current stimulatiuon (tDCS)				
Kumar (46)	tDCS *sham*	14	• DOSS	Enhanced recovery
Pingue (47)	tDCS *sham*	40	• DOSS	No difference
Suntrup-Krueger (48)	tDCS *sham*	60	• Fiberoptic Endoscopic Dysphagia Severity Scale	Enhanced recovery
Yang (49)	tDCS *sham*	16	• FDS	Enhanced recovery
Repetitive Transcranial magnetic stimulation (rTMS)				
Du (50)	rTMS high- and low-intensity *sham*	40	• SSA • WST • Degree of dysphagia	Enhanced recovery
Khedr (51)	rTMS *sham*	22	• WST • Degree of dysphagia	Enhanced recovery
Lim (37)*	rTMS *usual care*	29 (47 total w/ NMES)	• PAS • FDS • ASHA NOMS	Enhanced recovery with limitations: only first follow-up, liquids and instrumental scores
Tarameshlu (52)	rTMS + usual care and rTMS *usual care*	18	• MASA • FOIS	Enhanced recovery only for combined therapy
Khedr (53)	rTMS *sham*	26	• WST • Degree of dysphagia	Enhanced recovery
Park (54)	Bilateral rTMS, unilateral rTMS *sham*	35	• Clinical Dysphagia Scale • DOSS • PAS • VFS/VDS	Enhanced recovery only for bilateral rTMS

Summary of study characteristics. Summary of results show the statistical results as to the rejection of H_0. If VFS or FEES are mentioned, specific algorithm for detailed evaluation of the swallowing function have been established. VFS, Videofluoroscopy; VDS, Videofluoroscopic dysphagia scale; PAS, Penetration Aspiration Scale; FDS, Functional Dysphagia Scale; FOIS, Functional oral intake scale; MASA, Mann Assessment of Swallowing Ability; WST, water swallowing test; SSA, standardized swallowing assessment; DOSS, Dysphagia Outcome and Severity Scale; ASHA NOMS, American Speech-Language Hearing Association National Outcomes Measurements System (swallowing scale used).

**These studies used three arms with usual care being one of those, that is why these studies are listed in two interventional groups.*

TABLE 2 | Summary of risk of bias assessment.

Risk of bias domains	Randomization	Deviation from intervention	Missing outcome data	Outcome measurements	Reporting bias	Overall bias
Acupuncture						
Chen (14)	-	+	+	-	-	+
Xia (15)	O	+	-	-	-	+
Behavioral/physical therapy						
Carnaby (16)	-	+	-	-	-	+
Eom (17)	O	-	O	-	-	O
Guillen-Sola (18)*	-	-	O	-	-	O
Heo (19)	O	O	-	+	-	+
Hwang (20)	-	+	+	-	-	+
Kim (21)	O	+	O	-	-	+
Koyama (22)	-	O	+	-	-	+
Li (23)	+	+	-	o	-	+
Moon (24)	O	O	-	-	-	O
Moon (25)	-	+	+	0	-	+
Park (26)	-	+	+	-	-	+
Park (27)	-	+	-	-	-	+
Park (28)	-	+	O	-	-	+
Drug therapy						
Cui (29)	-	+	+	O	-	+
Feng (30)	-	O	-	O	-	O
Lee (31)	-	-	+	-	-	+
Perez (32)	-	-	-	-	-	-
Wang (33)	-	-	O	-	-	O
Neuromuscular electrical stimulation (NMES)						
Carnaby (34)	-	+	-	-	-	+
Guillen-Sola (18)*	-	O	O	-	-	O
Huang (35)	O	+	-	-	-	+
Konecny (36)	O	+	-	-	-	+
Lim (37)*	O	O	O	-	-	+
Power (38)	O	O	O	-	-	+
Umay (39)	-	O	O	-	-	O
Xia (40)	O	O	-	-	-	O
Lee (41)	-	O	-	-	-	O
Pharyngeal electrical stimulation (PES)						
Bath (42)	O	O	-	-	-	O
Dziewas (43)	-	-	+	-	-	+
Jayasekeran (44)	-	O	-	-	-	-
Vasant (45)	-	-	-	-	-	-
Transcranial direct current stimulatiuon (tDCS)						
Kumar (46)	-	O	O	-	-	O
Pingue (47)	-	O	-	-	-	-
Suntrup-Krueger (48)	-	-	-	-	-	-
Yang (49)	O	O	-	-	-	O
Repetitive transcranial magnetic stimulation (rTMS)						
Du (50)	-	-	-	-	-	-
Khedr (51)	O	O	-	-	-	O
Lim (37)*	O	O	O	-	-	+
Tarameshlu (52)	-	O	-	-	-	O
Khedr (53)	O	-	-	-	-	O
Park (54)	O	O	-	-	-	O

Risk of Bias assessment. Overview over consensus result of the risk of bias assessment, using the risk-of-bias-tool-2 according to Cochrane's handbook. – low risk, 0 some concerns or unclear risk, + high risk. Overall risk assessment according to RoB-2-algorithm.

**These studies used three arms with usual care being one of those. That is why these studies are listed in two interventional groups.*

with a vast majority due to concerns as to the deviation from intervention, to a major part because of blinding issues. The PES and tDCS group of trials were the only ones with the a relevant part of studies being assessed as low-risk (Detailed results in **Table 2**).

DISCUSSION

This systematic review gives an overview over the RCTs in the field of therapeutic interventions for post-stroke dysphagia. In this review, especially the (sub-)acute phase was of interest, so that only trials assessing therapeutic modalities, which have started within 3 months after stroke were included.

In total, 41 RCTs were included with seven different therapeutic concepts.

As to acupuncture, two studies were included, which showed an effect on post-stroke dysphagia. It has to be mentioned, though, that in one study (14), only a subgroup of these 250 participants received distinct dysphagia assessments and were therefore included in the statistical analyses. Together with the high risk of bias for both acupuncture studies, results of the study have to be interpreted cautiously. Having this in mind the European guidelines (55) give a weak recommendation that acupuncture may be used in the rehabilitation of swallowing function.

Most studies assess behavioral and physical options, but are at high risk of bias, so that conclusions cannot be made based on these results definitively. Additionally, most studies examine similar, but different kind of therapeutic maneuvers. It seems that the intensity of swallowing therapy has a positive effect on dysphagia recovery and should be a safe procedure. As to the specification of therapy, this review cannot give a clear answer. Respiratory muscle strength training seems to give a positive effect on post-stroke dysphagia based on the three studies (17, 18, 24) in this review. Otherwise, different kind of tongue strengthening interventions were observed with mixed result as to oropharyngeal dysphagia, since some showed only effect on the oral phase (without effect on the pharyngeal phase). Some studies only used clinical scores which are known to be less sensitive than instrumental ones. Jaw opening exercises failed to show an effect (for details see **Table 1** or **Supplementary Material**). If any, respiratory muscle strength training seem to be safe and potentially beneficial choice, but due to the high risk of bias the evidence has to be improved in this area. Nevertheless, a patient tailored behavioral therapy can be recommended.

As yet, no concept of drug therapy has been established, so that four different drug classes have been used. The mechanisms and concepts of drug therapy in the context of post stroke dysphagia mainly goes into the direction of increasing pharyngeal levels of substance P. This can be achieved by stimulating TRPV1 and TRPM8 (56, 57) agonists. Even ACE inhibitors are also believed to increase substance P (58). All drugs except Lisinopril have shown promising results with most of them leading to concerns about the risk of bias. Due to the lack of large clinical trials and systematic instrumental dysphagia assessments, Nifedipine and Capsaicin (TRPV1 agonist) are substances of interest but can't be recommended for clinical routine so far. Nevertheless, further studies with these substances to evaluate their clinical impact on clinical outcome measures in stroke patients are needed and should be performed.

The majority of studies about neurostimulation techniques in dysphagia are superficial stimulation (NMES), tDCS, rTMS and PES. The latter three endeavor to change neuroplasticity of specific brain areas. In theory, this can include facilitation of a lesioned brain region or facilitation of healthy brain areas. In case of post stroke dysphagia, the interventions have the goal to facilitate brain regions involved in swallowing through increasing synaptic efficiency and cortical reorganization. Functional imaging studies (59, 60) succeeded to show that the primary motor cortex seems to play a major role in the act of volitional swallowing and can be associated with post-stroke dysphagia (61).

The studies about tDCS in the rehabilitation of post stroke dysphagia can't be specified further as to the localization and mode of stimulation. Two out of the four studies used the anodal stimulation over the unaffected hemisphere and did show some effect. Another one stimulated the affected side and showed improved swallowing rehabilitation, too. The other study used a dual stimulation concept without the proof of benefit. These concepts have to be confirmed in further studies given the very low number of RCTs included in this review.

Studies investigating rTMS in the rehabilitation of post stroke dysphagia show also a fair methodological quality leading to some concerns of bias. All show some effect on post-stroke dysphagia. It does not come as a surprise that the trials with combined rTMS and standard therapy have better effects, neither that bilateral stimulation seems to have a more pronounced therapeutical impact. Different aspects of the swallowing function seem to be represented in different hemispheres and different parts of those (62). Furthermore, studies with instrumental and clinical testing of dysphagia assessment are broadly lacking because most of those included in this review have used either clinical or instrumental dysphagia assessments only.

The studies assessing PES are of comparably low risk of bias, but only two did show some effect on post-stroke dysphagia. This effect was only seen in one study in a subgroup of tracheotomized stroke survivors, which seemed to profit from the stimulation therapy.

The trials on neurostimulation all show some methodological weaknesses, leading to concerns about the risk of bias. Some effect, especially in combination with standard therapy or additional physical therapy has been shown and is promising. Nevertheless, this has to be proven in further high-quality research with clinical endpoints. The ESO guidelines (55) give a weak recommendation on the adjunct use of neurostimulation in post stroke dysphagia.

This review covers most of the relevant databases. The search strategy is quite selective due to restricting to RCT with inactive controls, allowing only interventions targeting the swallowing function and therefore leaving out preventive, dietary or nutritional measures. The selected start of the intervention within 3 months of stroke focused on the acute/subacute phase. Therefore, there could be a lack of some therapeutic concepts for post-stroke dysphagia, but we believe that it gives a comprehensive overview over the existing publications of

RCT in order to help to enhance further scientific research and develop therapies.

It becomes clear, that the field of dysphagia needs more research to establish therapeutic guidelines. According to the findings above it seems safe and reasonable to say that an intensive swallowing or respiratory muscle strength therapy should be applied with rTMS and some drug candidates as potential future options for additional therapeutical concepts. It has to be stated that main outcome measurements for primary endpoints should be instrumental in addition to clinical ones, whenever feasible.

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

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.2022.823189/full#supplementary-material

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Neuroimaging Parameters Are Not Associated With Chronic Post-stroke Fatigue in Young Stroke Patients

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Introduction: Post-stroke fatigue is frequently present in young adults, but its underlying mechanism is still unclear. The aim of the study was to investigate the association between lesion location, network efficiency and chronic post-stroke fatigue based on voxel-based lesion-symptom mapping and structural network connectivity analysis.

Patients and Methods: One hundred and thirty five young patients, aged 18–50 years, with a first-ever transient ischemic attack or cerebral infarction from the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, underwent 1.5T MRI and were assessed for fatigue using the self-report Checklist Individual Strength. Stroke lesions were manually segmented, and structural network efficiency was calculated using the diffusion MRI-based brain networks and graph theory for each patient. Univariate and multivariate analyses was performed to study the associations between MRI parameters and chronic post-stroke fatigue. In addition, we used voxel-based lesion-symptom mapping to analyze the relationship between the lesion location and chronic post-stroke fatigue.

Results: Mean age at index event was 39.0 years (SD ± 8.2), and mean follow-up duration was 11.0 years (SD ± 8.0). 50 patients (37%) had post-stroke fatigue. Voxel-based lesion-symptom mapping showed no significant relation between stroke lesions and the presence of chronic post-stroke fatigue. Furthermore, there were no significant associations between the lesion size or network efficiency, and the presence of chronic post-stroke fatigue.

Discussion: We did not find any association between stroke characteristics (lesion location and size) and chronic post-stroke fatigue (CIS20-R), nor associations between structural brain network connectivity and post-stroke fatigue on the long term in young stroke patients.

Keywords: young stroke, post-stroke fatigue, voxel-based lesion symptom mapping, brain network, graph theory

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INTRODUCTION

Stroke in young adults (18–50 years) has a high socioeconomic impact due to amongst other the lifelong post-stroke consequences including post-stroke fatigue (PSF) (1). PSF affects at least 40% of young stroke survivors and may even be present several years after stroke. Moreover, PSF is related to poorer functional outcome and a higher mortality rate (2–4). Furthermore, patients consider PSF as one of the worst symptoms of stroke as it has a substantial impact on their quality of life (4).

Despite its importance, little is known about the underlying mechanisms of PSF. Lesion location may be an important determinant of PSF, but the associations between stroke topology and PSF remain unclear, as most studies did not show any associations between stroke side, location, and size and PSF (5–8). One of the major limitations is that most of these studies compared lesion sides and locations based on clinical diagnoses or on visible lesions on CT/MR imaging, which may not be sensitive for determining such associations. More precise methods, such as voxel-based lesion-symptom mapping (VLSM), may provide more insight into the particular brain regions that are associated with PSF in young stroke patients. VLSM is an increasingly utilized method to study the relationship between the location of stroke lesions and behavioral symptoms (9). This approach can be used to anatomically localize behavioral symptoms and has been used for investigating the structural basis of post-stroke depression (10) and post-stroke apathy (11).

An alternative explanation is that PSF is not primarily determined by the location of the stroke lesions, but rather by the brain networks affected by stroke. Recent studies have shown that cognitive and behavioral functions are distributed in the brain via several interconnected brain regions (12, 13). Network analysis studies the connections between the brain regions by investigating the organizational properties of the brain networks and has been used to investigate behavioral symptoms after stroke (13). Brain networks can be assessed with diffusion tensor imaging (DTI) and tractography. Using these techniques, it has been reported that lower global efficiency in an apathy-related subnetwork was an independent risk factor for post-stroke apathy (14). Recent study showed that functional connectivity of the fronto-striato-thalamic network predicted the response for chronic PSF treatment with modafinil (15). However, in this study structural connectivity that provide structural basis for the functional interactions between brain regions, was not examined. Therefore, it is not known whether disruption of the structural brain network, while looking beyond the effects of the stroke location, is also related to chronic PSF.

The aim of this study was to investigate the association between the location of stroke lesions, network efficiency, and chronic PSF by using VLSM and structural network connectivity analysis based on DTI. We hypothesized that lesion location is not an important determinant of chronic PSF, but that lower structural network efficiency is associated with chronic PSF in young ischemic stroke patients.

METHODS

Patients

This study is part of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, which is a prospective cohort study in which the etiologies and consequences of young stroke were investigated (16). Inclusion criteria were the presence of a transient ischemic attack (TIA), ischemic stroke of presumed arterial origin or intracerebral hemorrhage, which occurred between 1980 and 2010 in young adults aged 18–50 years who visited Radboud University Nijmegen Medical Centre. Although, there is no uniform age cut-off for defining "young stroke," we used the age-limits 18–50 years (1, 17, 18). During the follow-up between 2009 and 2012 patients underwent neuropsychological screening and MRI scanning. The flowchart of the study population is shown in **Figure 1**. Only patients with the clinical diagnosis of an ischemic stroke or TIA and a supratentorial visible lesion on the MRI scan corresponding with the initial clinical diagnosis obtained at follow-up were included, which resulted in a total of 140 patients. We additionally excluded 5 patients (missing information on fatigue $n = 2$, and lack of T1 scans $n = 3$), yielding a total sample size of 135 patients for this study. The 135 patients included in this study had higher NIHSS-scores at admission [median 4 (IQR 2–10)] than patients excluded from the study ($n = 376$) [median 2 (IQR 0–4); $p < 0.001$] and more often had aphasia (24.6 vs. 10.4%, respectively, $p < 0.001$) based on NIHSS evaluated by the treating clinicians. Patients included in the study were also younger at the time of the index event compared to patients excluded from the study [mean 39.0 (SD 8.2) years vs. mean 40.7 (SD 7.7) years, $p = 0.04$]. No significant differences were found in clinical outcome at follow-up based on mRS.

Post-stroke Fatigue

The presence of fatigue was assessed with the fatigue subscale of the self-report Checklist Individual Strength (CIS20-R) (19, 20), a questionnaire validated in stroke survivors (19, 21). Patients had to score 8 items on the level of fatigue over the past 2 weeks with scores ranging from 1 (yes, that is true) to 7 (no, that is not true). Examples of items are "I feel tired" and "Physically, I feel exhausted." The total fatigue subscale score ranges from 8 to 56, with higher scores indicating more symptoms of fatigue. Severe fatigue is defined as a score >35 (2, 21, 22).

Other Measurements

We defined depressive symptoms and anxiety using the Hospital Anxiety and Depression Scale (HADS) (23). The Dutch scoring system was used for the level of education, with 1 being less than primary school and 7 a university degree (16). The modified Rankin Score (mRS) was used to define functional outcome. MRS ranges from no symptoms (0 points) to death (6 points). We defined a good functional outcome as mRS < 3 points (16).

MRI Data Acquisition

Images were acquired on a 1.5T S Magneton Sonata scanner (Siemens Medical Solutions, Erlangen, Germany). The scanning

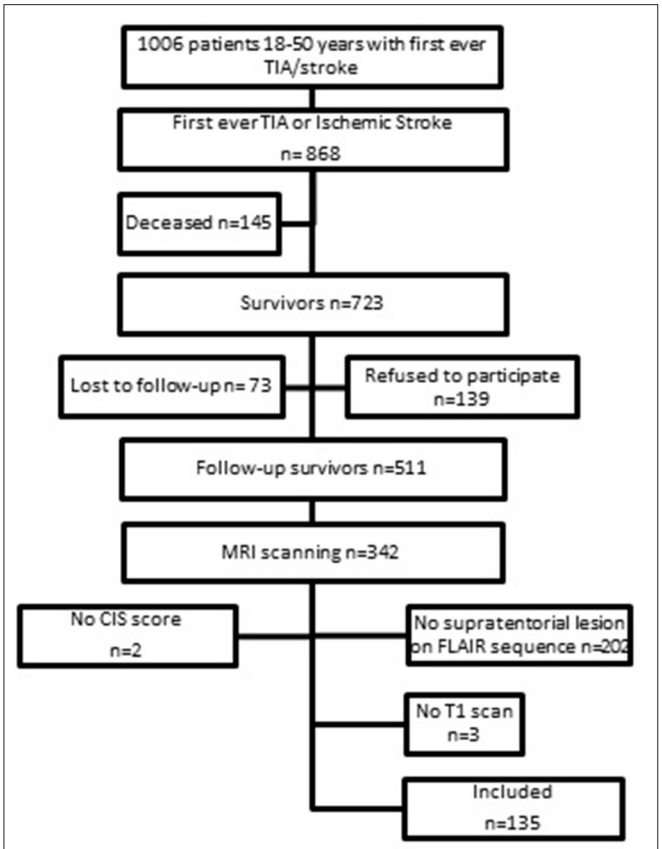

FIGURE 1 | Flowchart of study population.

protocol included (1) whole brain 3D T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE/TI 2730/2.95/1000 ms; flip angle 7°; voxel size 1.0 × 1.0 × 1.0 mm), (2) Fluid-attenuated inversion recovery (FLAIR) pulse sequences (TR/TE/TI 12220/85/2200 ms; voxel size 1.0 × 1.2 × 3.0 mm; slice gap 0.6 mm), (3) gradient echo susceptibility weighted imaging sequence (TR/TE 49/40 ms; voxel size 0.8 × 0.7 × 1.0 mm), (4) DTI (TR/TE 9100/98 ms; voxel size 2.2 × 2.2 × 2.2 mm; 7 unweighted scans, 61 diffusion-weighted scans, with non-co-linear orientation of the diffusion-weighting gradient, and b value 1,000 s/mm^2).

Lesion Segmentation

All chronic stroke lesions were manually segmented on the FLAIR sequence using ITK-SNAP by a trained investigator (SC). All lesion borders were checked by an experienced clinician (EB). We manually segmented stroke lesion and the adjacent glial scars. After lesion segmentation, we registered the lesion masks non-linearly to a standard space. To this end, the Functional MRI of the Brain non-linear registration tool (FNIRT) was used to non-linearly register the skull-stripped T1-weighted images to Montreal Neurological Institute (MNI) 152 template. Next, we registered both the masks of the stroke lesions and the FLAIR images to the standard space using the transformation matrix of T1-weighted images to standard space after linearly registering to T1-weighted image using Functional MRI of the brain linear image registration tool (FLIRT). We used FSL 5.0.5 tools (24).

Structural Network

We defined network nodes (i.e., brain regions) using the Automated Anatomical Labeling (AAL) template (25), which resulted in 90 regions (45 per hemisphere), excluding the cerebellum. The AAL image was registered to each participant's diffusion image space by using the earlier obtained transformation matrixes.

We defined our network edges [i.e., white matter (WM) connections] by the following procedures. First, we used "PATCH" on the raw diffusion data to correct for cardiac and head motion artifacts and for eddy currents (26). Second, we calculated the diffusion tensor and mean fractional anisotropy (FA) using DTIFit from FSL. Third, we used fiber assignment by continuous tracking (FACT) to generate the WM tracks for the whole brain for each participant. The tracking algorithm started at the center of the voxels with fractional anisotropy >0.2 and ended when the fiber tracks left the brain mask, encountered voxels with fractional anisotropy <0.2 or when the turning angle exceeded 60°. Two regions were considered connected if the endpoints of the reconstructed streamline lay within both regions. Fourth, the weight of the connection (e.g., the connection strength) was defined as mean fractional anisotropy (FA) of the reconstructed streamlines multiplied by the number of reconstructed streamlines connecting two regions (27). Finally, we corrected for the differences in the AAL regions size and the differences in brain size (28), resulting in an undirected, weighted 90 × 90 matrix for each participant.

Graph Theory Analysis

We assessed graph-theoretical network measures using the Brain Connectivity Toolbox (29). We calculated 5 different network measures: (1) network strength, (2) density, (3) global efficiency, (4) local efficiency and (5) nodal efficiency. Degree defines the number of neighbors of a node. Network strength is weighted variant of degree and represents the sum of all neighboring link weights. Density represents the fraction of present connections to possible connections. Global efficiency is the average inverse shortest path length in the network. Local efficiency is global efficiency computed on node neighborhoods. Nodal efficiency is the mean of the inverse of the shortest path length between the node and all other nodes in the network. Furthermore, we performed a *post-hoc* analysis in which the network measures were calculated from the unaffected hemisphere.

Statistical Analysis

We analyzed group differences between fatigued and non-fatigued patients for demographic, clinical variables using χ^2-tests or Fisher's exact tests for categorical variables and *t*-test for the continuous variables, where appropriate. To investigate the relationship between lesion location and the presence of

TABLE 1 | Demographic and clinical variables of fatigued and non-fatigue young stroke patients.

	Whole group (*n* = 135)	Fatigue (*n* = 50)	Non-fatigue (*n* = 85)	P-value
Age at index event, mean (sd)	39.0 (8.2)	39.5 (8.4)	38.8 (8.1)	0.62
Follow-up duration, mean (sd)	11.01 (8.0)	9.26 (8.0)	12.05 (7.8)	0.05
Male, *n* (%)	60 (44.4)	18 (36.0)	42 (49.4)	0.13
Education level (range)	4.71 (6)	4.58 (6)	4.79 (5)	0.35
Stroke type, *n* (%)				
• TIA	12 (8.9)	4 (8.0)	8 (9.4)	0.78
• Ischemic stroke	123 (91.1)	46 (92.0)	77 (90.6)	
NIHSS at admission, mean (sd)	6 (5)	6 (5)	6 (5)	0.79
CIS20-R fatigue score at follow-up, mean (sd)	30.3 (13.3)	44.8 (6.3)	21.8 (7.9)	**<0.001**
Recurrent stroke, *n* (%)	24 (17.8)	13 (26.0)	11 (12.9)	0.05
mRS score at follow-up, mean (sd)	1.24 (0.9)	1.50 (1.02)	1.09 (0.7)	**0.01**
Depression at follow-up, *n* (%)	20 (14.8)	16 (32.0)	4 (4.7)	**<0.001**
Anxiety at follow-up, *n* (%)	25 (18.5)	21 (42.0)	4 (4.7)	**<0.001**

sd, standard deviation; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; CIS, Checklist Individual Strength; mRS, modified Rankin Scale. Bold indicates significant P-values (P < 0.05).

TABLE 2 | MRI variables of fatigued and no fatigue young stroke patients.

Variable	Whole group (*n* = 135)	Fatigue (*n* = 50)	Non fatigue (*n* = 85)	*p*-value	OR^(95% CI)	P-value^
Lesion side, *n* (%)						
• Left	53 (39.3)	27 (54.0)	26 (30.6)	Ref	Ref	Ref
• Right	63 (46.7)	18 (36.0)	45 (52.9)	0.05[a]	0.34 (0.13-0.90)	0.06[a]
• Bilateral	19 (14.1)	5 (10.0)	14 (16.5)	0.21[a]	0.48 (0.12-1.98)	0.75[a]
Lesion size (ml), mean (sd)	46.26 (55.99)	36.88 (52.80)	51.42 (57.34)	0.18		
Density, mean (sd)	0.08 (0.01)*	0.08 (0.01)**	0.08 (0.02)***	0.46		
Strength, mean (sd)	4.05 (0.84)*	4.18 (0.84)**	3.98 (0.84)***	0.23		
Global efficiency, mean (sd)	1.67 (0.62)*	1.77 (0.63)**	1.62 (0.61)***	0.21		
Local efficiency, mean (sd)	1.63 (0.52)*	1.67 (0.51)**	1.61 (0.53)***	0.52		

**n = 121, patients without DTI were excluded, **n = 43, patients without DTI were excluded, ***n = 78, patients without DTI were excluded.*
^Adjusted for potential confounders (lesion size, age at follow-up, sex, educational level, depression, anxiety, and mRS).
[a]P-values are Bonferroni corrected.

chronic PSF, we used voxel-based lesion mapping (VLSM) (9) implemented in the non-parametric mapping (NPM) software of MRIcron. In the univariate analysis, we used the Brunner and Munzel test (30) and a *t*-test with 1,000 permutations with a p-threshold of 0.05, corrected for multiple comparisons using Benjamini-Hochberg (BH) false discovery rate (FDR) correction (31). Next, we performed a multivariate analysis by using NiiStat in Matlab (https://github.com/neurolabusc/NiiStat). We also analyzed group differences for imaging variables, including lesion location, lesion volume and network measures. For significant associations, we additionally adjusted for possible confounders; age at follow-up, education, depressive symptoms, anxiety, and mRS score during follow-up. In case of multiple comparisons, we used the Bonferroni correction to adjust for multiple comparisons. Furthermore, we investigated whether a specific subnetwork for chronic PSF could be found by analyzing group differences for nodal efficiency of each brain region, by using unpaired *t*-tests, corrected for multiple comparisons using BH FDR correction. All statistical analyses were carried out in the statistical software IBM SPSS Statistics 26 and Matlab R2021a.

RESULTS

Study Population

We included 135 patients with a mean age of 39.0 years (SD ± 8.2) at index event. Mean follow-up duration was 11.0 years (SD ± 8.0). The mean CIS20-R-score was 30.3 (SD ± 13.3) and 50 patients (37%) patient fulfilled the criteria of severe PSF. Depression and anxiety were significantly more present in the fatigued group than in the non-fatigued group. The demographic and clinical variables are shown in **Table 1**.

MRI Correlates of Fatigue in Young Stroke

Lesion Volume and Lesion Side

The results of the univariate and multivariate analyses are shown in **Table 2**. The univariate analysis showed a higher risk of

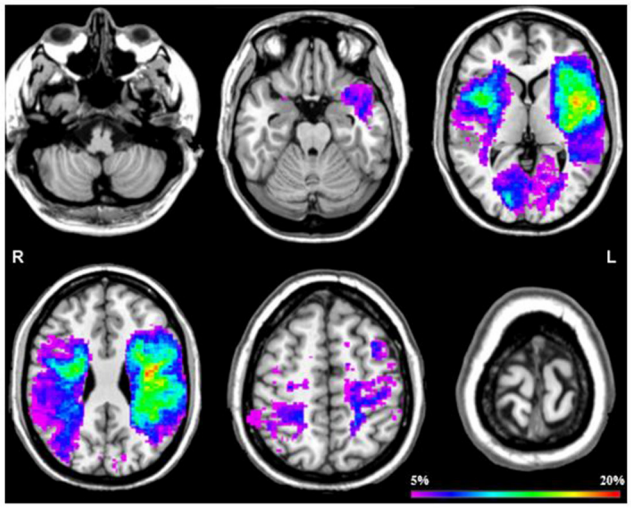

FIGURE 2 | Probability map of all stroke lesions. This probability map displays a overlap across all stroke patients by 6 slices at $z = 25$, $z = 50$, $z = 75$, $z = 100$, $z = 125$ en $z = 150$. The color scale saturates at 20% which means that in 20% of the patients that specific area was damaged.

chronic fatigue after left hemisphere stroke compared to right hemisphere stroke, which was not significant, after controlling for potential confounders (lesion size, age at follow-up, sex, educational level, depression, anxiety, and mRS) ($p = 0.06$).

Voxel-Based Lesion Mapping

Figure 2 shows an overlap image of all stroke lesions. The univariate VLSM analysis showed no significant difference in lesion location between the fatigued group compared to the non-fatigued group after correcting for multiple testing (FDR correction $q < 0.05$). This was further confirmed by the multivariate VLSM, while correcting for the potential confounders.

Brain Networks

Whole brain network strength, network density, global efficiency and local efficiency were not significantly associated with the presence of chronic PSF (**Table 2**). In the *post-hoc* analysis, network measures from the unaffected hemisphere were also not significantly associated with the presence of chronic PSF. Furthermore, we found no significant differences in the nodal efficiency of each brain region between the fatigued group compared to the non-fatigued group after correcting for multiple testing.

DISCUSSION

In this study, we found no association between stroke characteristics (e.g., lesion location or lesion volume) and chronic PSF (based on CIS20-R), nor between structural network connectivity and chronic PSF in young stroke patients. These findings indicate that structural brain measures (characteristics of stroke lesions and structural brain networks) are not important determinants of PSF on the long term in young stroke patients.

We performed VLSM to investigate the relationship between stroke location and chronic PSF in a more robust manner than previous studies. Our analysis did not show any differences in (damaged) brain structures in young stroke patients with chronic PSF compared to patients without PSF. Our findings are comparable to previous studies showing no associations between either visible stroke lesions or lesions detected with VLSM and PSF in patients during the chronic stage of stroke (32–36). This is in contrast with studies showing significant association between lesion location (e.g., infratentorial and deep circulation) and PSF (21, 37–41) that included patients in the acute phase of the stroke (21, 37–40, 42). There are several factors that may explain the lack of association between brain measures and PSF. First, fatigue is a multidimensional entity in which predisposing factors, coping skills, stroke outcome, and mood disorders (19, 43) may play an important role, with lesion location adding little to the explained variance, especially on the long term. Second, although stroke lesions are considered permanent, their relation to behavioral function may change over time due to neuroplasticity and recovery. These changes may explain the lack of an association between the stroke lesion and chronic fatigue more than a decade after the initial event. Third, stroke lesions may result in remote damage to structurally intact regions, leading to disruption of the structural networks. The stroke lesion itself might not truly represent the brain changes that might be involved in chronic PSF.

However, we did not find associations between structural network connectivity and chronic PSF. These results are in line with findings in the general stroke population showing no associations between chronic PSF and structural network measures or lesion characteristics (44). A recent study showed that the functional connectivity of the fronto-striato-thalamic network could predict the response for PSF treatment with modafinil (15). This suggests that specific subnetworks may be associated with PSF. In contrast, we did not find any differences in nodal efficiency of the brain regions between fatigued and non-fatigued patients in the chronic phase of stroke. This implies that a specific subnetwork is not involved in PSF in our study. An explanation, as we stated earlier, is that PSF is multifactorial (43) and other factors, for example mood disorders, are more important contributors.

Consistent with previous studies, we found that chronic PSF was associated with depressive symptoms and anxiety (21, 43, 45, 46). One explanation could be that fatigue may be the result of symptoms of depression and anxiety (21, 35). However, it has been shown that PSF and depression are two different clinical entities that can be dissociated from each other, since not all patients with PSF has depressive symptoms or anxiety and vice versa (37, 45). Furthermore, in this study, we used the CIS20-R fatigue score to assess the level of fatigue. Though validated to assess fatigue in stroke, we cannot distinguish between the different subtypes of fatigue. Since depression and anxiety are more likely correlated with psychological or mental fatigue and less likely with physical fatigue (21, 37), future research should investigate the association between depressive symptoms and

anxiety using instruments that enable to disentangle different subtypes of fatigue.

Strengths of our study include the large sample size of young stroke patients, the long follow-up duration of 11 years and the single-centre design. Furthermore, to the best of our knowledge, this is the first study to investigate the relationship between structural brain measures and chronic PSF using VLSM and structural network analysis in young stroke patients who are free from other neurological disorders.

However, there are several limitations to be mentioned. First, we do not have information about predisposing factors (43). In a conceptual model (43), predisposing factors may be involved in the occurrence of PSF, including vulnerability to stress (e.g., personality, coping style and illness perceptions), pre-stroke fatigue (6, 47) or pre-stroke depressive symptoms (41). Second, early effects of stroke, such as stroke lesions (21, 37–40, 42), stroke-related inflammatory and neuroendocrine changes, and attentional-executive impairments have been described as triggers for early fatigue. In this study, there is no information available about early fatigue. Also, we have no information on other stroke-related factors that might change over time and contribute to the presence of chronic PSF. Third, we used the fatigue cut-off score of 35 (indicating severe fatigue) as used in previous post-stroke fatigue studies (2, 21). We also performed additional analyses in which an alternative fatigue cutoff was considered to include patients with mild and moderate fatigue. However, the analyses with a cutoff score of >26 remained similar, showing no differences between patients with fatigue and without fatigue in terms of MRI parameters. Fourth, in this study, we included patients who had a mean follow-up duration of 11.0 years. In those years, several events (e.g., socio-economic and other life events, comorbidities and/or newly started medication) may have either attenuated, increased or resolved their fatigue. Fifth, the generalizability of our study might be affected because we were only able to use a subset of the FUTURE study cohort. The included patients were significantly older than the excluded patients, however the absolute difference in mean was 1 year. There is conflicting evidence about the association between age and the risk of post-stroke fatigue, as some studies showed a relation between increasing age and the risk of fatigue, while others showed no relation or even opposite relation (21, 48). Although the role of age as a factor for the risk of post-stroke fatigue still needs to be elucidated, it is unlikely that the lack of association between MRI-parameters and post-stroke fatigue in our study is influenced by age. Also, the patients included in this study were more affected at admission than the patients excluded from the study and there were no significant differences among clinical outcome at follow-up. At admission, the included patients more often had aphasia than the excluded patients. Although the evaluation of post-stroke fatigue in patients with aphasia can be challenging, there is some evidence that patients with language impairment more often have fatigue than patients without language impairment (49). In our study, however, no information was obtained during the follow-up regarding their language abilities. Therefore, we were unable to investigate the impact of aphasia at follow-up on (the report of) post-stroke fatigue. Furthermore, the prevalence of severe fatigue in this study (37%) was in line with the prevalence of severe fatigue in all ischemic stroke patients of the FUTURE study (2). Therefore, our results should be generalizable to the whole study population.

CONCLUSION

Chronic PSF in young stroke patients seems to be a multi-dimensional and multifactorial symptom, which is not associated with stroke characteristics and structural network measures. Future studies are needed to better understand the mechanisms of PSF, focusing more on the role of predisposing factors of fatigue and its different subtypes, and the role of stroke lesions in the acute phase.

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 Medical Ethics Committee Region Arnhem-Nijmegen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC, EB, and AT were involved in data analysis and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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External Validation of the Early Prediction of Functional Outcome After Stroke Prediction Model for Independent Gait at 3 Months After Stroke

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Introduction: The Early Prediction of Functional Outcome after Stroke (EPOS) model for independent gait is a tool to predict between days 2 and 9 poststroke whether patients will regain independent gait 6 months after stroke. External validation of the model is important to determine its clinical applicability and generalizability by testing its performance in an independent cohort. Therefore, this study aimed to perform a temporal and geographical external validation of the EPOS prediction model for independent gait after stroke but with the endpoint being 3 months instead of the original 6 months poststroke.

Methods: Two prospective longitudinal cohort studies consisting of patients with first-ever stroke admitted to a Swiss hospital stroke unit. Sitting balance and strength of the paretic leg were tested at days 1 and 8 post-stroke in Cohort I and at days 3 and 9 in Cohort II. Independent gait was assessed 3 months after symptom onset. The performance of the model in terms of discrimination (area under the receiver operator characteristic (ROC) curve; AUC), classification, and calibration was assessed.

Results: In Cohort I [$N = 39$, median age: 74 years, 33% women, median National Institutes of Health Stroke Scale (NIHSS) 9], the AUC (95% confidence interval (CI)] was 0.675 (0.510, 0.841) on day 1 and 0.921 (0.811, 1.000) on day 8. For Cohort II ($N = 78$, median age: 69 years, 37% women, median NIHSS 8), this was 0.801 (0.684, 0.918) on day 3 and 0.846 (0.741, 0.951) on day 9.

Discussion and Conclusion: External validation of the EPOS prediction model for independent gait 3 months after stroke resulted in an acceptable performance from day 3 onward in mild-to-moderately affected patients with first-ever stroke without severe prestroke disability. The impact of applying this model in clinical practice should be investigated within this subgroup of patients with stroke. To improve the generalizability of patients with recurrent stroke and those with more severe, neurological comorbidities, the performance of the EPOS model within these patients should be determined across different geographical areas.

Keywords: stroke, prognosis, external validation, gait, lower extremity, logistic model, outcome, rehabilitation

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INTRODUCTION

Recovery of gait is one of the main priorities in motor stroke rehabilitation (1). Knowledge regarding the prognosis of gait outcome is an integral part of clinical decision-making, allows stratifying patients for (research) interventions, can improve rehabilitation efficacy, and aids in properly informing patients and their relatives (2). Various prediction models for independent gait after stroke have been developed, and the Early Prediction of Functional Outcome after Stroke (EPOS) prediction model (3) has been indicated to be one of the most promising models (4, 5).

In 2011, the EPOS prediction model for regaining independent gait 6 months after stroke was developed in patients with first-ever ischemic stroke who were not able to walk independently within the first 72 h after symptom onset (3). The Functional Ambulation Categories (FAC) (6) was the selected measurement instrument to capture the gait abilities of a patient and based on which 'independent gait' was defined as a score of $\geq$4/5 and 'dependent gait' as a score of <4/5 (3). The multivariable logistic model contained two predictors: sitting balance as assessed by the Trunk Control Test (TCT-s) (7) and strength of the paretic lower limb, measured by the Lower Extremity subscale of the Motricity Index (MI-LE) (7). Patients who were able to sit unsupported for 30 s (TCT-s score of 25/25) and had some strength in the paretic leg (MI-LE score of $\geq$25/100) within 72 h post-stroke had a probability of 97% to walk independently 6 months later (3). The probability of patients not fulfilling these criteria was 27% at baseline (<72 h post-stroke) and decreased to 10% when the predictors were retested on day 9.

Although the EPOS model seems to be feasible to apply in clinical practice and its performance is encouraging, the model has not been externally validated until now. However, external validation is an important step toward the clinical application of prediction models. With external validation, the reproducibility and generalizability of the model, in an independent patient sample with a different case-mix, are tested by determining the model's level of overfitting and performance within this new sample (2, 8, 9). External validation is needed, as it has been shown that the performance of prediction models in an independent sample is often lower than that in the sample in which the model was developed (10).

The EPOS prediction model as developed in 2011 did use a 6-month endpoint for independent gait. However, 6-months might be too conservative, as most behavioral change takes place within the first week to the first few months (11). When looking at gait specifically, Kennedy and colleagues recently showed that the median time needed to walk 50 m without assistance was 6 (Q1 = 2, Q3 = 63) days and that by 3 months, 75% of the patients were able to walk 50 m unassisted (12). The percentage of 75% did not differ much from the 79% of patients who walked independently at 6 months in the EPOS study in 2011, suggesting that not many patients regained independent gait between 3 and 6 months after stroke. This emerged knowledge supports investigating the applicability of the EPOS model for the outcome of gait 3 months after stroke onset instead of the original 6 months.

Therefore, we aimed to perform a temporal and geographical external validation of the EPOS prediction model for independent gait after stroke (3) in two cohorts in Switzerland. However, contrary to the endpoint of 6 months post-stroke in the original study, the EPOS prediction model was externally validated for a 3-month endpoint. We hypothesized that the performance of the model in the validation cohorts would be acceptable but lower than that in the development cohort (10).

MATERIALS AND METHODS

Design

We carried out a secondary data analysis of two prospective longitudinal observational studies. Recruitment for study 1 (Cohort I) took place from 09/2017 until 11/2019 and the study included three visits. Visit 1 took place within 48 h, visit 2 on day 7 $\pm$ 2, and visit 3 on day 90 $\pm$ 7 after symptom onset. Study 2 (Cohort II) started on 09/2018 and ended on 03/2021, for this work relevant study visits included days 3 $\pm$ 2 (visit 1), 10 $\pm$ 2 (visit 2), and 90 $\pm$ 7 (visit 3) post-stroke. For both studies, patients consecutively admitted to the stroke unit of the Department of Neurology of the University Hospital Zurich (Switzerland) and diagnosed with a stroke were screened. Ethical approval from the cantonal ethics committee Zurich was obtained before the start of the studies (BASEC identifiers 2017-00889 and 2017-01070), and both studies were prospectively registered at ClinicalTrials.gov (Identifiers NCT03287739 and NCT03522519). The same ethical committee approved secondary data analysis (BASEC identifier 2020-00218). Reporting was done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (13) and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statements (14).

Patients

Study characteristics for Cohorts I and II are described in **Table 1**. At the University Hospital Zurich, the median length of hospital stay for stroke patients was 6 (Q1 = 2, Q3 = 11) days, and patients typically received 45–75 min of individualized physical and occupation therapy per day during their stay at the acute stroke unit 5 days a week. All patients of Cohort I were discharged to an inpatient rehabilitation center. In Cohort II, 77 out of 78 patients (99%) received inpatient stroke rehabilitation, and one patient did not receive any rehabilitation after hospital discharge. In both cohorts, patients were treated according to the current national guidelines (15) and local protocols. Motor rehabilitation was patient-centered and was applied with a task-oriented approach with repetitive nature.

Data Collection

Trained, unblinded physical therapy researchers performed assessments. The predictors were collected during the hospital stay. The outcome of 3 months post-stroke was assessed during an outpatient visit at the hospital or at the patient's place of residence.

TABLE 1 | Key characteristics of the development and validation studies.

Characteristic	Development cohort (3) (*N* = 154)	Validation cohort I (*N* = 39)	Validation cohort II (*N* = 78)
Recruitment period	02/2007–11/2009	10/2017–11/2019	09/2018–12/2020
Setting	9 acute hospital stroke units in the Netherlands	1 acute hospital stroke center in Switzerland	1 acute hospital stroke center in Switzerland
Inclusion criteria	(1) First-ever ischemic anterior circulation stroke (2) ≥18 years (3) Mono- or hemiparesis <72 h (4) Premorbid Barthel Index ≥19 (5) No severe deficits in communication, memory, or understanding (6) Written informed consent (7) FAC <4 within 72 h	(1) First-ever unilateral ischemic stroke <48 h, confirmed by MRI-DWI and/or CT (2) ≥18 years (3) NIHSS arm ≥1 (4) Prestroke modified Rankin Scale ≤2 (5) Able to follow one-staged commands (6) Informed consent after participants' information	(1) First-ever ischemic or hemorrhagic stroke, confirmed by MRI-DWI and/or CT (recurrent strokes are allowed when already included in this study after a first-ever stroke) (2) ≥18 years (3) Motricity Index (sum of the upper and lower extremity subscales) <200 (4) Prestroke modified Rankin Scale ≤2 (5) Written informed consent of the patient or its legal representative after participants' information
Exclusion criteria	Not formulated	(1) Neurological or other diseases affecting the upper limb(s) before stroke (2) Intravenous line in the upper limb(s) that limited assessment (3) Contra-indications on ethical grounds (4) Expected or known non-compliance, severe drug and/or alcohol abuse (5) For the current work: FAC ≥4 within 48 h	(1) Neurological or other diseases affecting upper limb use and/or physical activity before stroke (2) Contra-indications on ethical grounds (vulnerable persons) (3) Known or suspected non-compliance, drug and/or alcohol abuse (4) For the current work: FAC ≥4 at day 3 ± 2
Outcome	FAC: <4 vs. ≥4; 6 months post-stroke	FAC: <4 vs. ≥4; 3 months post-stroke	FAC: <4 vs. ≥4; 3 months post-stroke
Predictors*	TCT-s: <25 vs. 25; days 2, 5, and 9 post-stroke MI-LE: 25 vs. ≥25; days 2, 5, and 9 post-stroke	TCT-s: <25 vs. 25; days 1 and 8 post-stroke MI-LE: 25 vs. ≥25; days 1 and 8 post-stroke	TCT-s: <25 vs. 25; days 3 and 9 post-stroke MI-LE: 25 vs. ≥25; days 3 and 9 post-stroke

**, dichotomized predictors are coded 0 and 1; CT, Computed Tomography; FAC, Functional Ambulation Categories; MI-LE, Motricity Index – Lower Extremity subscale; MRI-DWI, Magnetic Resonance Imaging – Diffusion Weighted Imaging; NIHSS, National Institutes of Health Stroke Scale; TCT-s, Trunk Control Test – Sitting Balance item.*

Outcome

The dependent variable was independency in gait 3 months after stroke as measured by the Functional Ambulation Categories (FAC) (6, 16, 17). The FAC is an observational scale that classifies the walking ability of a patient, regardless of whether walking aids or orthoses are used. The FAC-score ranges from 0 to 5, with higher scores indicating a better walking ability. FAC was dichotomized into ≥4/5 points (independent gait; favorable outcome) and <4/5 points (dependent gait; unfavorable outcome) (3). A score of 4 means that the patient is able to walk on level surfaces, while with a score of 5, the patient can walk independently anywhere.

Predictors

The independent variables included the sitting balance item of the Trunk Control Test (TCT-s, score range 0–25) (7) and the lower extremity subscale of the Motricity Index (MI-LE, score range 0–100) (7) as measured during study visits 1 and 2. According to the EPOS prediction model, the TCT-s was dichotomized into 25/25 (1, sitting balance present) vs. <25/25 points (0, sitting balance absent). The MI-LE was dichotomized into ≥25/100 (1, strength present) vs. <25/100 (0, strength absent).

Data additionally collected to characterize the patients of the validation cohorts to allow comparison with the development cohort and judge whether the results are applicable to patients seen in clinical practice included patient demographics, stroke characteristics, the National Institutes of Health Stroke Scale (NIHSS) (18, 19), the Fugl-Meyer Motor Assessment (20), and the modified Rankin Scale (mRS) (21).

Differences Between Development and Validation Studies

Key characteristics of the development study (3) and the two validation studies are presented in **Table 1**.

Sample Size

This is a secondary data analysis and, therefore, no sample size calculation was performed.

Statistical Analysis

Patients who died before the day-90 visit were excluded from the analysis. Baseline characteristics of the included patients were analyzed by nonparametric descriptive statistics. The EPOS model for independent gait was developed for making a prediction at days 2, 5, and 9 post-stroke (3). The model for day 2 was validated using the data from visit 1 and the model at day 9 was validated with the data from visit 2. As none of the studies had a measurement time point nearing day 5 post-stroke, the model at day 5 was not externally validated.

Differences between patients with and without missing data on predictors and/or outcome were formally tested with the Mann–Whitney *U*-test or chi-squared test. Missing data on predictors and outcomes were imputed by the R package

'Multivariate Imputation by Chained Equations' (mice) with 100 imputations and 5 iterations (22). Data used for imputation included the raw values of the TCT-s at visits 1 and 2, MI-LE at visits 1 and 2, FAC at visit 3, the NIHSS total score at visit 1, age, gender (women/men), affected side (left/right), and the NIHSS items consciousness and hemianopia at visit 1 (23). After imputation, patients without an outcome were excluded (24, 25). The imputed data were used for the primary analysis. In addition, the analysis with raw data was presented.

The following equations were used to describe the probabilities of achieving independent gait 3 months post-stroke:

$$\text{Day } 2: P = 1/1 + \left(exp^{[-(-0.982 + 2.691\ ^{*}\text{TCT-s} + 2.083\ ^{*}\text{MI-LE})]}\right)$$
$$(\text{presence} = 1, \text{absence} = 0)$$

$$\text{Day } 9: P = 1/1 + \left(exp^{[-(-2.226 + 3.629\ ^{*}\text{TCT-s} + 1.854\ ^{*}\text{MI-LE})]}\right)$$
$$(\text{presence} = 1, \text{absence} = 0)$$

Discrimination of the EPOS model was determined based on the area under the receiver operating characteristic (ROC) curve (AUC) with its 95% confidence interval (CI), with an AUC of >0.75 reflecting a clinically useful model (26). The classification was assessed by the sensitivity, specificity, and positive and negative predictive values. Calibration plots visualized the agreement between predicted and observed probabilities. RStudio version 3.6.3 was used for all analyses (27) and a value of $P < 0.05$ was considered to be statistically significant.

RESULTS

In total, 39 non-ambulatory patients were analyzed in Cohort I and 78 in Cohort II (**Figure 1**). Patients in Cohort I had a median (Q1–Q3) age of 74 (69–77) years, 13 (33.3%) were women, 13 (33.3%) had suffered a left hemispheric stroke, and the baseline NIHSS amounted to 9 (5.5–13.5). Patients included in Cohort II had a median (Q1–Q3) age of 69 (60–77) years, 29 (37.2%) were women, 60 (76.9%) had an ischemic stroke, 37 (47.4%) had a lesion in the left hemisphere, and the median baseline NIHSS was 8 (5–12). Visit 1 took place on day 1 post-stroke in Cohort I and on day 3 in Cohort II. The second visit in Cohorts I and II was performed on days 8 and 9, respectively. In Cohort I, 17 (43.6%) patients had a TCT-s of 25/25, and 28 (71.8%) patients

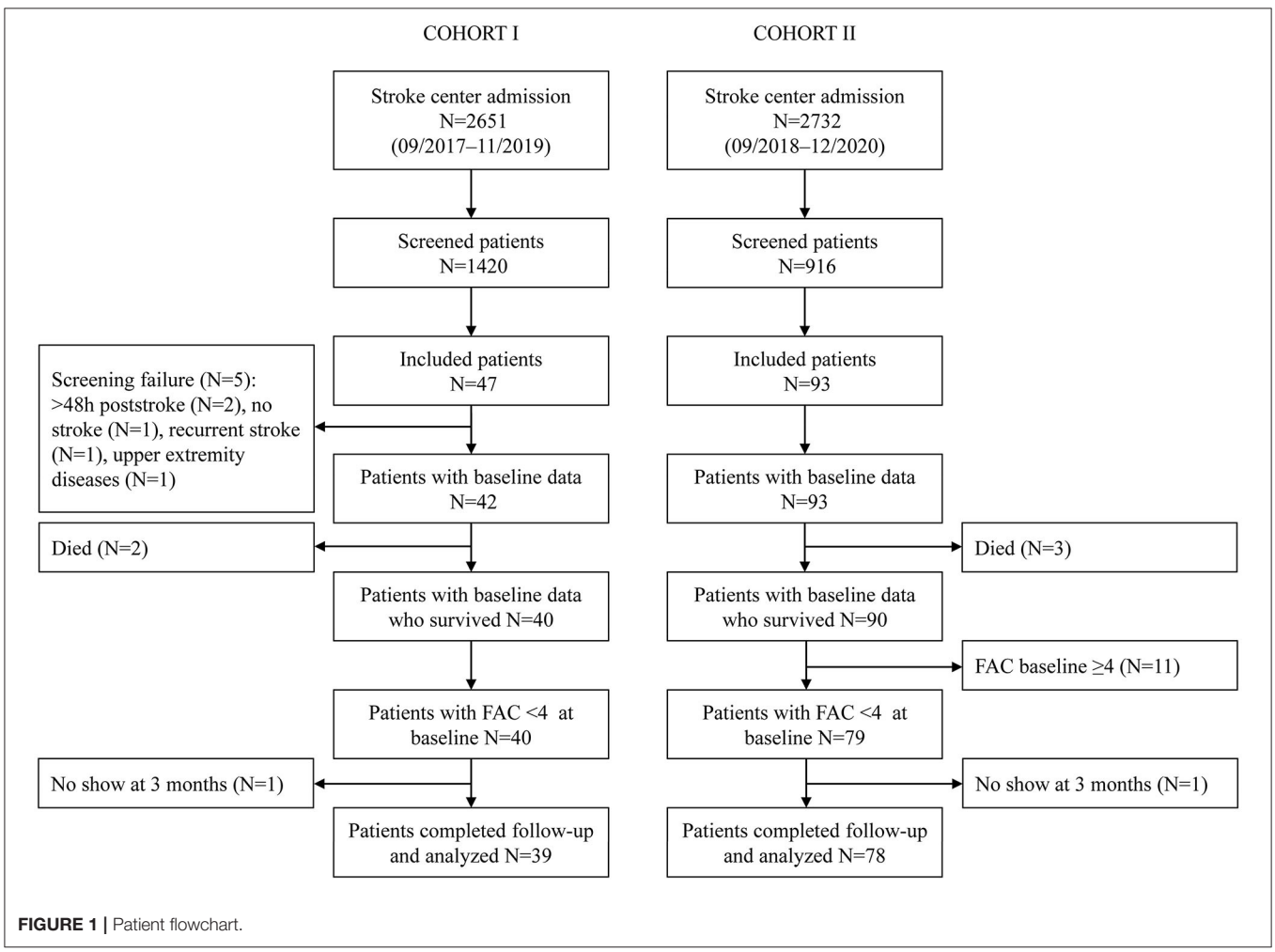

FIGURE 1 | Patient flowchart.

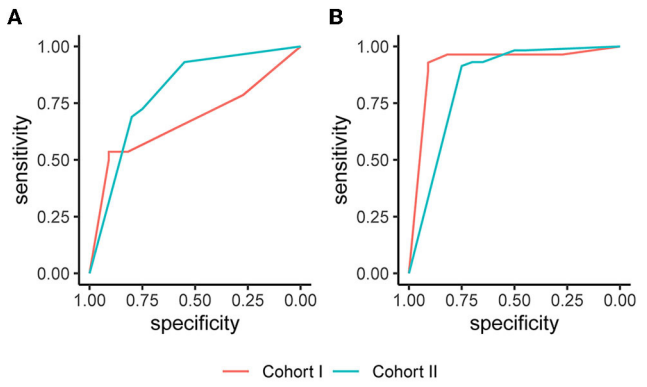

FIGURE 2 | Receiver operating characteristic (ROC) curves based on the imputed datasets. **(A)** The Early Prediction of Functional Outcome after Stroke (EPOS) model for day 2, measured on day 1 in Cohort I and on day 3 in Cohort II; **(B)** The EPOS model for day 9, measured on day 8 in Cohort I and day 9 in Cohort II.

had an MI-LE score of ≥25/100 at visit 1. In Cohort II, 47 (60.3%) had a TCT-s of 25/25, and 60 (76.9%) an MI-LE score of ≥25/100 at visit 1. In validation of Cohorts I and II, 71.8 and 74.4% of the patients were able to walk independently at 3 months post-stroke, respectively. The patient characteristics of the validation cohorts are described in more detail in **Supplementary Table 1** and can be compared with the development cohort that is described in the same table. Early changes in the walking ability are described in **Supplementary Tables 2**, **3** for Cohorts I and II, respectively. At the second study visit, 10 patients in Cohort I and 22 patients in Cohort II walked independently.

In both validation cohorts, full data on FAC outcomes were available in the analyzed samples. In Cohort I, the following data on predictors were missing: MI-LE visit 1 ($N = 1$), TCT-s visit 1 ($N = 2$), and MI-LE visit 2 ($N = 3$). For Cohort II, there were missing data for visit 2 for both the TCT-s and MI-LE ($N = 4$ each). Patients with missing data did not significantly differ from those without missing data (**Supplementary Table 4**).

In Cohort I, analysis of the imputed data resulted in an AUC (95% CI) of 0.675 (0.510, 0.841) on day 1 and 0.921 (0.811, 1.000) on day 8. In Cohort II, the AUC (95% CI) amounted to 0.801 (0.684, 0.918) on day 3 and 0.846 (0.741, 0.951) on day 9. The corresponding ROC curves are displayed in **Figure 2**. The sensitivity in Cohort I increased from 0.786 on day 1 to 0.964 on day 8, and the specificity improved from 0.273 on day 1 to 0.727 on day 8. In Cohort II, the sensitivity was 0.931 on days 3 and 9, and the specificity values were 0.550 on day 3 and 0.650 at day 9. Full information on the discrimination and classification measures of the EPOS model in the two independent cohorts are reported in **Table 2**.

The agreement between predicted and observed probabilities is presented in the calibration plots of **Figure 3**. For patients in Cohort I who had a low probability of regaining independent gait as predicted by the EPOS model on day 1, the predicted probability was lower than the observed probability (**Figure 3A**). On day 8, the difference between predicted and observed probabilities for patients with a low predicted probability was no longer significant (**Figure 3B**). For patients with a higher predicted probability of regaining independent gait, the observed probabilities matched the predicted probabilities on both days (**Figures 3A,B**). In Cohort II, the predicted and observed probabilities did not significantly differ for both days 3 and 9 (**Figures 3C,D**).

The results of the analysis based on the raw data are reported in **Supplementary Table 3** and **Supplementary Figure 1** and did not show differences.

TABLE 2 | Discrimination of the Early Prediction of Functional Outcome after Stroke (EPOS) model for independent gait in the development and validation cohorts based on imputed datasets.

	Development cohort (3)	Validation cohort I	Validation cohort II
Model day 2	$N = 154$	$N = 39$	$N = 78$
Accuracy (95% CI)	0.889	0.641	0.833
Sensitivity	0.926	0.786	0.931
Specificity	0.750	0.273	0.550
Positive predictive value	0.933	0.733	0.857
Negative predictive value	0.727	0.333	0.733
No information rate	N/R	0.718	0.744
P-Value (Acc > NIR)	N/R	0.892	0.041
AUC (95% CI)	N/R	0.675	0.801
		(0.510, 0.841)	(0.684, 0.918)
Model day 9	$N = 154$	$N = 39$	$N = 78$
Accuracy (95% CI)	0.916	0.897	0.859
Sensitivity	0.959	0.964	0.931
Specificity	0.750	0.727	0.650
Positive predictive value	0.936	0.900	0.885
Negative predictive value	0.828	0.889	0.765
No information rate	N/R	0.718	0.744
P-Value (Acc > NIR)	N/R	0.007	0.010
AUC (95% CI)	N/R	0.921	0.846
		(0.811, 1.000)	(0.741, 0.951)

Acc, accuracy; AUC, area under the curve; CI, confidence interval; N/R, not reported; NIR, no information rate.

DISCUSSION

This is the first external validation of the EPOS model for predicting independent gait after stroke, marking an essential step toward clinical implementation. An important difference with the original study is that the endpoint was assessed 3 months after symptom onset instead of 6 months. Even though the timing of the endpoint was earlier, the temporal and geographical external validation showed an adequate performance on days 3, 8, and 9, but not on day 1 post-stroke. The discriminative ability of the EPOS model on day 3 was good and further increased when predictors were retested on day 8 or 9. In analogy to this, the positive predictive and negative predictive values were high on days 3, 8, and 9, with the positive predictive value slightly outperforming the negative predictive value at both time points. The agreement between predicted and observed

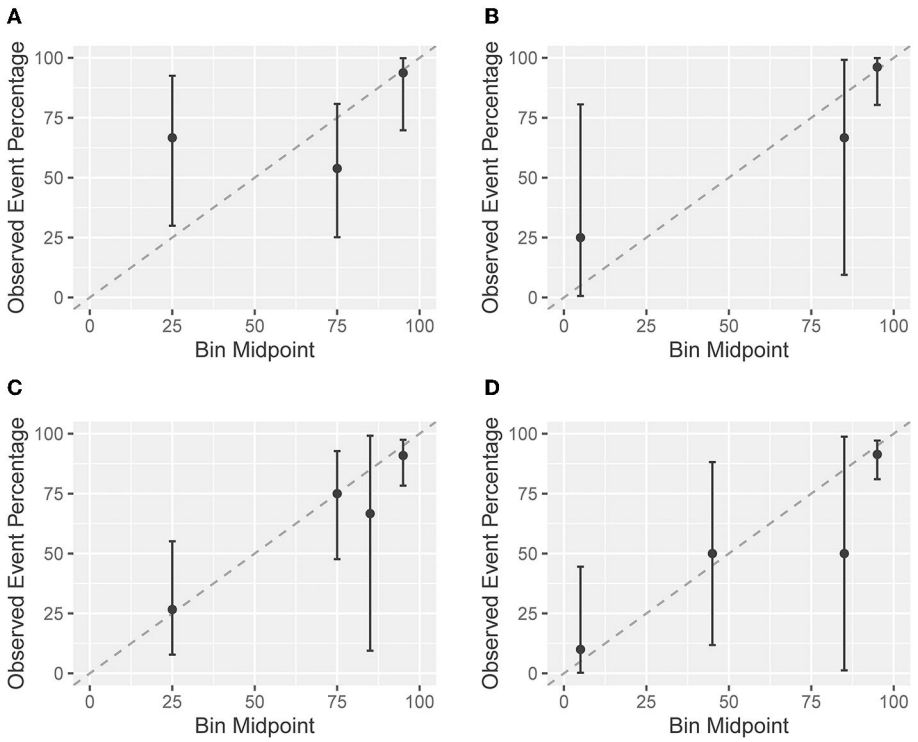

FIGURE 3 | Calibration plots based on the imputed datasets. A calibration plot shows the agreement between the predicted probabilities based on the Early Prediction of Functional Outcome after Stroke (EPOS) model for independent gait on the *x*-axis and the in the observed probabilities of validation cohorts on the *y*-axis. The closer the points are to the plotted diagonal line, the better the calibration. Points above the diagonal line indicate that the model is rather pessimistic, points below the line indicate that the model is rather optimistic. Confidence intervals (CIs) overlapping with the diagonal 45 degree line indicate no significant difference between predicted and observed probabilities. Cohort I: **(A)** the EPOS model for day 2, measured on day 1 post-stroke; and **(B)** the EPOS model for day 9, measured on day 8 post-stroke. Cohort II: **(C)** the EPOS model for day 2, measured on day 3 post-stroke; and **(D)** the EPOS model for day 9, measured on day 9 post-stroke.

probabilities was good, although CIs were relatively wide, except for patients with a low predicted probability on day 1. For these patients, the observed probability was significantly higher than the predicted probability.

The performance of the EPOS model for independent gait from day 3 onward matches the performance that was found in the development study, even though the endpoint in the validation cohorts was 3 months instead of the 6-month endpoint that was applied in the development study. Furthermore, the validation cohorts had a different case-mix and were recruited in another country with a different healthcare system (Switzerland vs. the Netherlands). With that, this external validation study shows that the EPOS model can be applied to predict outcomes at 3 months after stroke. This finding supports the assumption described in the introduction that, when patients regain independent gait after stroke, they do so within the first 3 months after stroke, and there are hardly any patients who shift from 'dependent gait' to 'independent gait' between 3 and 6 months. This matches the earlier finding of Baer and Smith, that patients with stroke achieve independent gait at a mean [standard deviation (SD)] of 16.0 (29.7) days (28). Our data furthermore showed that a proportion of patients shift from 'dependent' to 'independent' within a week after the first assessment of predictors: 27% of the patients in Cohort I and 30% in Cohort II achieved a FAC of $\geq$4/5 at the second study visit. Although in all cohorts patients with first-ever stroke who were independent before their stroke were included, there are differences between the development and validation cohorts, such as the lower proportion of women included in the validation cohorts, a higher median age in Cohort I, the inclusion of patients with hemorrhagic stroke in Cohort II, and the prevalence of thrombectomy as an acute medical treatment in both validation cohorts. This supports the generalizability of the EPOS model to a wider stroke population than that included in the development study. Additionally, this study highlights that an application of the EPOS model on day 1 post-stroke seems to be invalid as the low specificity and low negative predictive value indicate that the model is too pessimistic at this early time point. This could be explained by the dynamics of neurological functions in the (hyper)acute phase in which a portion of the patients show a quick neurological recovery (29), or masking of the patient's ability by, e.g., vertigo, hypotension, or fatigue. It could also be attributable to the fact that patients were not or not often mobilized before the TCT-s was performed, and thus, the test score represents one of their first attempts to sit at the edge of the bed.

This first external validation of the EPOS model for independent gait is promising, and although the model can be applied to a defined subgroup of patients with stroke, there are steps that need to be taken before the model is ready for a

large-scale implementation. Validation studies are needed that preferably recruit a large and heterogeneous group of patients at different sites, such as those with recurrent strokes, other neurological diseases, and more comorbidities. These studies should not only be performed in western European countries but also in geographical regions with different healthcare systems. On a smaller scale, both the impact and the implementation of applying the EPOS model in clinical practice should be investigated. Although it is assumed that the application of prediction models has several benefits for the healthcare system, including increased efficiency through stratified medicine, it remains unknown how the application of the EPOS model affects these aspects. No impact studies are available for the recovery of gait after stroke. However, an impact study of the Predict REcovery Potential (PREP2) model for upper limb outcome post-stroke showed increased efficiency in terms of a reduced length of stay, a change in therapy content, as well as higher therapist confidence (30). Implementation of prediction models in clinical practice is challenging, as it requires a behavioral change of the treating therapists. Similarly, with outcome assessments (31), there are two stages that can be identified. First, the predictors have to be assessed and next, the information regarding the expected outcome has to be used in the rehabilitation of a patient (32). Studies on implementing prediction models in stroke are scarce. A study investigated the implementation of the PREP2 model and critical factors were the staff's level of knowledge regarding the model, their beliefs and self-efficacy, and the perceived benefits of applying the model (33). Predictors are most often assessed with standardized outcome measures, and from implementation research on stroke assessments (34), it is known that the willingness and ability to change are additionally hampered by the lack of familiarity with the assessments (31, 34), having difficulty with changing routines (34), time and equipment needed to perform assessments (31, 34), and the lack of support from the management staff or team members (31). Whether the assessment is performed is highly dependent on the inability of a patient to participate in the testing due to, for example, communication or cognitive deficits (31, 35). Based on the available implementation literature, an approach to implement the EPOS model for independent gait would be initiated by therapists themselves, having support from the management staff, having a close collaboration between researchers who developed the model and clinicians, providing ongoing education and 'teaching on the job,' and having directions on important treatment foci (33).

Apart from continuing with the external validation of the EPOS model for independent gait in a more heterogeneous sample of patients and across different geographical regions and investigating the model's impact, an extension of the model applying a more fine-grained classification of FAC scores below 4 is needed. Even though a score below 4 means that the patient is not able to walk independently, the scores 0–3 cover a wide spectrum of walking abilities, ranging from 0 (i.e., not able to walk) to 3 (i.e., walking under supervision). Reaching a FAC of 2 (i.e., walking with intermittent or continuous light physical support for balance and/or coordination) or 3 could be highly valuable for patients and their caregivers and being able to make a more fine-grained prognosis with the following levels, (a) not regaining gait, (b) regaining gait with light physical support or supervision, and (c) regaining independent gait, would support clinicians in evidence-based goal setting and rehabilitation design.

Limitations of the current study includes a relatively low number of patients in the validation cohorts who were recruited in one center. Furthermore, there was a difference in the measurement time points of the predictors of the two validation cohorts that did not allow us to investigate the performance of a model on day 5. The inclusion of patients with first-ever stroke without large preexisting disability (mRS $\leq$2) hampers the generalizability of patients with recurrent strokes and those who were more disabled prior to their stroke. However, the only prestroke disability category missing is the mRS score of 3, as patients with a score of 4 or 5 cannot walk independently, and it is unlikely that they will regain this independence after stroke. Furthermore, patients in Cohort I were included earlier post-stroke than in the development cohort and one would assume that a large number of patients are unable to walk independently at this early time point after stroke. However, the inspection of the FAC scores at visit 2 showed that none of the patients had a score of 4 or 5. Last, we did not perform an update of the model, but this can be justified by the acceptable performance in the independent cohorts as well as the fact that the size of our cohorts would have resulted in an overfitted model (36).

CONCLUSION

The external validation of the EPOS model for the outcome of independent gait 3 months after stroke was successful when sitting balance and strength of the paretic leg were assessed from day 3 onwards. With that, the model is generalizable to patients who had a first-ever ischemic or hemorrhagic stroke and were independent prior to their stroke. To increase the applicability of the EPOS model to a wider patient population, future multicenter validation studies should recruit a larger and more heterogeneous sample of patients, including those with recurrent strokes, neurological diseases, and higher levels of comorbidity. In addition, these validation studies should be performed in different geographical areas to extend the geographical validity of the EPOS model for independent gait.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee Zurich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JV and JH conceptualized and designed the study. JV, JP, and JH acquired data and interpreted the data. JV performed the analysis and drafted the manuscript. JP, JH, and AL revised the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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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.2022.797791/full#supplementary-material

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Evaluating the Abnormality of Bilateral Motor Cortex Activity in Subacute Stroke Patients Executing a Unimanual Motor Task With Increasing Demand on Precision

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Abnormal contralesional M1 activity is consistently reported in patients with compromised upper limb and hand function after stroke. The underlying mechanisms and functional implications of this activity are not clear, which hampers the development of treatment strategies targeting this brain area. The goal of the present study was to determine the extent to which contralesional M1 activity can be explained by the demand of a motor task, given recent evidence for increasing ipsilateral M1 activity with increasing demand in healthy age-matched controls. We hypothesized that higher activity in contralesional M1 is related to greater demand on precision in a hand motor task. fMRI data were collected from 19 patients with ischemic stroke affecting hand function in the subacute recovery phase and 31 healthy, right-handed, age-matched controls. The hand motor task was designed to parametrically modulate the demand on movement precision. Electromyography data confirmed strictly unilateral task performance by all participants. Patients showed significant impairment relative to controls in their ability to perform the task in the fMRI scanner. However, patients and controls responded similarly to an increase in demand for precision, with better performance for larger targets and poorer performance for smaller targets. Patients did not show evidence of elevated ipsilesional or contralesional M1 blood oxygenation level-dependent (BOLD) activation relative to healthy controls and mean BOLD activation levels were not elevated for patients with poorer performance relative to patients with better task performance. While both patients and healthy controls showed demand-dependent increases in BOLD activation in both ipsilesional/contralateral and contralesional/ipsilateral hemispheres, patients with stroke were less likely to show evidence of a linear relationship between the demand on precision and BOLD activation in contralesional M1 than healthy controls. Taken together, the findings suggest that task demand affects the BOLD response in contralesional M1 in patients with stroke, though perhaps less strongly than in

healthy controls. This has implications for the interpretation of reported abnormal bilateral M1 activation in patients with stroke because in addition to contralesional M1 reorganization processes it could be partially related to a response to the relatively higher demand of a motor task when completed by patients rather than by healthy controls.

Keywords: fMRI, stroke, motor cortex, hand function, motor recovery-cerebral infarct

INTRODUCTION

Persistent compromised hand function is recognized as one of the most common long-term deficits after stroke (1). It is well known from non–human primate studies that normal hand function relies on the integrity of the corticospinal tract (CST) that directly connects primary motor cortex (M1) neurons to spinal alpha motoneurons (2–5) and that hand function recovery after stroke relies on the anatomo-functional reorganization of viable neuronal tissue in M1 of the lesioned hemisphere (6). What is less understood is the role of the M1 of the hemisphere not injured by stroke (contralesional M1) in supporting skilled hand function. In early task-based imaging studies of patients with stroke, bilateral activation of motor areas, including the primary motor cortex (M1), has been reported when moving the affected hand (7–13). Because this was not seen in healthy controls and there was a shift toward a more normal unilateral activation pattern of ipsilesional motor areas accompanying an improvement in patient performance during the post-stroke recovery process, bilateral activation was reported as abnormal compared to healthy controls (7–13). Following up on these early findings, subsequent task-based fMRI studies demonstrated that the persistence of the bilateral activation pattern was associated with poorer motor function and recovery after stroke (14–17). This has prompted rehabilitation treatment approaches that target contralesional M1 using non–invasive neuromodulation (18).

However, the role of contralesional M1 in supporting upper limb and hand function is not clear and some seemingly contradictory results were reported with respect to neuromodulation treatment approaches targeting contralesional M1. Contralesional M1 activity appears to interfere in at least a subset of patients (19–21). In these patients, decreasing contralesional M1 excitability by cortical stimulation results in improved performance of the paretic limb (21–23). However, other reports indicate that contralesional M1 activity supports upper limb and hand function (13, 24–29) and decreasing contralesional M1 activity may result in deterioration of paretic limb performance (28, 29). There is evidence derived from rodent stroke models that reorganizational changes in contralesional M1 occur that include long-term changes in neurotransmitter systems, dendritic growth, and synapse formation (30–36). Inhibiting the contralesional hemisphere generates more behavioral deficits in the impaired forelimb in comparison to control animals, indicating that these reorganized neuronal circuits support the function of the forelimb (37).

More recent evidence of ipsilateral M1 activity in healthy subjects when executing tasks of increasing complexity or demand on precision (38–42) raises the question of whether, in addition to reported stroke-related contralesional M1 reorganization processes in pre-clinical studies (36, 43, 44), contralesional M1 activity during motor performance post-stroke could also be partially explained by task demand (13, 45). In previous imaging studies, only simple motor tasks such as hand grip or wrist movements were tested, so patients with more impaired hand function may have activated bilateral M1 in response to increased task demand compared to patients with only mild to moderate impairment. Further, in several imaging studies, mirror movements of the non-affected hand during movements of the affected hand (18) were reported. These data raise the possibility that contralesional M1 activity is partially related to mirror movements of the non-affected hand (46). As mirror movements and co-activation of the non-affected hand occur more frequently in patients with greater impairment of upper extremity function (46, 47), the presence of these movements could distort the interpretation of persistent bilateral M1 activation. Taken together, there are remaining questions about reported abnormal contralesional M1 activity in patients with compromised upper limb and hand function after stroke, which hampers the development of treatment strategies targeting this brain area.

In the present study of subacute patients with stroke, our aim was to determine the extent to which contralesional M1 activity is related to the demand on precison of a motor task and whether this activity differs between patients and healthy age-matched controls. A strong demand-dependent increase in contralesional M1 would suggest that some of the reported findings on increased contralesional M1 activity in patients with stroke could be explained by the relatively higher demand for executing a task with the impaired limb rather than reorganizational changes. We hypothesized that patients with stroke would exhibit higher activity in contralesional M1 than healthy controls and that contralesional M1 activation would depend on the demand for precision in a hand motor task.

MATERIALS AND METHODS

Study Design

We conducted a prospective longitudinal study of patients with stroke to study motor recovery. Measures of brain structure and function, as well as hand motor function, were obtained at two-time points, in the subacute (1-month post-stroke) and the chronic stroke recovery period (6 months). In the present paper, we report the results of fMRI of the brain during a hand motor task obtained in patients with stroke during the subacute recovery period and in healthy right-handed, age-matched controls. This experiment was designed for a subset

of patients with stroke with sufficient dexterity of affected hand function to execute a skilled hand motor task to determine the extent to which contralesional M1 activity is related to the demand on the precision of a hand motor task and whether it differs from a healthy age-matched control population.

Participants

All patients with stroke referred to centers of the NIH StrokeNet of all genders, all races, and ethnicity aged 40–80 years were considered for inclusion in the main study provided they met the following inclusion criteria (1): Single lesion cerebral ischemic infarction < 1 month affecting the M1 output system of the hand (M1 or CST) at a cortical or subcortical level as defined by MRI of the brain (2), paresis of the upper extremity (as assessed by NIHSS at admission or chart review) (3), no other neurological disorders (4), no aphasia that prevented participants from following instructions or from communicating effectively with the study team, (5) no dementia (see below for details) (6), no or only mild depression [Hamilton Depression score of ≤13 (48)] (7) no contraindication to transcranial magnetic stimulation or MRI (8), no intake of CNS active drugs that block plasticity (for example benzodiazepines) (9), the ability to give informed consent. For participation in the fMRI study, patients had to meet additional inclusion criteria with respect to their level of affected hand function. Participants had to be able to manipulate a joystick with the affected hand with sufficient precision to achieve a minimum accuracy standard on the hand motor task (see below for details). Hand function was assessed using the Jebsen Hand Function Test (JHFT), a standardized test of hand function (49). The raw score was normalized to age- and sex-matched standard scores that accounted for hand dominance (49, 50). A normalized score greater than zero indicated abnormal hand function, with higher values indicating more severe impairment.

Healthy control participants fulfilled the same criteria for participation in the present study (age between 40 and 80 years; no neurological or psychiatric disorders; no current usage of central nervous system active drugs; no contraindication for MRI; normal cognitive function as evaluated by the RBANS) except for the criteria pertaining to the stroke, as all had normal neurological examinations and normal brains as evaluated by MRI. In addition, all control participants were strongly right-handed as confirmed by the Edinburgh Handedness Inventory (51).

All procedures involving human participants were approved by the Institutional Review Board at Emory University. Procedures followed were in accordance with the ethical standards of the Institutional Research Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent and were blinded to the stated hypothesis of the experiments.

MRI Acquisition

Structural and functional MRI scans of all participants were collected on a Siemens Prisma 3T MRI system with a 64-channel head coil. T1-weighted structural scans were collected according to the HCP Lifespan Project (52, 53) MPRAGE protocol: TR = 2,400 ms, TE = 2.24 ms, flip angle = 8 degrees, FOV = 256 x 240 x 208 mm, voxel size 0.8 mm^3. In a separate scanning session, task-based functional MRI runs were collected with the following protocol: TR = 2,000 ms, TE = 28 ms, flip angle = 90 degrees, FOV = 192 x 192 x 102 mm, voxel size = 3 mm^3, 163 volumes per run. Patients with stroke completed four task runs (total duration 22 min) using the affected hand only, while healthy controls were able to tolerate a longer scanning session without fatigue and completed eight task runs, four with the dominant right and four with the non–dominant left hand (total duration 44 min). These scan parameters were also used to acquire data from a separate motor localizer task to independently define the M1 region of interest (ROI) used in all analyses. Participants repeatedly opened and closed either their right or left hand at approximately 1 Hz in response to a visual cue. Twenty movement blocks of 10 s (10 per hand) alternated with 10 resting blocks of 10 s (165 functional volumes, total duration 5 min and 30 s). An arrow or rest cue on the visual display specified which hand was to perform the action in each block.

fMRI Hand Motor Task

The hand motor task used during fMRI data collection allows for parametric manipulation of the demand on the precision of a hand movement by requiring participants to use a joystick to move a cursor into targets of varying sizes (13, 40, 41, 54) (**Figures 1A,B**). The use of the term 'demand' refers to the demand on movement precision. Stimuli were projected onto a screen that was viewed *via* a mirror mounted onto the head coil using Presentation® software (www.neurobs.com). With the participant in a supine position on the scanner bed, the base of the joystick base was strapped to the torso of the participant with Velcro straps (**Figure 1C**). It was positioned in such a way that the participant could rest the wrist on the base of the joystick comfortably and could manipulate the joystick without moving the distal or proximal arm. Foam pads supported the arm so that participants did not have to use muscular effort to actively maintain the position of the arm or the hand on the base of the joystick. Movement epochs (16 s x 12) alternated with resting epochs (9 s x 11). Trials were blocked by target size, with four trials per movement epoch. Each target size block was presented three times per run. The order of target size blocks was randomized within each run. Patients with stroke completed four runs with the affected hand. Healthy control participants completed four runs with one hand (right or left) and then four runs with the other hand, in a counterbalanced order across participants. A trial was counted as an accurate "hit" if the midpoint of the cursor was within the boundaries of the target square at the end of the 2 s trial. Movement time was defined as the time between the onset of the target and the time at which the cursor reached and remained within the target square.

At least one day prior to scanning, participants completed a training session to familiarize themselves with the pointing task, ensure that patients had enough hand function to perform the task at a minimum level of accuracy, and minimize learning effects during the fMRI experiment. This training procedure was used to account for the differences in the

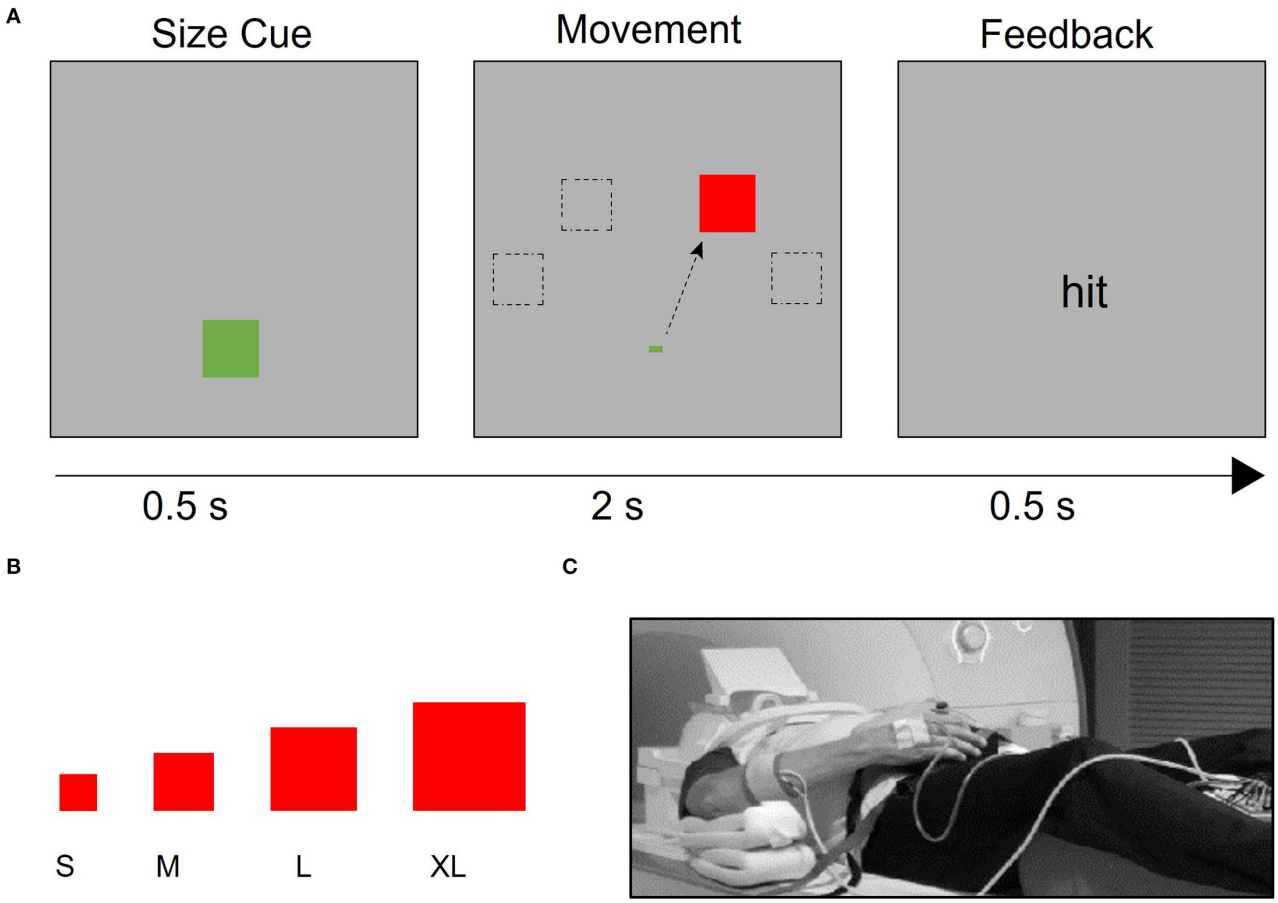

FIGURE 1 | Task design. **(A)** After a target size cue, the target appears in one of four possible locations (−60°, −30°, 30°, and 60° relative to the vertical meridian). Participants were instructed to use the joystick to move the cursor to the target as quickly and accurately as possible. If the cursor began at the starting point and was inside the target 2 s after the target presentation, participants received "hit" feedback; otherwise, they received "miss" feedback. **(B)** Four different target sizes were used to vary the demand on precision, **(C)** Participants used an MRI-compatible joystick to perform the task. The joystick was secured to their body with straps and pads were placed to support the arm and minimize elbow and shoulder movement. EMG electrodes were placed on participants' right- and left- extensor carpi ulnaris (ECU) muscles, which support the manipulation of the joystick.

level of baseline performance across participants (54). Control participants performed up to three training runs of three blocks each (seven trials of the same target size per block) with both their right and left hands. Participants completed fewer than three training runs if they had > 50% accuracy on the smallest target size at the end of a run or had improved to >50% accuracy on the next largest target size that was below 50% accuracy after the first run. Patients with stroke performed the task with the affected hand and were required to achieve a minimum accuracy of 50% on the largest target size to participate in the fMRI scanning session.

EMG Recording and Data Analysis

The objective of the EMG analysis was to determine whether the task in the scanner was done strictly unimanually (13, 40, 41). Continuous EMG was recorded with the BrainAmp MR plus system (Brain Vision, LLC, Morrisville, NC, USA) from both extensor carpi ulnaris (ECU) muscles in the scanner, using MRI-compatible surface electrodes (Brain Vision, LLC, Morrisville, NC) placed 2 cm apart in a belly tendon montage. The ECU muscle was recorded because manipulating the joystick involved extensions and flexions of the hand (40, 41). EMG signals were band-pass filtered (5 Hz−1 kHz), amplified, digitized, sampled at a 5,000 Hz frequency, and stored for offline analysis. EMG data for the non–performing hand were first corrected for MR artifacts in BrainVision Analyzer 2 (version 2.1.2, Brain Products GmbH, Gilching, Germany) using the artifact subtraction method (55) with template drift detection and a sliding average calculation of 11 TR intervals (22 s). Next, data were downsampled to 1,000 Hz, baseline-corrected, rectified, and segmented into the task (16 s) and rest (9 s) blocks. Following Barany et al. (41), mean EMG activity for the non–performing hand was compared for task and rest blocks. EMG activity of the performing hand was not quantified due to the additional MR artifacts induced by large movements. The absence of task-related changes in the non-performing hand activity was assumed

when the mean EMG amplitude of the ECU muscle of the non-performing hand during movement blocks was similar to that in resting blocks (13, 40, 41). For healthy control participants, a repeated-measures ANOVA with task period (movement/rest) and non-performing hand (right/left) as factors were used to determine whether performing hand activity (i.e., during the task period or during the rest period) was related to changes in mean EMG amplitude of the non-performing hand. As the patients with stroke only performed the task with the affected hand, a paired *t-test* was used to evaluate whether EMG activity for the non-performing hand differed between the active and rest blocks.

MRI Data Analysis

All processing of the fMRI data used Analysis of Functional NeuroImages [AFNI; (56)]. fMRI preprocessing steps included slice time correction, head motion correction, 12-parameter affine alignment between the structural and functional images, and non-linear warping between the structural image and the MNI152 2009 template in MNI space, smoothing with an FWHM 6 mm smoothing kernel, and conversion to percent signal change. As the brains of individuals with stroke are more difficult to normalize, we used enantiomorphic normalization (57) to transform the patient brains, with the transformation from non-linear warping of the "healed" structural image applied to the original lesioned brain image. The transformations for head motion correction, coregistration, and normalization were concatenated and applied in a single step to the functional data before smoothing to reduce the number of interpolation steps. Following preprocessing, a general linear model (GLM) analysis was performed using AFNI's 3d Deconvolve tool. Separate regressors were created for each combination of target size and hand, with block time (16 s) convolved with the GAM function. In addition to these task regressors, six head movement vectors were included as regressors of no interest. Volumes with more than 0.9 mm total head movement were censored.

Hand motor localizer task data were analyzed separately, with regressors for blocks of right- and left-hand movement. For each participant, functional ROIs were created by selecting a threshold (mean ± SD; $t = 10.5 \pm 4.2$) at which a cluster of 50 contiguous voxels centered in anatomical M1 could be found for the comparisons of left hand > rest and right hand > rest. For patients with stroke, any voxels intersecting the lesion mask of the individual were subtracted from the ROI. Due to the contiguity requirement, clusters with exactly 50 voxels could not be found for 19 of the 100 ROIs, so the cluster size closest to 50 voxels was used (mean ± SD cluster size: 50.2 ± 1.9 voxels). These ROIs were then used to extract beta values for each combination of target size and hand for the fMRI joystick pointing task. A representative sample ROI for one participant is shown in **Figure 2A**. As seen in **Figure 2B**, ROI location varied from participant to participant but was densely clustered over the posterior aspect of the precentral gyrus including the hand knob and the central sulcus. For three patients with stroke, the hand localizer task did not generate reliable clusters of 50 voxels that rose above the level of general noise in one or both hemispheres. For these three patients, we substituted a 50-voxel ROI generated from a group-level analysis of the healthy control participants' hand localizer data, with any intersections with the lesion mask subtracted out. The results reported below do not differ if the data from these three participants are excluded.

Statistical Analysis

In our previous work (40, 41), we have used repeated-measures ANOVAs to look for group-level effects of target size on brain activity or on certain aspects of behavioral performance like accuracy or movement time. However, this approach only indicates that target sizes are responded to differently but does not require activation changes to be ordered or linear and fails to capture individual differences in how target size may affect behavioral performance or brain activation. Thus, we additionally find a best-fitting line for the four target size data points (for either task accuracy or BOLD activation) for each participant and take the slope of that line as a measure of the demand on the precision of the motor task, henceforth the *demand function* for each participant; essentially, a measure of how much the behavior of an individual or brain activation changes linearly as the demand on movement precision increases.

RESULTS

Participants

In total, 19 patients (12 F, mean age ± SD: 59.4 ± 9.9, range 40–76) and 31 healthy, right-handed, age-matched controls (17 F, age: 61.7 ± 9, range 50–78) participated in the study. The mean age of the two groups did not differ [$t(48) = 0.84$, $p = 0.4$]. Data from a subset of the healthy controls were reported in a previous paper (41). Demographic information, including neuropsychological testing and stroke-specific information, is summarized in **Table 1**. A lesion overlap mask for the 19 patients with stroke is in **Figure 2C**. Half of the patients had a dominant affected hand, and five patients were left-handed (see **Table 1** for details). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (58) was used to screen for cognitive impairment. Any patient scoring 2 SD below the mean (Total Index Score < 70) was clinically assessed for impairment that would indicate dementia and to determine whether they had the cognitive ability to consent and follow task instructions. Except for two patients with stroke, total index scores of all participants were above 70 (see **Table 1**). Two patients with stroke scored below 70 but had no clinical signs of dementia. As a group, the healthy control participants had significantly higher RBANS scores than the patient group [$t(48) = 3.23$, $p < 0.01$].

Hand Motor Task Behavior

As a group, the patients with stroke showed significant impairment on the pointing task relative to the healthy control participants (**Figures 3A,B**). A mixed-model ANOVA with target size as a within-subject factor and group (stroke: affected hand / control: non–dominant hand) as a between-subject factor revealed significant main effects of group [$F(1, 48) = 10.22$, $p = 0.002$] and target size [$F(2.47, 118.33) = 72.54$, $p < 0.001$] on accuracy, but no interaction of group and target size [$F(2.47, 118.33) = 0.31$, $p > 0.2$]. Patients with poorer hand function (as measured by the JHFT) tended to have lower overall task

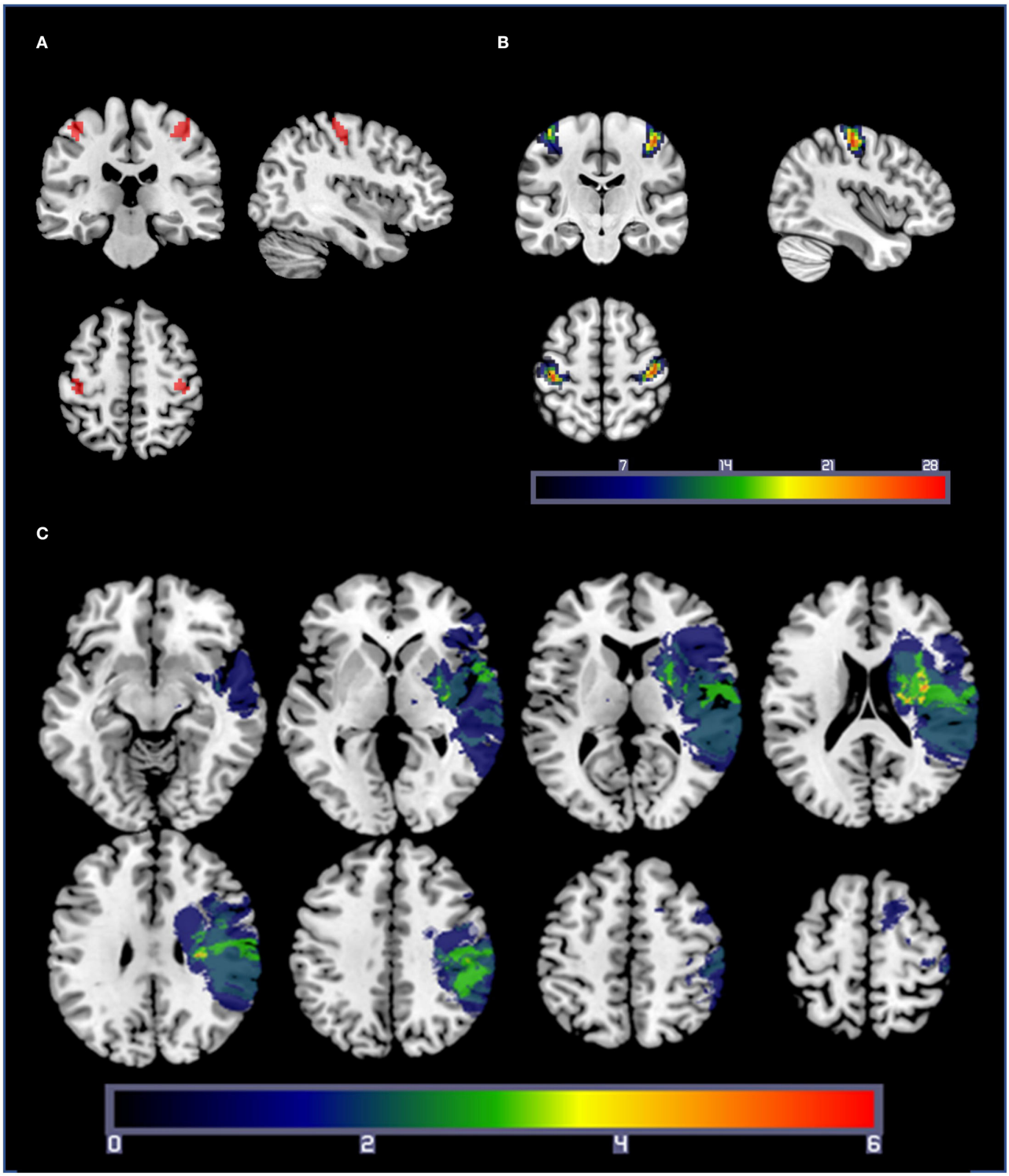

FIGURE 2 | (A) A representative set of M1 ROIs from a healthy control participant, based on the comparisons of right-hand movement > rest and left-hand movement > rest from the hand localizer scan. Statistical thresholds were set on an individual basis to identify a cluster of 50 contiguous voxels centered in M1 for each participant. **(B)** ROI overlap map: Summation of M1 ROIs for each participant (healthy controls and patients with stroke). Warmer colors indicate a voxel is included in more ROIs. ROIs were densely clustered over the posterior aspect of the precentral gyrus including the hand knob and the central sulcus. **(C)** Lesion overlap map: lesion masks from the 19 patients with stroke projected into standard space. Lesions from the right hemisphere were flipped across the sagittal axis for illustration purposes only. Warmer colors indicate a voxel is present in more participants' lesion masks.

TABLE 1 | Participant characteristics.

	Patients with stroke	Healthy controls
Group size	19	31
Age	59.4 (9.9)	61.7 (9.0)
Sex	12 F / 7 M	17 F / 14 M
Race	1 Asian	1 Asian
	9 Black	10 Black
	9 White	18 White
		2 DNR
Dominant hand	14 R / 5 L	31 R / 0 L
Affected hand	8 R / 11 L	
Concordance	9 concordant	
	10 discordant	
Time since stroke (days)	18.9 (7.3)	
JHFT	0.21 (0.19)	
WMFT-T (s)	2.49 (1.48)	
WMFT-GS (kg)	25.8 (13.8)	
HD	2.37 (1.98)	1.60 (2.44)
RBANS	91.9 (18.1)	105.8 (12.4)

The format is mean (SD). DNR, did not respond; JHFT, Jebsen Hand Function Test; JHFT scores are normed for age, sex, and handedness. WMFT, Wolf Motor Function Test (mean time = T, grip strength = GS). For Hamilton Depression (HD) score, one healthy participant's data were incomplete for more than 1 item and were excluded from this analysis. In participants with single items missing, the highest score for that item was used. RBANS Total Index Mean = 100 +/– 15. The two groups did not differ on age [$t(48) = 0.85$, $p > 0.2$] or depression score [$t(48) = 1.16$, $p > 0.2$] score, but the control participants had significantly higher scores on the RBANS than the patients [$t(48) = 3.23$, $p < 0.01$].

accuracy than patients with better hand function, indicated by a trend relating JHFT score and overall task accuracy (R^2 =0.167, p = 0.08). A separate mixed-model ANOVA with target size as a within-subject factor and group as a between-subject factor showed the same pattern of effects on movement time as accuracy, with significant effects of group [$F(1, 48)$ = 10.14, p = 0.003] and target size [$F(1.73,82.8)$ = 47.67, p < 0.001] but no interaction of group and target size [$F(1.73,82.8)$ =0.1, $p > 0.2$]. For simplicity, we report only the comparisons between the affected hand of the patients with stroke and the non–dominant (left) hand of the control participants, but the results are the same when comparing affected hand performance against dominant (right) hand performance for the controls.

Patients with stroke showed significantly lower accuracy and longer movement times than healthy controls. Nevertheless, accuracy and movement time were clearly demand-dependent in both patients and control participants. There were significant main effects of target size in both the accuracy and movement time analyses reported above. The mean demand slope measures were significantly greater than zero in all cases [control left hand: $t(30) = 9.3$, $p < 0.001$; control right hand $t(30) = 7.01$, $p < 0.001$; stroke-affected hand $t(18) = 9.21$, $p < 0.001$), indicating that accuracy decreases and movement time increases as the demand on precision increases, consistent with Fitts' Law (59, 60). The presence of this relationship in the patients with stroke indicates that their behavior followed this basic principle and supports the notion that patients and healthy participants demonstrated comparable effort despite the differences in overall accuracy and movement time.

Overall M1 ROI Activation

While performance of patients on the pointing task was slower and less accurate than controls, mean activation in either the ipsilesional or contralesional M1 ROI in the stroke patient sample was not significantly different than mean activation in the corresponding contralateral or ipsilateral M1 ROIs of the healthy control participants. Two mixed model ANOVAs with target size as a within-subject factor and group (stroke: affected hand/ control: non–dominant hand) as a between-subject factor showed significant main effects of target size in both M1 ROIs (ipsilesional/contralateral: F (3,144) = 10.58, p <0.001, contralesional/ipsilateral: $F(3,144) = 2.85$, p =0.04), but there were no main effects of group (ipsilesional/contralateral: F (1,48) = 1.01, p >0.2, contralesional/ipsilateral: F (1,48) =0.85, p >0.2) or interactions between group and target size (ipsilesional/contralateral: F (3,144) = 1.35, p >0.2, contralesional/ipsilateral: $F(3,144) = 1.67$, p =0.18), indicating that patients with stroke and healthy controls did not significantly differ in mean BOLD activation or in how the BOLD response was affected by target size (**Figures 3C,D**). We report the comparison against the healthy control non-dominant (left) hand, but the results do not differ if healthy control data from dominant (right) hand task performance is used. Neither patients with stroke nor controls showed a significant correlation between average task accuracy and average ROI BOLD activation, in either the contralateral/ipsilesional M1 ROI (stroke affected hand: R^2 = 0.019, control right hand: R^2 = 0.002, control left hand: R^2 = 0.056, all $p > 0.2$) or the ipsilateral/contralesional M1 ROI (stroke affected hand: $R^2 = 0.032$, control right hand: $R^2 = 0$, control left hand: $R^2 = 0.023$, all $p > 0.2$), indicating that participants with better (or worse) task accuracy do not necessarily have higher (or lower) levels of M1 activation.

Demand-Dependent M1 Activation

As shown above, the main effect of target size indicates that participants responded differently to differently sized targets in both the contralesional/ipsilateral and ipsilesional/contralateral M1 ROIs. To determine whether patients with stroke and controls showed evidence of a linear relationship between BOLD activation and task demand in the ipsilesional/contralateral M1 ROI, we calculated the slope of the line best fitting the BOLD activation data for the four different target sizes for each participant. For both healthy controls and patients, these demand-dependent slopes were significantly non-zero in the ipsilesional/contralateral M1 ROI [control left hand: t (30) = −5.5, p < 0.001; control right hand t (30) = −5.56, p < 0.001; affected hand t (18) = −2.51, p = 0.022] with increasing BOLD activation as target size gets smaller and demand on precision increases. Demand-dependent slopes did not differ between patients and controls [F (1,48) = 1.12, $p > 0.2$]. In contrast, in contralesional/ipsilateral M1, only healthy control participants showed significantly non–zero demand slopes for the ipsilateral

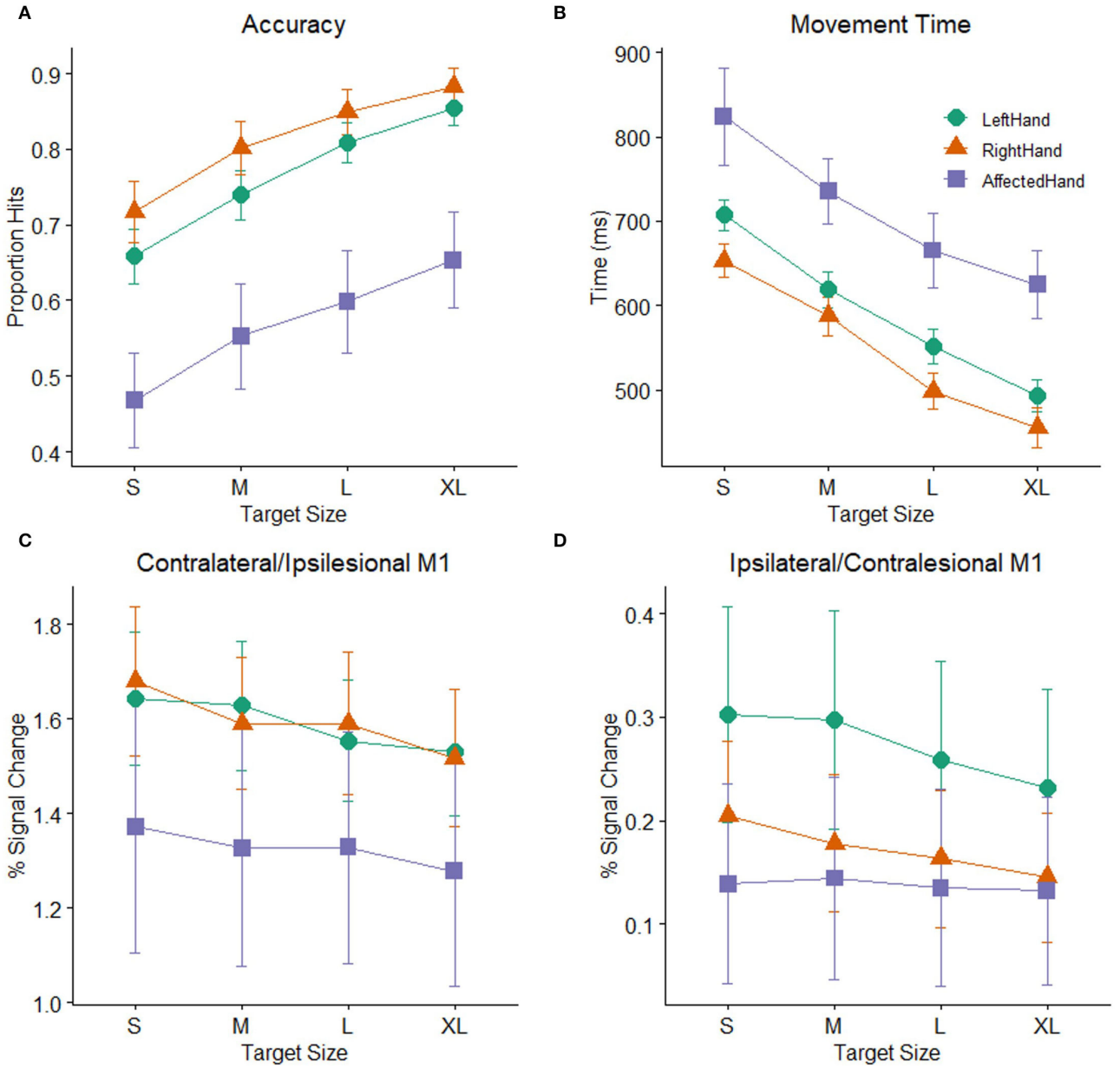

FIGURE 3 | Task performance: **(A)** Accuracy (proportion hits) for each combination of hand (affected hand in patients with stroke, left hand and right hand in healthy control participants) and target size [small (S), medium (M), large (L), extra-large (XL)] during the hand motor task. Error bars represent SEM. **(B)** Mean time (in ms) from the onset of the target to when the cursor hit and remained on the target for each combination of hand and target size. Consistent with Fitts' law, participants showed greater accuracy and faster movement times as the target size increased. **(C)** BOLD response (percent signal change) during movement to targets of different sizes plotted for the contralateral M1 ROI (healthy controls) or ipsilesional M1 ROI (patients with stroke). **(D)** BOLD response (percent signal change) during movement to targets of different sizes plotted for the ipsilateral M1 ROI (healthy controls) or contralesional M1 ROI (patients with stroke).

M1 ROI [control left hand: $t\ (20) = -3.08$, $p = 0.004$; control right hand $t\ (30) = -2.57$, $p = 0.015$]. For the patients with stroke, the demand slopes were not significantly different from zero [$t\ (18) = -0.56, p > 0.2$] in the corresponding contralesional M1 ROI (**Figure 3D**). Furthermore, an inspection of **Figure 3D** suggests that the slopes are different between patients with stroke and controls, with an almost flat line across target sizes in the patients. However, this difference did not reach statistical significance [$F\ (1,48) = 3.97$, $p = 0.052$].

As reported above, an individual's mean BOLD activation did not correlate with their mean accuracy on the task. However, there was a relationship between the overall level of BOLD activation in an individual's M1 ROI and the likelihood of observing a non-zero slope in the BOLD response as the target

size changed. This was true for both hemispheres and for both patients with stroke and healthy controls (stroke ipsilesional $R^2 = 0.432$, $p = 0.002$; healthy right contralateral $R^2 = 0.123$, $p = 0.052$; healthy left contralateral $R^2 = 0.165$, $p = 0.023$; stroke contralesional $R^2 = 0.236$, $p = 0.035$; healthy right ipsilateral $R^2 = 0.17$, $p = 0.021$; healthy left ipsilateral $R^2 = 0.252$, $p = 0.004$). Specifically, individuals with higher M1 ROI activation (in either hemisphere) tended to have larger changes in BOLD activity across target sizes in that hemisphere (**Figure 4**).

Exploratory Analysis: Handedness

Because we have previously reported subtle differences in demand-dependent activity in ipsilateral M1 depending on whether the dominant right hand or non-dominant left hand was used in right-handed healthy controls (41), we explored the factor of handedness in our patients with stroke. Our sample of patients with stroke performed the hand motor task only with the affected hand, but of the patients who had individually localizable M1 hand ROIs (see *MRI Data Analysis*), the (previously) dominant hand was affected in eight patients and the non–dominant hand was affected in eight patients (see **Table 1** for details about left and right-handedness). We examined whether there was evidence for demand dependence in contralesional M1 when the dominant or non-dominant hand was used, though caution in interpreting these results is warranted due to the very small sample sizes. Average task performance did not differ between the two groups [mean dominant = 0.542, mean non-dominant = 0.609, t (14) = 0.48, $p > 0.2$]. Patients who performed the task with an affected non-dominant hand showed evidence of increasing contralesional M1 activation with increasing task demand, with non-zero activation slopes [mean slope = −0.015, t (7) = 1.9, $p = 0.05$] indicating demand dependency, but patients who were tested using their affected dominant hand did not [mean slope = 0.001, t (7) = 0.24, $p > 0.2$] (**Figure 5**).

Exploratory Analysis: Cognition

The JHFT used here to measure impairment of hand function in the patients with stroke is a timed test and may therefore be subject to motivational or cognitive constraints. In our patient sample, scores on the JHFT were significantly related to cognitive function as assessed by the RBANS; patients with higher RBANS scores showed significantly less impairment on the JHFT ($R^2 = 0.46$, $p = 0.002$). However, the pointing task used here is also time-limited and could be subject to similar motivational or cognitive constraints. Indeed, across all patient and control participants, individuals with higher RBANS scores performed better on the pointing task ($R^2 = 0.26$, $p < 0.001$); this trend was present but weaker in just the patient sample ($R^2 = 0.16$, $p = 0.09$).

EMG Activity of the Non-performing Hand

Electromyography data from two patients with stroke and six healthy participants were excluded from further analysis due to missing data or excessive artifacts. Both healthy control and stroke participants were able to perform the hand motor task unimanually, as mean EMG activity for the non–performing

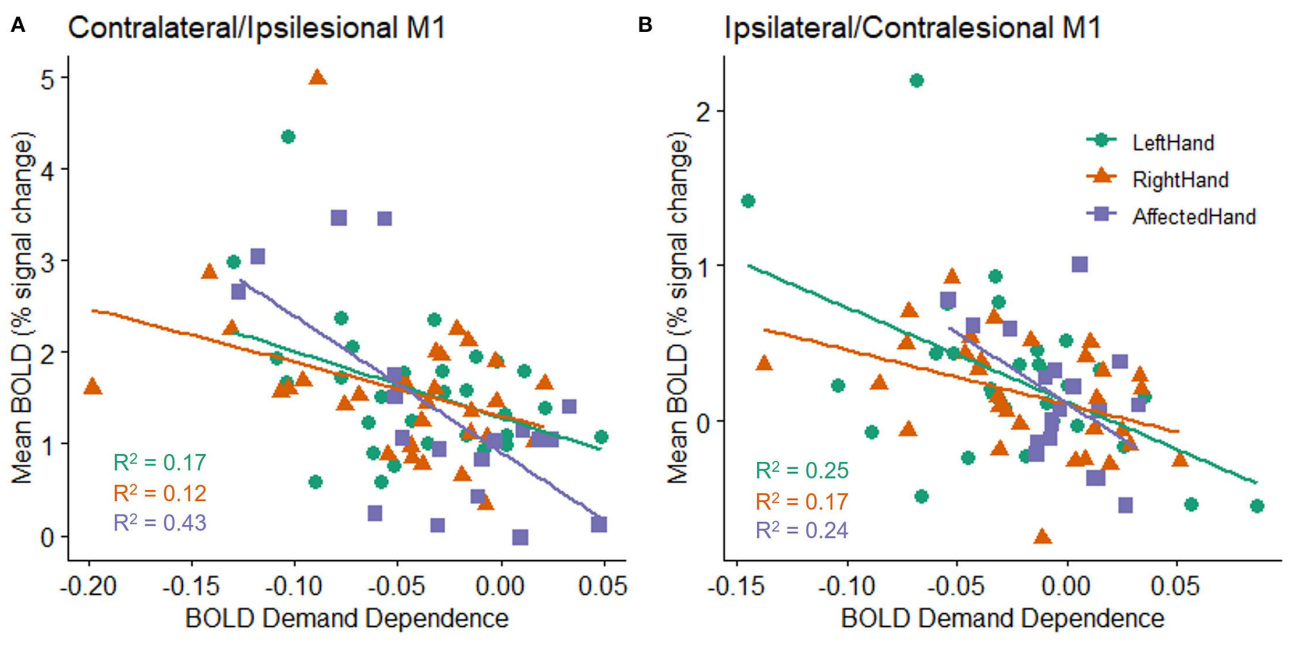

FIGURE 4 | Relationship between an individual's mean BOLD response (percent signal change) across all target sizes and the slope fit to an individual's BOLD response (BOLD demand dependence) during movement to each of the four different target sizes in the **(A)** contralateral (healthy subjects) or ipsilesional (patients with stroke) M1 ROI, and **(B)** ipsilateral (healthy controls) or contralesional (patients with stroke) M1 ROI. All groups show a statistically reliable correlation between BOLD activity and BOLD demand dependence, with higher mean BOLD activation related to a steeper slope in M1 activation changes (i.e., a larger decrease in activation for the largest targets relative to the smallest targets). A negative demand dependence slope indicates less activation for large targets than small targets.

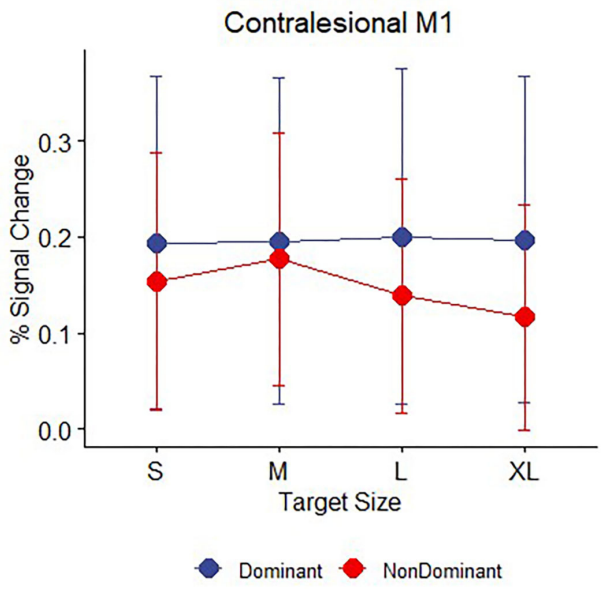

FIGURE 5 | Contralesional M1 mean BOLD response (percent signal change) during movement to targets for n = 16 patients with stroke divided by whether the affected hand was dominant (blue, $n = 8$) or non-dominant (red, $n = 8$) prior to their stroke. Error bars represent SEM.

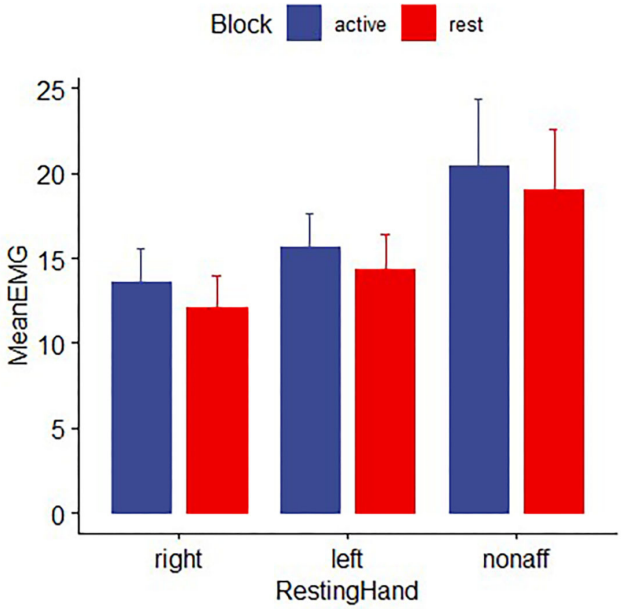

FIGURE 6 | EMG activity for healthy controls and patients with stroke for the non-performing hand during time periods while the other hand was moving the joystick for the pointing task (active block) or resting (rest block). EMG in the nonperforming hand did not differ significantly between movement and rest blocks, indicating the absence of mirror movements. Error bars reflect SEM.

hand did not differ between movement and rest blocks for either group [controls: F (1,92) = 0.48, $p > 0.2$; patients: t (16) =0.93, $p > 0.2$; **Figure 6**].

DISCUSSION

The goal of the present study was to determine the extent to which, in patients with stroke and mild to moderate impairment of hand function due to injury of M1 or CST, activation of contralesional M1 can be explained by the demand of a motor task. While patients showed significant impairment relative to controls in their ability to perform the hand motor task in the fMRI scanner, both patients and healthy controls showed demand-dependent task performance with higher accuracy and faster movements for larger targets than smaller targets. The demand for the precision of the motor task affected the BOLD response for both M1 ROIs in patients and in healthy controls, indicating that targets of different sizes were responded to differently. However, while in healthy controls, this differential response took the form of a linear relationship between M1 BOLD activation and demand on precision in both contralateral and ipsilateral hemispheres, a similar demand-dependent profile was only seen in the ipsilesional M1 in patients with stroke, suggesting a weaker relationship between demand dependency and BOLD activation in contralesional M1. Furthermore, neither ipsilesional nor contralesional M1 showed evidence of elevated BOLD activation relative to healthy age-matched controls when executing a strictly EMG confirmed, a unimanual task with the affected hand.

Because the EMG recordings of the non-performing hand during the scanning procedures did not show any task-related changes in the magnitude of EMG activity, it is very unlikely that the BOLD response in contralesional M1 is due to mirror movements. Instead, the results of the EMG recordings demonstrate strictly unimanual execution of the task with the affected hand. Our findings confirm earlier reports of contralesional M1 activity in patients with subacute stroke involving M1 or its CST projections and mild to moderate impairment of hand function (13). The task from this early study consisted of a non-sequential finger sequence and was not designed to quantify the kinematic details that allow the parametric increase in demand on precision. In contrast to the present study, healthy age-matched controls did not show corresponding ipsilateral M1 activity when executing the non-sequential finger movement task. While we do not know the kinematic details of that task, the lack of observable activation in the ipsilateral M1 in healthy participants in that study is likely due to the relatively lower task demand (40, 41).

Because the motor task employed in the present study keeps important kinematic variables (e.g., force, amplitude, and frequency) and the muscles supporting the motor task similar across different levels of demand, the weaker relationship between the contralesional M1 BOLD response to demand on precision is likely not due to differences in the execution of the task. This notion is supported by the similarity in the demand slopes, indicating that the patients and controls responded similarly to an increase in demand on precision, with

better (faster and more accurate) performance for larger targets and poorer performance for smaller targets. However, while important kinematic variables for this task were matched and both groups showed similar demand-dependent performance, patients also had significantly worse accuracy and slower movement times than controls. This raises the possibility that differences between the groups may arise due to these performance differences rather than differing neural responses to the task. Task performance was also related to cognitive function, which also differed between the groups. However, if these differences had an impact on the BOLD activity, we would expect an increase in BOLD activity in patients relative to controls since patients found the task more difficult, with longer movement times and lower accuracy. Instead, we see reduced or similar activation in the patient group. Therefore, differences in M1 activation between patients and controls cannot be explained by differences in task performance or cognitive function.

We do not have direct data on the vasculature in our participants and the patients likely have an arteriosclerotic disease that may compromise their hemodynamic response function. However, there is no statistically significant difference between the overall BOLD activation in contralesional M1 compared to the healthy control ipsilateral M1 or the ipsilesional M1 compared to healthy control contralateral M1. Further, we would not expect compromised hemodynamic response function to have a systematic impact on one hemisphere (i.e., contralesional M1) compared to the other hemisphere (i.e., ipsilesional M1) or for this to explain the weaker relationship between M1 BOLD activation and demand on precision in contralesional M1.

Compared to the mean ipsilesional/contralateral M1 BOLD response, the mean contralesional/ipsilateral M1 ROI BOLD response is substantially smaller. While we did not find that an individual's mean BOLD activation correlated with their mean performance on the task, there was a significant relationship between the overall level of BOLD activation in an individual's M1 ROI and the likelihood of observing a non-zero slope in the BOLD response as target size changed. This raises the question of whether there could be a floor effect, with a linear change in activation less likely to be detected due to noise levels if all activation values are low. However, a floor effect solely affecting the patients is unlikely, given the mean BOLD response did not differ between the contralesional/ipsilateral M1s in patients and controls, and a linear relationship was detected in ipsilateral M1 in the healthy control participants. Additionally, the sample size of stroke participants is approximately two-thirds of the sample size of the control group. Combined with the lower overall activation in contralesional/ipsilateral M1, the small sample size may prevent us from detecting demand-dependent activation in the stroke patient sample, though a direct comparison of the demand slopes for patients and controls suggests that the slopes are significantly different between the two groups.

Another possible consideration for explaining differences in the demand dependence of contra- and ipsilesional M1 is related to the concept of hemispheric specialization and whether the task was executed with the dominant or non-dominant hand. Here, each M1 contributes differently to the control of both hand movements and motor learning/adaptation [see (61) for a review]. Specifically, in this model, the left hemisphere provides predictive control mechanisms specifying aspects such as movement direction and curvature, whereas the right hemisphere specializes in impedance control to improve final position accuracy. While this is an important model for understanding motor control, in the current analysis we could not consider hemispheric specialization with respect to the left and right sides because of the mixed handedness of our patients (see **Table 1**). Relating differences in the demand-dependent BOLD response of contralesional M1 to hemispheric specialization must be addressed in a future study.

Sensorimotor brain areas beyond M1 are active in this and other motor tasks and contribute to post-stroke motor control and functional recovery (17, 62–65). However, given that M1 is a common target of various rehabilitation treatment approaches (28, 66), our hypothesis about the role of contralesional M1 in supporting hand motor function after stroke is specific to M1. We have limited our analyses here to individually localized functional ROIs that largely encompass the M1 hand area in both hemispheres.

Here we show that, similar to healthy age-matched controls, patients with subacute ischemic stroke performing a skilled hand motor task show demand-dependent accuracy and movement times and a linear increase in their BOLD response in ipsilesional M1. In contrast to the controls, this relationship was weaker in the contralesional M1. Longitudinal work assessing changes in demand-dependent activity over time and its relationship to the recovery of function in patients with stroke is needed to further clarify if reorganizational changes in M1 are driving the observed weaker relationship between the contralesional BOLD response and the demand on precision. However, this is a possible explanation given the evidence from the rodent stroke models (30–36) and non-human primates (67–69). It also remains to be determined whether this is also seen in patients with greater injury to M1 and CST. The findings described above suggest that some of the BOLD response observed in contralesional M1 is related to the demand of the motor task being performed. Therefore, some of the reported abnormal bilateral M1 activations in patients with stroke (13) could be a response to the relatively higher demand of the task when compared to healthy controls. In future studies, care should be taken to quantify the demand of a motor task to account for these differences. An improved understanding of the role of contralesional M1 in supporting compromised hand function is critical for the design and selection of safe and evidence-based treatment approaches in neurorehabilitation.

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 Emory University Institutional Review Board. The

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

AUTHOR CONTRIBUTIONS

KR, CB, and MH conceived and designed research. KR, CB, DB, AC, and IV collected the data. FN, SB, IV, and CB selected and recruited stroke patients for potential participation. KR, DB, MH, SR, and JT analyzed data. KR, CB, and DB interpreted results of experiments. KR prepared figures. KR and CB drafted the manuscript. KR, DB, MH, SB, FN, and CB edited and revised manuscript. KR, DB, AC, IV, SR, JT, SB, FN, MH, and CB approved final version of manuscript. All authors have read and agreed to the published version of the manuscript.

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