Neural Plasticity

Interventions to Enhance Adaptive Plasticity after Stroke: From Mechanisms to Therapeutic Perspectives

Guest Editors: Adriana Conforto, Annette Sterr, Ela Plow, and Leonardo Cohen

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Editorial

Interventions to Enhance Adaptive Plasticity after Stroke: From Mechanisms to Therapeutic Perspectives

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Disability from stroke represents a great burden worldwide. The science of stroke rehabilitation flourished in the last decades, as the concept of brain plasticity advanced. It is now known that the adult brain can rewire in response to experience and training in healthy subjects and in disease states such as stroke. However, there is a gap between plasticity studies in animals demonstrating "rewiring" of neuronal circuits and the availability of neurorehabilitative strategies in the clinical domain. Although mechanisms underlying recovery are not completely understood, there is some evidence to suggest that recovery at least entails resolution of acute tissue damage and behavioral compensation, as well as functional and structural changes. There is evidence that better outcomes are associated with the greatest return of brain function toward the normal state of organization before stroke. How to drive adaptive reorganization remains an open question. In this special issue, five manuscripts address questions related to interventions that aim to enhance adaptive plasticity after stroke. How do we capitalize on mechanisms of plasticity to develop effective therapeutic approaches? How do we individualize therapy in such a heterogeneous condition as stroke?

Over the past decades, the interest in the potential use of brain stimulation to boost adaptive plasticity and enhance motor and language functions has steadily grown. According to one of the hypotheses of recovery after stroke, increased activity of the unaffected hemisphere and decreased activity of the affected hemisphere can be detrimental to motor and language performance. In this special issue, J. C. Griffis et al. assessed the effects of ten sessions of neuronavigated intermittent theta-burst stimulation (iTBS) given to residual left inferior frontal gyrus (IFG) in four patients with anomic aphasia and four patients with Broca's aphasia, in the chronic phase after left-hemisphere strokes. They intended to upregulate activity in the left IFG and decrease possibly detrimental hyperactivity in the right IFG. They went a step further and evaluated changes in connectivity between the right and left IFG after this intervention. Indeed, they observed a shift in the functional magnetic resonance imaging (fMRI) lateralization of IFG during a covert verb generation task after iTBS, as well as a decrease in connectivity between right and left IFG after treatment. Even though these preliminary results from a pilot, open-label study appear to be promising, larger, sham-controlled trials of iTBS are needed. A challenge in designing such trials is to define selection criteria that would help identify patients with the greatest likelihood of showing clinically meaningful improvements with brain stimulation treatment.

E. B. Plow et al. have suggested ways to address this challenge in the next manuscript. They have explained how one can personalize brain stimulation to improve motor outcomes for both patients with mild as well as patients

with severe upper limb paresis. A model of individualized interventions that tailor treatments to each patient is proposed. The idea is to stratify paradigms of stimulation according to mechanisms underlying plasticity. Upregulation of excitability of the affected hemisphere and downregulation of excitability of the unaffected hemisphere according to the model of interhemispheric inhibition are not always beneficial. Therefore, strategies to match the right strategy to the right patient according to baseline level of severity of damage and paresis as well as structural or functional imaging were discussed. While emphasis of their discussion was on improving motor function, E. B. Plow et al. also discussed studies that extended the idea of tailoring interventions to treat language and mood disorders. The need to devise therapies that can decrease the burden of stroke in mildly affected patients, but especially in those with severe impairments, was highlighted. Still, models discussed in this manuscript have largely been theoretical; empirical investigations to test effectiveness of many models are still underway.

In a different manuscript, L. Furlan et al. reviewed studies that contributed to unveil the neural correlates of effects of upper limb immobilization and proposed that this intervention could be a valuable tool to develop novel strategies for patients with poor upper limb performance. Upper limb immobilization is one of the components of the original constraint-induced movement therapy (CMIT) protocol for stroke. CMIT has emerged as an evidence-based intervention to improve use of the paretic arm in relatively high-functioning subjects with stroke. This intervention has not yet been proven to benefit low-functioning patients, who present deep nonuse of the affected upper limb. However, upper limb immobilization can be employed as a model of low-functioning upper limb paresis and hence help to understand mechanisms underlying poor upper limp function, as well as refining treatments that can enhance outcomes in severely affected patients. Testing effects of motor imagery, action observation, peripheral somatosensory stimulation, and brain stimulation in the context of upper limb immobilization could advance the neurobehavioral framework and foster fine tunings in rehabilitation paradigms in order to potentiate adaptive plasticity as well as motor gains in these patients.

Similar to the notions suggested in manuscripts by J. C. Griffis et al. and E. B. Plow et al., where knowledge of mechanisms of plasticity is believed to be elemental to help match the right patient to the right treatment, M. Gandolla et al. investigated mechanisms of functional electrical stimulation (FES) treatment for foot drop in order to predict responsiveness to treatment. Some patients can relearn the ability to dorsiflex the ankle after finishing one month of gait rehabilitation aided by FES of the *tibialis anterior* muscle ("carryover") while others cannot. The study aimed to evaluate mechanisms of the FES carryover effect by comparing differences in brain activity before FES treatment, in patients who presented a carryover effect, in patients who did not present this effect after treatment, and in controls without stroke, who did not undergo treatment. Brain areas of investigation were chosen based on previous knowledge about mechanisms underlying sensorimotor integration and voluntary movement. The authors were able to separate patients who evolved with and without a FES carryover effect after treatment, based on brain responses in the contralateral supplementary motor area (SMA) and angular gyrus. Furthermore, patients with a carryover effect, but not those without, had responses in SMA and in the primary motor cortex that were similar to those found in healthy controls. This manuscript is an example of how to translate data about mechanisms underlying plasticity into information that can be clinically useful, for instance, to help selecting patients in future trials in order to maximize potential treatment benefits. It also suggests that central plasticity can be induced by manipulating afferent input at the periphery, in line with other studies.

Another manuscript that evaluated effects of a peripheral intervention based on augmentation of somatosensory input in order to drive central motor plasticity was authored by C. Garcia et al. The authors applied electric currents to the skin overlying forearm muscles at four different frequencies in up to fourteen healthy subjects, for 5 minutes or 30 minutes. No changes in amplitudes of motor evoked potentials (MEPs), and no changes in H-reflexes were observed. The authors also studied five patients who had experienced upper limb spasticity in the chronic phase after stroke. Patients received 30 minutes of somatosensory stimulation delivered at 3 Hz. Again, the intervention failed to elicit changes in MEP amplitudes or spasticity tested during the performance of passive movement of the wrist. The results are very preliminary, considering the sample sizes, but suggest that short periods of electrical stimulation of the skin overlying forearm flexor muscles may not lead to measurable changes in cortical or spinal excitability or that if such changes occur, they are not captured by evaluation of MEPs or H-reflexes. Other peripheral interventions, such as somatosensory stimulation in the form of peripheral nerve stimulation or muscle vibration, seem more promising.

The articles published in this special issue underscore the importance of identifying the functional role of specific brain areas as well as brain networks that can assume functioning of lesioned tissue to develop interventions that can improve clinically significant outcomes. Effects of particular interventions not only on specific brain areas but also on interactions between areas should be tested in order to bridge the gap between animal studies, translational research, and clinical rehabilitation.

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Research Article

The Neural Correlates of Long-Term Carryover following Functional Electrical Stimulation for Stroke

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Neurorehabilitation effective delivery for stroke is likely to be improved by establishing a mechanistic understanding of how to enhance adaptive plasticity. Functional electrical stimulation is effective at reducing poststroke foot drop; in some patients, the effect persists after therapy has finished with an unknown mechanism. We used fMRI to examine neural correlates of functional electrical stimulation key elements, volitional intent to move and concurrent stimulation, in a group of chronic stroke patients receiving functional electrical stimulation for foot-drop correction. Patients exhibited task-related activation in a complex network, sharing bilateral sensorimotor and supplementary motor activation with age-matched controls. We observed consistent separation of patients with and without carryover effect on the basis of brain responses. Patients who experienced the carryover effect had responses in supplementary motor area that correspond to healthy controls; the interaction between experimental factors in contralateral angular gyrus was seen only in those without carryover. We suggest that the functional electrical stimulation carryover mechanism of action is based on movement prediction and sense of agency/body ownership—the ability of a patient to plan the movement and to perceive the stimulation as a part of his/her own control loop is important for carryover effect to take place.

1. Introduction

Stroke is one of the leading causes of adult disability [1]. Advances in acute treatment have led to improvements in survival and so establishing effective rehabilitation strategies has become even more important. This process is likely to be facilitated by establishing a mechanistic understanding of how to use adjunctive therapies to augment standard rehabilitation approaches.

Functional electrical stimulation (FES) is a commonly used adjunctive therapy in the rehabilitation of stroke [2]. It is primarily used for the orthotic correction of foot drop, but a proportion of patients relearn the ability to voluntarily dorsiflex the ankle without the device [3]. This phenomenon, referred to as the "carryover effect," has been observed in a number of subsequent studies [4, 5]. To date, the mechanism of this effect is unknown, although it has been hypothesised that an interaction between volitional effort and the electrical stimulation of FES results in a neuroplastic effect on the central nervous system [6–9]. However, the carryover effect has been observed only in subgroups of neurological patients and the characteristics of those with and without FES carryover are not clear.

In this work, we used functional magnetic resonance imaging (fMRI) to examine the neural correlates of the key ingredients of FES, namely, volitional intent to move and concurrent electrical stimulation, in a group of chronic stroke patients receiving FES treatment for foot drop. We were then

interested to see whether brain activity during movement or stimulation (or the interaction between the two) before FES treatment would have any value in predicting whether individual patients would have a carryover effect on volitional ankle dorsiflexion after removal of FES.

In healthy subjects, the interaction between volitional movement and proprioceptive feedback occurs in primary sensory and motor cortex [9]. We might expect to see "normal" brain response to the elements of FES in those with carryover and diminished responses in those without carryover. However, sensorimotor systems are organised differently after stroke particularly in primary and secondary areas. The interaction (or lack of it) between volitional movement and proprioceptive feedback might therefore occur in nonprimary sensory (secondary somatosensory area, SII, and posterior parietal cortex) and motor (lateral and medial premotor cortex) areas. The sensitivity and spatial resolution of fMRI allow us to make specific conclusions about the cortical regions active during key elements of FES and to investigate the likely neural mechanism of the carryover effect following FES treatment.

2. Materials and Methods

2.1. Participants. Patients were recruited from the outpatient and inpatient services at the Villa Beretta Rehabilitation Centre (Costa Masnaga, LC, Italy). All patients had suffered from first-ever stroke > 6 months previously, resulting in weakness of at least the tibialis anterior muscle (to <4+ on the Medical Research Council (MRC) scale [10]). Exclusion criteria consisted of (i) less than 10° in FES-induced ankle dorsiflexion; (ii) language or cognitive deficits sufficient to impair cooperation in the study; (iii) inability to walk even if assisted; (iv) high spasticity at ankle joint plantar flexor as measured by the modified Ashworth scale index > 2 [11].

The age-matched control group was composed of healthy volunteers with no neurological or orthopaedic impairment. Their results have been fully reported previously [9].

Experiments were conducted with approval from the Villa Beretta Rehabilitation Centre Ethics Committee and all subjects gave informed written consent in accordance with the Declaration of Helsinki.

2.2. Clinical and Instrumental Measures for Impairment Assessment. Patients' impairment at the time of recruitment for this study was evaluated using a battery of clinical and instrumental tests. In particular, they were evaluated through a gait analysis test performed following the standard Davis evaluation protocol [12] along with the correspondent dynamic electromyography test and the 6-minute walking test [13]. Moreover, they were scored by the clinician on the MRC scale index at ankle dorsiflexion.

From these tests, a set of five outcome measures was designed to assess different aspects of patients' functional condition:

(i) Gait velocity as measured during the gait analysis test.

(ii) Endurance velocity, as calculated during the 6-minute walking test.

(iii) Paretic step length as measured during the gait analysis test.

(iv) Tibialis Anterior Activation Index defined as the ratio between the activity of the tibialis anterior muscle between toe off and toe strike and that during the whole gait cycle [14].

(v) MRC index [10].

Patients were trained 5 times per week for 4 weeks. Each of these 20 sessions consisted of 30 minutes of walking supported by a commercial electrical stimulator. Two commercial devices were available at the Villa Beretta Rehabilitation Centre: Bioness L300 (Bioness Inc.) and WalkAid (Innovative Neurotronics). Two stimulating electrodes were placed superficially along the peroneal nerve to elicit tibialis anterior muscle contraction during the swing phase of gait. Swing phase was detected online by wireless heel switches (Bioness) or by accelerometers (WalkAid). The more suitable commercial device was selected for each patient depending on his/her best responsiveness to stimulation, best wearability, and reliability of swing phase detection. Current stimulation amplitude was selected for each participant at the beginning of each session so as to be able to elicit ankle dorsiflexion during gait but at the same time to remain within the tolerance level.

Impairment was evaluated at the time of recruitment for this study (t_1: within 5 days before the start of the treatment) and after the intervention (t_2: within 5 days since the end of the treatment) using the same battery of clinical and instrumental tests.

The carryover effect was determined using a novel algorithm based on variables minimum detectable change that combines the outcome measures to obtain a unique parameter, Capacity Score, where a higher Capacity Score indicates higher residual ability. In particular, for each assessment session, patients were assigned to a point in an n-dimensional space, where n corresponds to the number of outcome measures considered. The n-dimensional space was centred on the outcome measures derived from healthy subjects, and therefore the further away the patient is from the origin, the more impaired he/she is. Moreover, the outcome variables have been normalized with respect to the corresponding minimum detectable change. The difference in the n-dimensional space between (i) the Euclidean distance of "subject zero" (a patient that scores zero in all outcome measures, i.e., the most impaired patient in our space) with respect to the origin (i.e., distance of the "subject zero" from the healthy control group) and (ii) the Euclidean distance of each patient with respect to the origin (i.e., distance of the "subject zero" from the healthy control group) is defined as Capability Score. The difference between Capacity Scores at different timing (i.e., post-pre) is thresholded to obtain carryover effect assessment. The algorithm has been validated against clinical evaluation [15].

2.3. Experimental Setup. The experimental setup was composed of 1.5 T MRI scanner (GE Cv/I), a motion capture system (Smart μg; BTS), and an electrical stimulator (RehaStim

proTM; HASOMED GmbH), as previously described and validated [16, 17].

2.4. Experimental Design. A 2 × 2 event-related fMRI design was carried out. Experimental factors were (i) volitional intention to perform ankle dorsal-plantar flexion (ADF) [V: with the levels "volitional" and "passive"] and (ii) FES [F: with the levels "present" and "absent"]. Each patient was instructed to execute the protocol with the plegic ankle. During a continuous 10-minute scanning session, subjects performed 20 alternate 9-second OFF and 21-second ON blocks. The 4 conditions that constituted our factorial design were performed during the ON blocks in a semirandomized order: (i) FV: attempted voluntary ADF with concurrent FES-induced ADF; (ii) FP: FES-induced ADF, with no attempt to move the ankle; (iii) V: voluntary ADF without FES; (iv) P: passive dorsiflexion (by the experimenter) of the subject's ankle without FES. Subjects were specifically instructed to remain completely relaxed during FP and P conditions and to equally voluntarily contribute during V and FV conditions. Dorsiflexion was paced every 3.5 seconds (for 6 repetitions within a block) with an auditory cue (i.e., movement rate 0.3 Hz) [18]. The auditory cues were presented through an earphone. Prior to scanning, subjects practiced the protocol until being comfortable with the task; the experimenter was assisting the training to check the correct execution of the protocol and equate effort across subjects. All subjects were free to choose the amplitude of their active movement to preclude fatigue. Indeed, Ciccarelli and colleagues [18] did not find any effect of movement amplitude (10°–55°) on magnitude or pattern of brain activity, suggesting that if the movement does not have any external reference and it is self-paced, there is no difference due to amplitude in associated cortical activity. Subjects were instructed to keep eyes closed and head movements were minimized with rubber pads and straps. To ensure minimum transmission of movements to the head, knees were bent with the subject's legs lying on a pillow.

2.5. FES Stimulation Paradigm. Functional electrical stimulation was applied to the peroneal nerve through superficial self-adhesive electrodes, with biphasic balanced current pulses at 20 Hz fixed frequency. The pulse width had a trapezoidal profile (maximum pulse width 400 μs) and the current amplitude was set subject by subject so as to produce ADF movement, within the tolerance threshold. Current amplitude and pulse width were kept the same for both FP and FV conditions.

2.6. Images Data Acquisition. A GE Cv/I system, operating at 1.5 T, was used to acquire both T1-weighted anatomical images (0.94 × 0.94 × 4 mm voxels) and T2*-weighted MRI transverse echo-planar images (1.8 × 1.8 × 4 mm voxels, TE = 50 ms) with blood oxygenation level dependent contrast. Each echo-planar image comprised 22 contiguous axial slices, positioned to cover the temporoparietal and occipital lobes, with an effective repetition time of 3 seconds per volume. Due to technical reasons, it was not possible to acquire the cerebellum. The first six volumes were discarded to allow for T1 equilibration effects. A total of 200 brain volumes were acquired in a single run lasting 10 minutes.

2.7. Kinematic Measures and Analysis. A motion capture system previously validated for recording during scanning allowed us to record 3D trajectories of retroreflective markers to measure the ankle angle during fMRI acquisitions and to determine the movement onset for event-related fMRI time series analysis. Two separate acquisition sessions were performed. The first was a static acquisition performed before the scanning, but while lying in the scanner, to estimate the coordinates of the medial and lateral malleoli for both lower limbs. During the static acquisition, a plate with 3 markers was placed on each tibia and 4 sticks with two markers each were placed on the four malleoli. The relative positions of the malleoli with respect to the plates (i.e., left and right plates) were computed and the transformation matrices were estimated under the assumption that tibia and malleoli were rigidly connected. The second acquisition, dynamic acquisition, was performed during the fMRI scanning. Only the two plates on the tibia were used to estimate the tibia 3D position and the malleoli. Four additional markers were placed over the four metacarpi. Markers were always visible during ADF for all different conditions. The sampling frequency was set at 120 Hz.

Markers trajectories were analysed with a custom algorithm running in Matlab (MatlabR2010b) to obtain onsets and amplitude of ADF movements. In particular, for each leg, the ADF angle was calculated as follows: the mean points between the medial and lateral malleoli (mean malleolus) and between the medial and lateral metacarpi (mean metacarpus) were calculated. The ADF angle was taken as the angle between the line passing through the more proximal tibial marker and the mean malleolus and the line passing through the mean malleolus and the mean metacarpus [9].

2.8. fMRI Data Preprocessing. Imaging data were analysed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (MatlabR2010b). A skull stripping procedure, on the structural image for each subject, was performed to improve the coregistration of functional and structural images. Participants with right-sided infarcts (left-leg weakness) were flipped about the midsagittal line, such that all subjects were considered to have left-sided infarcts. All fMRI volumes were then realigned and unwarped to suppress task-related motion artefacts [19]. Realignment parameters were assessed for excessive motion after unwarping procedure. A threshold of 4 mm in translation and 5° in rotation was applied [20]. The skull stripped structural image was then coregistered to the mean image of the functional realigned volumes and segmented. The spatial normalization transformation (to the Montreal Neurological Institute (MNI) reference brain in Talairach space [21]) was then estimated using the segmented structural image. The structural image and functional volumes were normalized and resampled to 2 mm × 2 mm × 2 mm voxels. Functional

normalized images were then smoothed with an isotropic 8 mm full-width half-maximum kernel [22]. The time series in each voxel were high pass filtered at (1/128) Hz during subsequent modelling to remove low frequency confounding factors.

2.9. Statistical Analysis. Statistical analysis was performed in two stages using the standard summary statistic approach. In the first stage, functional images were analysed separately for each patient. We were interested in the analysis of brain regions active during each condition, (i) FV, (ii) V, (iii) FP, and (iv) P, as well as (v) their interaction, defined as (FV-V) versus (FP-P) which identifies regions in which the effect of FES is modulated by the presence or absence of volitional intent. From the kinematic measures, two ADF covariates were defined for each condition: onsets and amplitude covariates. All ADF onsets belonging to the same condition were defined as a single event type and modelled as delta functions in the corresponding stimulus function. The amplitude covariate was defined as a delta function scaled by the actual amplitude of each ADF for each condition, and it was mean corrected and orthogonalised with respect to the corresponding onset covariate [23]. All onset and amplitude stimulus functions were then convolved with a canonical hemodynamic response function, together with its temporal and dispersion derivatives [23], and used as regressors in a general linear model of the observed fMRI time series. Linear contrasts of parameter estimates were generated for each subject (i.e., contrast images) and used for the creation of statistical parametric maps at the second (between-subject) stage.

In the second stage, the following analyses were performed:

(i) One-sample t-tests were performed using appropriate contrast images for each condition to investigate the main effects of each condition in the stroke group.

(ii) Two-sample t-tests using appropriate contrast images for each subject were performed to examine the differences between patients and control subjects groups for each condition. Conjunction analyses (i.e., two separate null hypotheses to be contemporarily denied) were performed between groups for each condition to determine common activation.

(iii) Contrast images were entered into a regression analysis with subject-specific values for the carryover effect to investigate whether there are any areas in which pretreatment brain activity (in any of the conditions) correlates with the subsequent carryover effect of each patient.

Results of all second-stage analyses were thresholded at $p < 0.05$ corrected for multiple comparisons within specific regions of interest (ROIs). Our predefined area of investigation included the following seven areas bilaterally: leg primary motor (M1) and sensory (S1) cortices, secondary somatosensory area (SII), parietal rostroventral area (PR), supplementary motor area (SMA), premotor cortex (PM), and angular gyrus (AG). In particular, our predefined area of investigation included the following seven areas bilaterally: leg primary motor (M1) and sensory (S1) cortices, secondary somatosensory area (SII), parietal rostroventral area (PR), supplementary motor area (SMA), premotor cortex (PM), and angular gyrus (AG). Contralateral primary sensorimotor cortex (i.e., M1, S1) is the primary site of ADF control, and it has been shown to be the site of interaction between volitional intention and FES in healthy controls [9]. In turn, ipsilateral primary sensorimotor cortex has been demonstrated to be active for poststroke patients while executing simple motor tasks [24]. The two secondary somatosensory areas (cSII, i cSII) have been selectively linked to proprioceptive processing and integration [25], attention to proprioceptive stimuli [26], painful and nonpainful stimulus processing [27], and complex object manipulation [28]. Moreover, the secondary somatosensory area has been demonstrated to be active during stimulation nonselectively [9] and selectively [7] with respect to voluntary effort in controls. PR areas have been identified as potential sites of sensorimotor integration [25] by virtue of their anatomical connections with premotor and primary motor cortices [29]. PR area has been shown to have an activation pattern similar to SII and so might have a similar role in processing sensorial stimuli [9, 25]. Bilateral premotor and supplementary motor areas are a highly consistent finding after stroke during simple motor tasks execution [30]. Right AG has been demonstrated to be the site of self-representation of movement [7, 31], and it has been demonstrated to be more active during passive than active FES. Moreover, AG has been suggested to be the recipient of proprioceptive information encoded in the postcentral gyrus [32].

Based on previous work, ROIs were defined as follows using the MNI coordinates system. Primary motor (M1) and primary sensory cortices (S1) were defined as 10 mm spheres centred, respectively, on [$x = \pm 6$, $y = -28$, $z = 60$] and [$x = \pm 4$, $y = -46$, $z = 62$] [33]; bilateral secondary somatosensory cortices (SII) as 10 mm spheres centred on [$x = \pm 58$; $y = -27$; $z = 30$] [7, 34]; PR as 10 mm spheres centred on [$x = \pm 54$; $y = -13$; $z = 19$] [25]; SMA and PM were defined as 15 mm spheres centered, respectively, on [$\pm 20; -8; 64$] and [$\pm 8; -6; 64$] [34]. AG was anatomically defined using the WFU PickAtlas [35]. Anatomical attribution was performed by carefully superimposing the maxima of significant effects both on the MNI brain and on the normalized structural images averaged across all subjects and then labelling with the aid of the atlas of Duvernoy [36].

3. Results

3.1. Participants. The healthy control group was aged between 22 and 61 years [mean (standard deviation): 36 (14) years], comprising 8 male and 9 female subjects. Fourteen poststroke patients were recruited [range: 19–64 years, mean (standard deviation): 44 (14)], comprising 8 male and 6 female subjects. There was no significant difference between the groups in terms of age ($p = 0.15$). Patient characteristics along with the degree of functional recovery at the time of scanning as measured by the selected outcome measures are listed in Table 1.

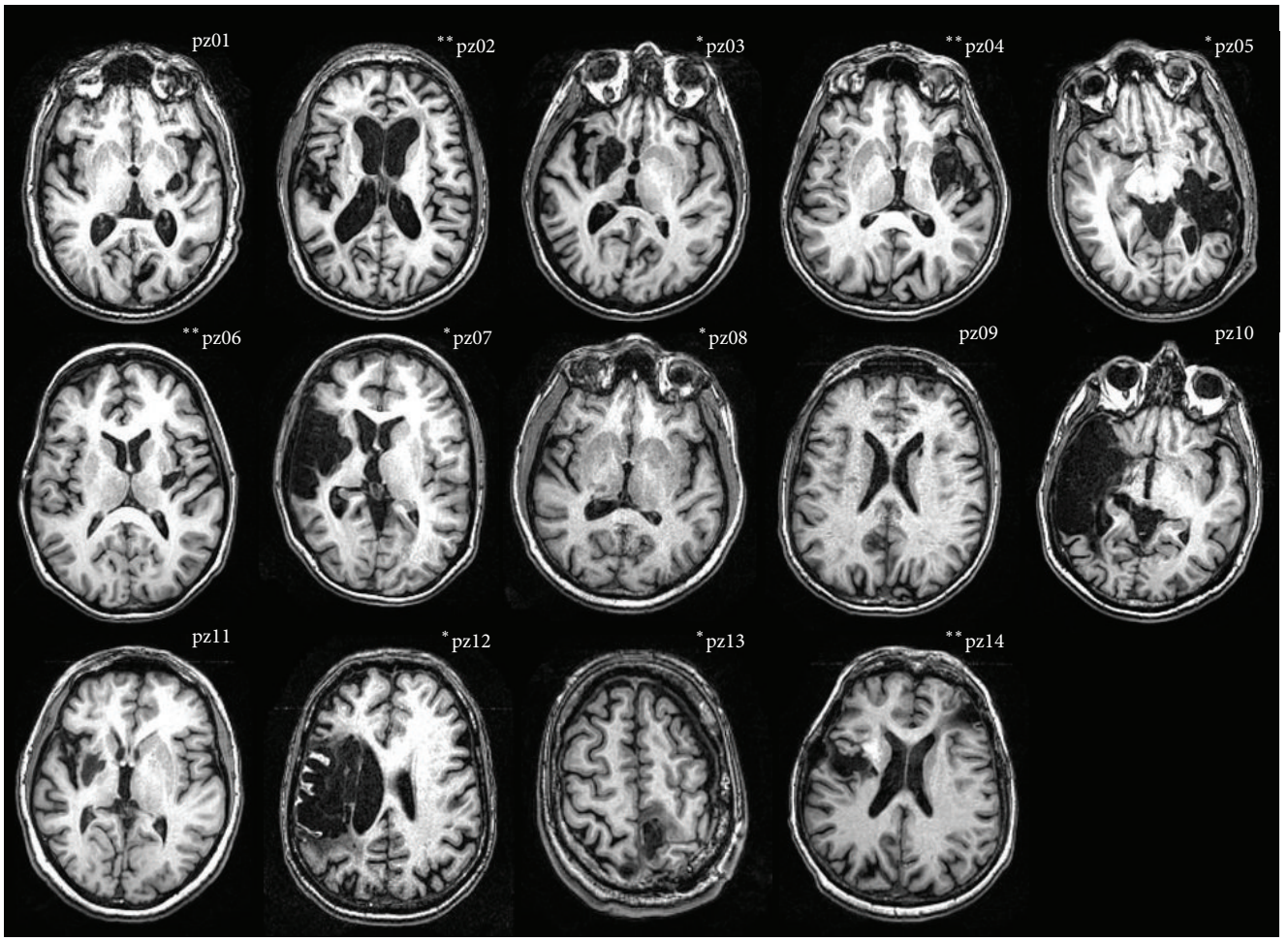

Figure 1: The site of cerebral infarction as determined from the T1-weighted structural MRI. ∗∗: patient with FES carryover (responder); ∗: patient with no FES carryover (i.e., nonresponder).

For eight patients, stroke resulted in left hemiparesis and for six in right hemiparesis. The site of cerebral infarction was determined from the T1-weighted structural MRI (Figure 1).

The carryover effect was not predicted by age, sex, side of the lesion (i.e., right/left), time since stroke acute event, the baseline impairment, and the type of device used for training, as determined by multiple linear regression.

Ten out of the fourteen patients completed the FES-based rehabilitation treatment, receiving the same dosage of therapy, and so we were able to assess the carryover effect in only a subgroup of participants (Table 1). A follow-up assessment was planned for all patients one month after the end of the treatment to check for long-term effects of carryover. Six patients were available for this extra visit, and the carryover effect presence/nonpresence was demonstrated to be stable for all patients but for one where the effect was no longer present [15]. The patients that did not complete the treatment/assessment were outpatients, and they discontinued the treatment for personal reasons, mainly linked to difficulties in logistically managing an everyday treatment in clinic or managing a further travel.

3.2. Kinematic Measures. Mean ADF amplitude across subjects along with its standard deviation for V condition was $18^\circ \pm 11^\circ$, for FV condition $20^\circ \pm 11^\circ$, for FP condition $18^\circ \pm 11^\circ$, and for P condition $21^\circ \pm 13^\circ$. All ADF angles for all subjects were within the 10°–70° interval [18].

3.3. Images Analysis. All controls and patients were able to perform the task adequately. No subjects displayed mirror movements at bedside observation or when performing the motor paradigm outside the scanner. However, a number of patients did exhibit synergistic contralateral ankle dorsiflexion during motor paradigm execution in the scanner (Table 1). However, a linear regression analysis with mirror movements (i.e., present/absent) as independent categorical variable and carryover effect as dependent variable demonstrated the independence of the two elements (p value = 0.4860).

Realignment parameters were assessed for excessive motion after unwarping procedure, and the maximum translational displacement was 0.27 mm in all directions and the maximum rotational displacement was 0.0029°.

Table 1: Patients characteristics.

Pz	Age [years]	Sex [male/female]	Site of lesion	Type of stroke	Time [months]	Gait velocity [m/s]	Endurance velocity [m/s]	Paretic step length [mm]	TAAI [0–1]	MRC [1–5]	Capacity Score	Mirror movements [condition]	Training device	Carryover effect evaluation
pz01	53	M	L GP	H	37	0.43	1.02	490	0.68	3	20.67	V	WalkAid	—
pz02	23	M	R MCA	H	23	0.64	0.82	486	0.60	3	20.30	No	WalkAid	Yes
pz03	38	F	R GP	I	23	0.25	0.28	194	0.48	2	8.15	V	Bioness	No
pz04	64	F	L MCA	H + I	13	0.32	0.50	345	0.56	3	14.33	No	WalkAid	Yes
pz05	19	M	L MCA	H	44	0.82	1.01	561	0.44	3	23.42	No	WalkAid	No
pz06	47	F	L GP	H	44	0.52	0.82	513	0.46	3	21.26	FV, V	WalkAid	Yes
pz07	25	F	R MCA	I	30	0.70	0.98	591	0.62	3	24.50	FV, V	WalkAid	No
pz08	46	M	R GP	I	13	0.49	0.58	420	0.43	3	17.31	FV, V	WalkAid	No
pz09	57	M	L caudate nucleus	I	6	0.33	0.50	310	0.70	2	12.97	No	Bioness	—
pz10	49	M	R MCA	I	89	0.33	0.58	340	0.65	2	14.26	V	WalkAid	—
pz11	45	F	R MCA	I	9	0.26	0.71	250	0.68	3	11.18	No	Bioness	—
pz12	57	M	R parietal sub. + BG	I	18	0.39	0.75	350	0.68	2	14.93	No	WalkAid	No
pz13	33	M	L parac. lobule	I	6	0.34	0.32	410	0.82	3	16.25	No	WalkAid	No
pz14	61	F	R MCA	H	158	0.40	1.36	430	0.69	2	18.50	No	WalkAid	Yes

Minimum to maximum scores (or units) are expressed under each outcome score. Pz: patient; M: male; F: female; R: right; L: left; MCA: middle cerebral artery; ACA: anterior cerebral artery; GP: Globus Pallidus; parac.: paracentral; sub.: subcortical; BG: Basal Ganglia; H: haemorrhagic; I: ischemic; time: time since stroke at the time of first assessment; TAAI: Tibialis Anterior Activation Index; MRC: Medical Research Council index; FV: fMRI protocol condition, attempted voluntary movement with concurrent FES; V: fMRI protocol condition, voluntary movement without FES.

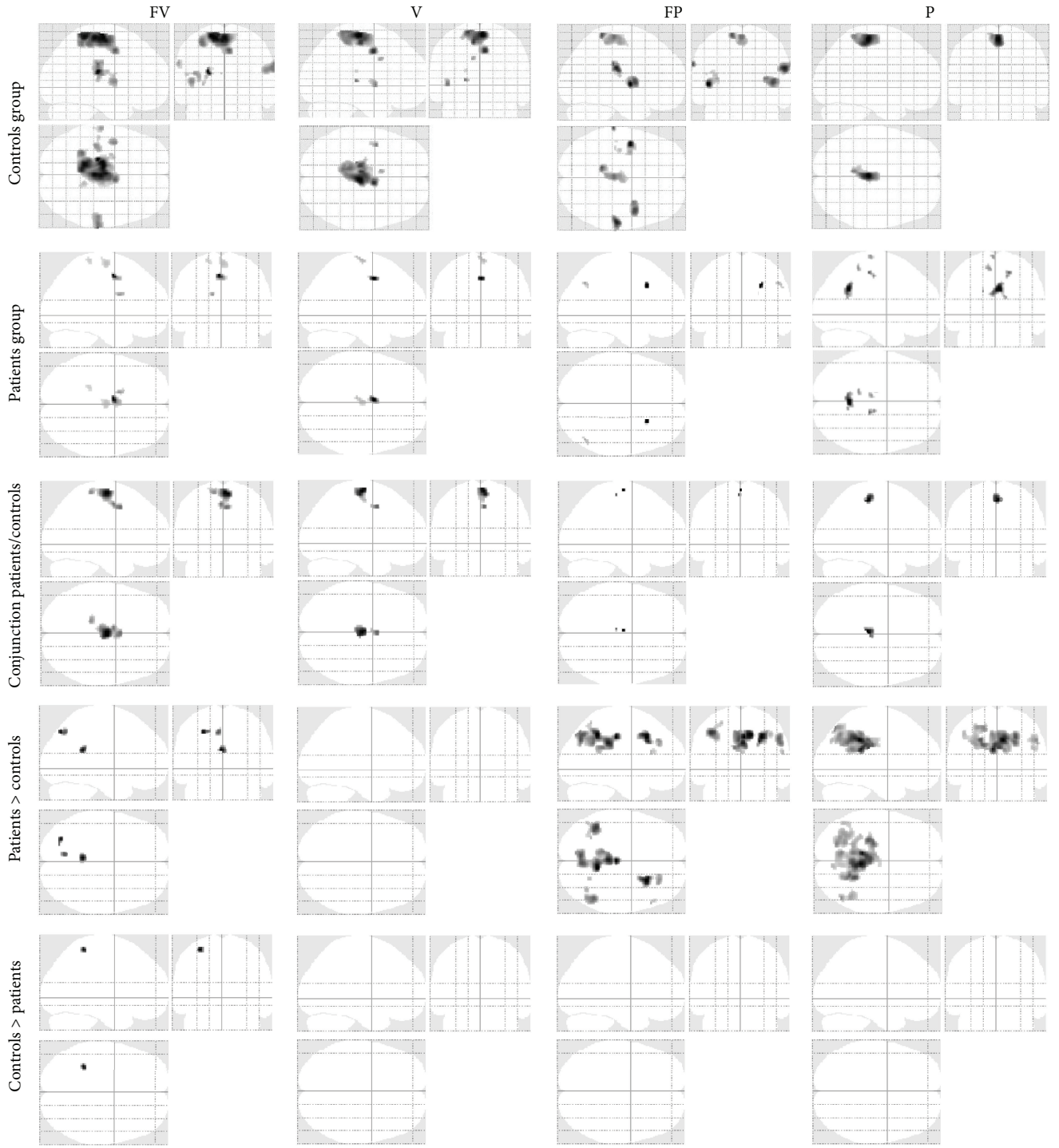

Figure 2: Activation maps for the experimental conditions. Regions active during each experimental condition (i.e., V, FV, FP, and P) in the controls and patients groups separately, as well as the conjunction analysis, and comparison between patients and controls. Statistical parametric maps (thresholded at $p < 0.001$, uncorrected for display purposes) showing regions activated in the four conditions using a maximum intensity projection format.

Figure 2 shows brain regions active during each condition (i.e., V, FV, FP, and P) in the controls and patients groups separately, as well as the conjunction analysis, and comparison between patients and controls:

(i) Patient group: as reported in Table 2, patients show task-related activation in primary and secondary sensorimotor areas, in contralateral paracentral lobule [37], bilateral frontal cortex, cingulate gyrus,

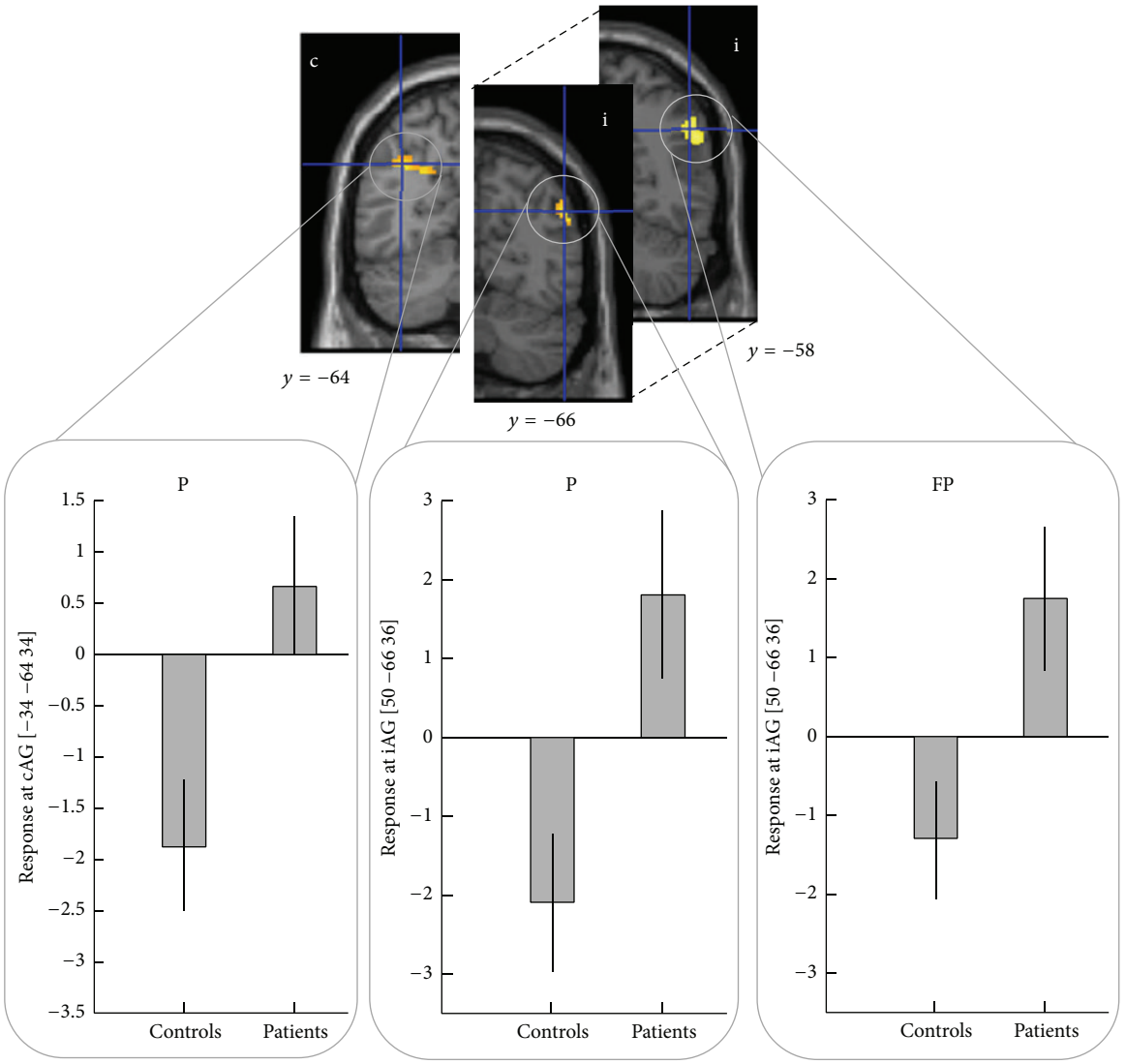

Figure 3: Brain responses in controls and patients groups in angular gyrus (AG). P: passive experimental condition; FP: FES passive experimental condition; c: contralateral; i: ipsilateral.

precuneus, and supramarginal gyrus. AG area is only activated by patients, ipsilaterally in FP condition, and contralaterally shows an interaction between design factors (i.e., volitional intention and FES).

(ii) Patients versus healthy controls: controls show clear activation in all conditions in motor and somatosensory areas known to be involved in ADF execution and in accord with previous studies [7, 9, 18], as expected. Patients and controls primarily show common activation in bilateral sensorimotor (all conditions) and supplementary motor (for conditions where volitional intention is present: FV, V) areas. However, compared to the control group, patients tend to overactivate right AG when there is no volitional intention to move (i.e., FP, P conditions) and left intraparietal sulcus during passive movement (Figure 3).

(iii) Prediction of carryover effect in patient group: in those patients with carryover after FES, contralateral SMA was more active during stimulation and voluntary conditions (FV, V, and FP conditions), and ipsilateral M1 was more active during voluntary movement (V condition). In those without carryover effect, we saw a greater interaction between factors, that is, (FV-V) > (FP-P) in contralateral AG. By looking at the response for the peak voxel for cSMA, iM1, and cAG areas (Figures 4(a)–4(c)), it can be seen that patients who experienced the carryover effect have responses in SMA and M1 that correspond to healthy controls, whilst responses in these regions in patients without carryover are diminished. Conversely, the interaction between factors in contralateral AG is seen only in those without carryover but not in those with carryover or healthy controls. In other words, we see quite consistent separation of those with and

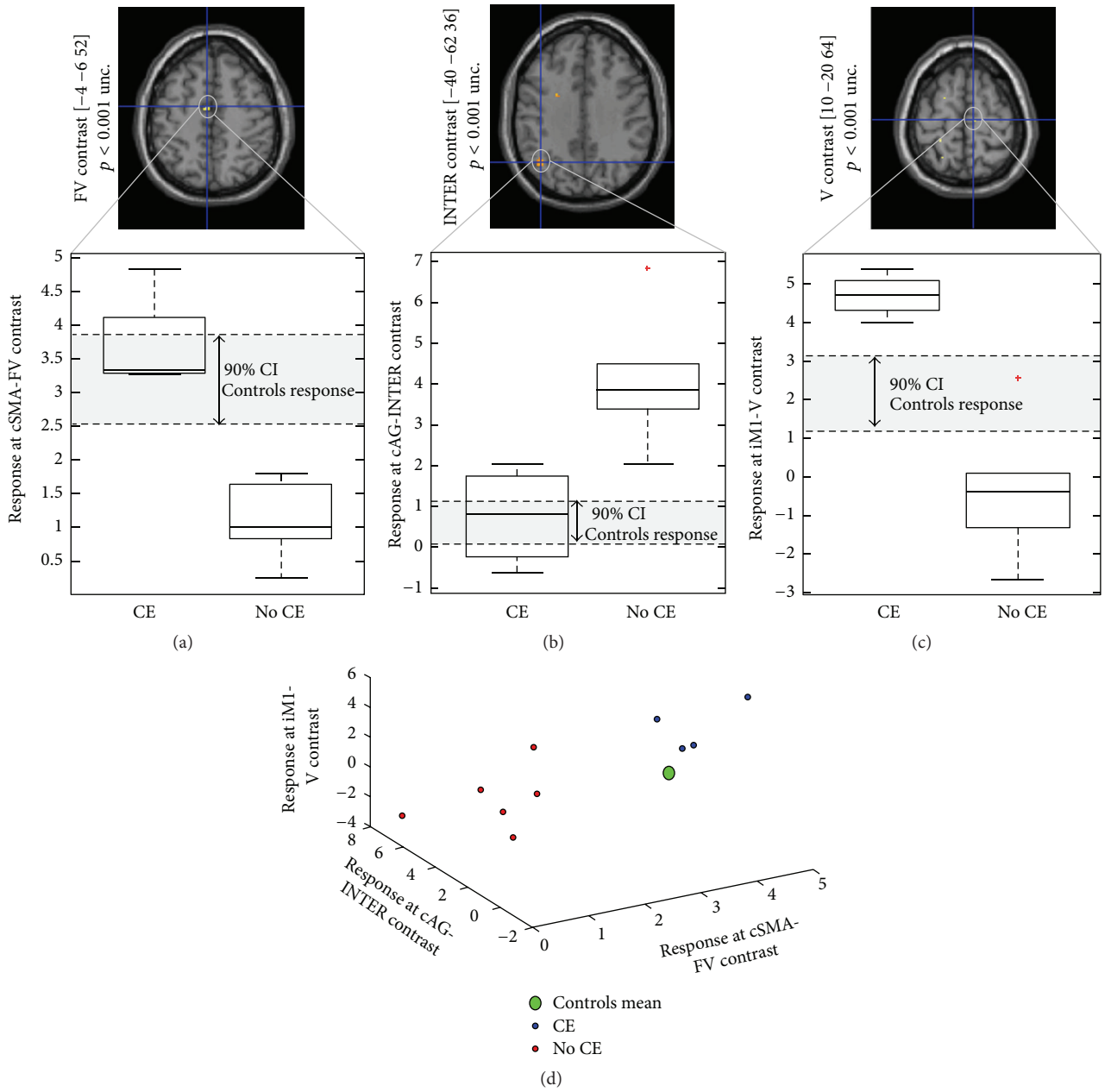

Figure 4: Separation of patients with and without carryover effect on the basis of the brain responses. Response for the peak voxel for cSMA (a), cAG (b), and iM1(c) areas in patients who experienced/did not experience the carryover effect. (d) 3D representation of the responders/nonresponders groups on the basis of brain responses. CE: patients group with FES carryover (responders); non-CE: patients group with no FES carryover (nonresponders); FV: FES with volitional contribution; INTER: interaction contrast; V: volitional ankle dorsiflexion; SMA: supplementary motor cortex; M1: primary motor cortex; AG: angular gyrus; c: contralateral; i: ipsilateral.

without FES carryover on the basis of the brain responses in these regions (Figure 4(d)). In particular, those with FES carryover appear to have "normal" responses, whilst those without do not.

4. Discussion

A prolonged carryover effect from FES is a desirable rehabilitation outcome. Knowing who is most likely to achieve this and how would be useful in a stratified rehabilitation strategy. The motivation for this study was therefore to explain how a peripheral stimulus can facilitate long-term motor relearning (i.e., FES carryover) after a lesion in the central nervous system [6, 38]. It has been suggested that the mechanism of FES carryover is central in origin [6], but this has never been tested in neurological patients. In this study, we have used functional brain imaging to examine brain responses to key components of FES (electrical stimulation and attempted volitional movement, both separately and

Table 2: Brain regions activation.

	MNI coordinates			Z	Side	ROI
	x	y	z			
(i) Patients group						
V > Rest	−2	−2	46	4.24*	i	Cingulate g.
	2	−18	70	3.32*°	i	SMA
	0	−16	70	3.31°	c/i	SMA
	−4	−24	74	3.31*	c	Parac. lobule
	4	−20	62	2.98°	i	M1
	−6	−4	50	5.06*°	c	SMA
FV > Rest	−14	4	24	3.88*	c	Caudate nucleus
	−20	−36	70	3.34*	c	Postcentral g.
	−4	−20	72	3.09*	c	Parac. lobule
FP > Rest	24	18	36	3.81*	i	Sup. front. g
	48	−66	40	3.29*	i	AG
	52	−62	36	3.16°	i	AG
P > Rest	2	−52	32	4.12*	i	Cingulate g.
	10	−55	22	3.40*	i	Precuneus
	16	−26	52	3.66*	i	SMA
	−10	−40	58	3.47*	c	S1
	−6	−24	54	3.46*	c	Parac. lobule
	−2	−30	54	3.28°	c	M1
	0	−28	54	3.23°	c/i	M1
	0	−62	40	4.41*	c/i	Precuneus
INTER	−42	−64	40	3.30*	c	AG
	−44	−58	36	3.20*	c	AG
	10	−54	28	3.20*	i	Precuneus
(ii) Conjunction between patients group and healthy control group						
V > Rest	2	4	46	4.62*	i	SMA
	2	−16	66	4.07*°	i	SMA
	4	−20	62	3.92°	i	M1
	0	−22	64	3.76°	c/i	M1
	0	−4	46	3.26*	c/i	Cingulate g.
	0	−12	54	3.23°	c/i	SMA
FV > Rest	2	−14	64	4.36*°	i	SMA
	6	−12	64	3.85°	i	PM
	6	−20	64	3.83°	i	M1
	−2	−20	64	3.80°	c	M1
	2	4	46	3.74*	i	SMA
	−4	−6	50	3.69*°	c	SMA
	−14	−36	66	3.56*	c	Parac. lobule
	64	−22	28	3.30°	i	SII
FP > Rest	−2	−14	68	3.13*	c	Parac. lobule
	−4	−24	62	3.11*°	c	M1
	−2	−30	54	3.78*°	c	M1
P > Rest	0	−28	56	3.73°	c/i	M1
	4	−24	58	3.38*°	i	M1
	−10	−40	58	3.35*°	c	S1
	−4	−22	68	3.31*	c	Parac. lobule
INTER	0	−60	40	3.26*	c/i	Precuneus
(ii) Patients group > healthy control group						
FV > Rest	−4	−44	22	3.73*	c	Cingulate g.
	−28	−74	46	3.65*	c	Supramarg. g.
	−8	−70	44	3.48*	c	Precuneus

Table 2: Continued.

	MNI coordinates			Z	Side	ROI
	x	y	z			
FP > Rest	26	18	40	4.50*	i	Sup. front. g.
	10	−50	42	4.49*	i	Precuneus
	2	−22	40	4.46*	i	Cingulate g.
	−42	−52	46	4.15*	c	Supramarg. g.
	50	−58	36	3.71*°	i	AG
	28	34	34	3.61*	i	Middle front. g.
	20	34	30	3.53*	i	Sup. front. g.
	56	24	38	3.42*	i	Inf. front. g.
	38	−64	44	3.41*	i	AG
	−28	−58	58	3.34*	c	Sup. parietal g.
	−46	−52	44	3.31*	c	Supramarg. g.
P > Rest	6	−40	36	5.26*	i	Cingulate g.
	−4	−32	30	4.68*	c	Cingulate g.
	50	−66	36	3.94*°	i	AG
	−34	−64	34	3.77°	c	AG
INTER	16	−54	26	3.60*	i	Precuneus
	−50	18	36	3.52*	c	Middle front. g.
	−40	−22	40	3.44*	c	Postcentral g.
	−18	28	46	3.39*	c	Sup. front. g.
(ii) Healthy control group > patients group						
FV > Rest	−32	−44	60	3.81*	c	Sup. parietal g.
(iii) Responders > nonresponders						
V > Rest	−6	−4	50	3.62*°	c	SMA
	−22	−38	66	3.62*	c	Postcentral g.
	10	−20	64	3.15°	i	M1
FV > Rest	−4	−6	52	3.70*°	c	SMA
FP > Rest	−2	−10	66	3.81*°	c	SMA
	−34	48	14	3.36*	c	Middle front. g.
P > Rest	46	−10	18	3.45*	i	Rolandic operc.
	30	−42	50	3.74*	i	Supramarg. g.
(iii) Nonresponders > responders						
INTER	−40	−62	36	4.32*°	c	AG
	−20	−24	64	3.24*	c	Precentral g.
	10	−16	68	3.47*	i	SMA
	−36	0	48	4.53*	c	Precentral g.
	22	6	46	3.69*	i	Sup. front. g.
	−10	−2	52	3.38*	c	SMA
	−16	−6	70	3.58*	i	Sup. front. g.
	−32	−26	46	3.62*	c	Postcentral g.

°Significant activation at Familywise Error (FWE) corrected $p < 0.05$ within predefined regions of interest. *Significant activation at uncorrected $p < 0.001$. ROI: region of interest; FV: fMRI protocol condition, attempted voluntary movement with concurrent FES; V: fMRI protocol condition, voluntary movement without FES; FP: fMRI protocol condition, FES-induced movement, with no attempt to move the ankle; P: fMRI protocol condition, passive movement (by the experimenter) of the subject's ankle without FES; c: contralateral side; i: ipsilateral side; g.: gyrus; parac.: paracentral; sup.: superior; front.: frontal; supramarg.: supramarginal; inf.: inferior; operc.: operculum; SMA: supplementary motor area; M1: primary motor cortex; AG: angular gyrus; S1: primary somatosensory cortex; PM: premotor cortex; SII: secondary somatosensory cortex.

in combination) that characterise those who exhibit the carryover effect. These characteristics might be considered as biomarkers for successful FES-based rehabilitation after stroke.

Our results point to supplementary motor area (SMA) and angular gyrus (AG) as key regions involved in mediating the carryover effect, since they are differentially active during the key components of FES in those patients with and without carryover. It is first worth considering the normal roles of SMA and AG in sensorimotor tasks. SMA is linked to movement preparation and planning and is often noted to be overactive compared to controls during attempted movement in chronic stroke subjects [39]. Indeed, in our patients, SMA is bilaterally active during conditions where volitional intention is present (i.e., FV, V), as expected. In turn, AG appears to be a recipient of proprioceptive information and a specific area for somatosensory calculation of the reach vector during upper limb reaching [32]. AG processes discrepancies between intended action and movement consequences in such a way that these will be consciously detected by the subject. It has been suggested that AG is activated during intersensory conflicts that may result in a loss of body ownership [31, 40]. On the other hand, damage to AG results in altered awareness of voluntary action [41].

Our results show that those with and without FES carryover have opposite patterns of activity in SMA and AG. In particular, those who have FES carryover exhibit SMA activation during concurrent FES and volitional movement (i.e., FV condition), but they do not show an interaction between FES and volitional movement in AG. In both instances, the neural responses to key elements of FES are more like a normal healthy subject, whereas those without carryover have "abnormal" responses in both SMA and AG (Figure 4). We therefore suggest that the carryover effect is mediated through movement prediction (SMA area) and sense of agency/body ownership (AG area). Specifically, the concept of sense of agency appears to be neuroanatomically associated with primary [31] and secondary [42] sensorimotor areas. The prediction of the sensory consequences of a self-generated action is compared against the actual sensory consequences, where stronger correspondence is associated with a stronger experience of agency (i.e., self-generated action). In other words, those with FES carryover correctly plan the movement when executing the movement with concurrent volitional intention and FES, and as a consequence movement is perceived as self-generated. By doing so, the patient correctly updates the motor control loop [43] that likely enhances a long-term potentiation effect following Hebbian principles. Indeed, the combination of volitional effort and the perception of a "normally" completed movement provides somatosensory feedback that facilitates Hebbian-like plasticity [44]. This is in line with the suggestion that gradual motor learning/adaptation might be also mediated by extracerebellar mechanisms [45] and that the generalization of learning (in particular adaptive learning) is improved when the nervous system assigns errors to "self" rather than the environment [46] or, in this case, the device.

In healthy control subjects, the interaction between volitional intent to move and proprioception was mediated by primary motor and somatosensory areas [9]. In our poststroke patients, bilateral primary sensorimotor cortices are active under all conditions but are not differentially activated by our experimental factors. The function of primary sensorimotor cortices role in mediating the FES effect might therefore be supported by secondary areas, representing a plasticity mechanism that exploits available resources [47]. In fact, it has been repeatedly shown that normal input/output processes of primary sensorimotor cortices are impaired in many neurological patients, with consequent recruitment of a complex network that includes primary and secondary areas to generate even simple motor tasks [34, 48].

The other predefined areas of investigation do not appear to be crucial nodes for mediating FES carryover. In particular, although premotor areas are known to be overactive in many stroke patients [46], they do not appear to be crucial for our patients during ADF, being only ipsilaterally active in FV condition. It has been suggested that the human SI and SII cortices may be sequentially activated within one hemisphere, whereas SII ipsilateral to the stimulation may receive direct input from the periphery, at least when normal input from SI is interrupted [49]. In our control group, bilateral SII was active for the FES conditions (i.e., FV, FP), possibly as the direct recipient of the stimulus [8, 50]. In patients, we observed only ipsilateral SII activation, which preserves its presumed role of processing electrical stimulation as in healthy controls [9, 49, 50]. On the other hand, we suggest either that contralateral SII is not primarily involved in somatosensory information processing or that contralateral stimulus processing is impaired in our group of patients.

An important limitation of this study was the inability to collect data from the cerebellum due to technical constraints. We tried to overcome this limitation as far as we could, by training the subjects outside the scanner so that they were familiar with the stimulus during FES conditions. However, the cerebellum is thought to be part of the motor control loop, and it has been shown to be differentially involved during FES supported and nonsupported by volitional contribution [7]. Moreover, computing predictions of sensory consequences is seen in the literature as a major role of the cerebellum (together with the parietal cortex) within the sensory-motor control loop [51]. Further, the focus of this work was comparing the patients who show carryover effect against those who do not after the identical treatment based on FES. In this view, a group of patients with no treatment was not included as this was beyond the purpose of the current study. The number of recruited patients was limited, but nevertheless the results reported are statistically robust and point towards a biological basis for the carryover. Further larger prospective studies are recommended to explore those aspects.

5. Conclusions

In conclusion, we suggest that the mechanism of action of FES carryover is based on movement prediction and sense of agency/body ownership. In other words, the ability of a patient to plan the movement and to perceive the stimulation as a part of his/her own control loop is important for the FES carryover effect to take place. Although we

point to abnormal responses in SMA and AG as indicators that FES carryover effect is unlikely, it might be that in future a behavioural questionnaire devoted to the evaluation of self/non-self-perceived FES-induced movement might be useful in predicting the carryover effect in routine clinical settings.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Review Article

Models to Tailor Brain Stimulation Therapies in Stroke

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A great challenge facing stroke rehabilitation is the lack of information on how to derive targeted therapies. As such, techniques once considered promising, such as brain stimulation, have demonstrated mixed efficacy across heterogeneous samples in clinical studies. Here, we explain reasons, citing its one-type-suits-all approach as the primary cause of variable efficacy. We present evidence supporting the role of alternate substrates, which can be targeted instead in patients with greater damage and deficit. Building on this groundwork, this review will also discuss different frameworks on how to tailor brain stimulation therapies. To the best of our knowledge, our report is the first instance that enumerates and compares across theoretical models from upper limb recovery and conditions like aphasia and depression. Here, we explain how different models capture heterogeneity across patients and how they can be used to predict which patients would best respond to what treatments to develop targeted, individualized brain stimulation therapies. Our intent is to weigh pros and cons of testing each type of model so brain stimulation is successfully tailored to maximize upper limb recovery in stroke.

1. Introduction

Stroke is a leading cause of long-term adult disability [1]. Of its 7 million survivors in the United States, a majority require help with self-care and report restriction in daily activities [2, 3]. Chronic paresis of the hemiplegic upper limb is at the core of stroke-related disability because >78% patients never reach age-based norms, and 67% perceive upper limb disuse disabling despite rehabilitation [4, 5]. Several adjunctive therapies have been proposed to maximize and accelerate rehabilitative outcomes of the upper limb. One of the most popular techniques involves stimulating the motor cortices. Stimulation can be applied using invasive, implanted electrodes [6] or noninvasive techniques that deliver currents via electromagnetic induction (transcranial magnetic stimulation, TMS) or direct current application over the scalp and skull (transcranial direct current stimulation, tDCS) [7, 8]. The essential premise is that electrically stimulating the motor cortices could serve to potentiate plasticity that underlies recovery of the paretic upper limb [7, 9–19]. Several studies have demonstrated promise of brain stimulation towards affecting recovery. Therapeutic effect sizes range anywhere from 10% to even 30% relative to baseline [7].

Despite the promise, neither invasive nor noninvasive stimulation is used in outpatient clinical settings. The approach has shown mixed efficacy in recent clinical studies [6, 15, 17, 20, 21]. A key limitation, as is believed, is the use of generic, unvarying methodology; given the heterogeneity

that is characteristic of stroke, several groups acknowledge that a one-type-suits-all methodology would naturally be variable [15, 16, 22]. Ward et al. best summarize a potential solution [23]: "Stroke patients are a heterogeneous group. By explaining this heterogeneity between stroke patients in terms of measurable parameters, it should be possible to predict the response to treatments with known mechanisms and therefore to target individuals appropriately." It is in this context that the present report seeks to propose potential frameworks and models that could help stratify patients for tailored or personalized cortical stimulation therapies. In the absence of prospective data, hypotheses here are still conceptual, hence by no means complete to represent possible means to personalize stimulation.

The present report arrives at a discussion of the potential frameworks to tailor stimulation by discussing the following pieces of evidence:

(1) What is the existing approach to cortical stimulation in stroke?

(2) When, and why, does the existing approach fail?

(3) What are the likely alternate approaches to support recovery?

(4) How does one determine the alternate substrate that would most likely benefit an individual's recovery?

2. What Is the Existing Approach to Stimulation in Stroke?

The current approach believes that plasticity of the primary motor cortex (M1) in the ipsilesional (affected) hemisphere most impacts recovery and that intact, contralesional cortices (in the unaffected hemisphere) compete with and inhibit ipsilesional plasticity [13, 24–29]. Therefore, the approach calls for facilitating excitability of ipsilesional M1 and suppressing excitability of contralesional M1. The premise that plasticity of residual M1 supports recovery and intact contralesional cortices inhibit ipsilesional plasticity emerges from two critical sources of evidence.

2.1. Evidence That Ipsilesional M1 Is Central to Plasticity for Stroke Recovery. M1 is considered the most critical part of the executive motor system adapted especially for selectively activating muscles involved in skilled upper limb motor behavior [30, 31]. Tremendous neurophysiologic and neuroimaging evidence has helped formulate the premise. Two landmark investigations have presented some of the earliest accounts of how plasticity of M1 underlies recovery in stroke. Nudo and colleagues demonstrated in nonhuman primate models of stroke that over the course of spontaneous recovery and learning-based skill training territories within ipsilesional M1 remap [32, 33]. Territories devoted to different parts of the upper limb were mapped at first using intracortical microstimulation (ICMS). After an infarct destroyed a substantial portion of the territories devoted to the distal forelimb, Nudo and colleagues witnessed functional remapping in M1. Residual representations devoted to the distal forelimb diminished while their territories came to be occupied by representations of the more proximal and less-affected elbow/shoulder segments during the course of spontaneous recovery [32]. When animals were trained on skilled tasks involving the affected distal forelimb, however, M1 remapped differently. This time residual distal forelimb representations expanded into territories occupied previously by the proximal forelimb [32–34]. Such rapid shifts in peri- and ipsilesional territories of M1 that have the potential to reverse sequela of disease have become the most popular substrate to target with cortical stimulation.

Evidence from functional neuroimaging reinforced these early theories derived from neurophysiology. Serial functional MRI (fMRI) or Positron Emission Tomography (PET) revealed how activation patterns evolve in humans from hyperacute to chronic poststroke recovery, speaking to the importance of ipsilesional M1 [35–37]. fMRI and PET capture real-time activity of the brain during movement of the paretic limb. As individuals recover hand function, activation becomes localized to ipsilesional sensorimotor cortex and ipsilesional M1; individuals with incomplete recovery, however, continue to demonstrate bilateral and contralesional activation ipsilateral to the moving paretic limb [35]. From these studies a consensus emerged that boosting plasticity within ipsilesional M1 could profoundly impact recovery.

Besides cortical activation, evidence pertaining to physiologic excitability and output of pathways too validated the role of ipsilesional M1 in recovery of the paretic upper limb. One can typically capture excitability and output of pathways from M1 using transcranial magnetic stimulation (TMS) [38–40], akin to ICMS in animal models. TMS is applied to a single site or to a grid of several sites. With rehabilitation, typically, excitability and output would improve thresholds to activate residual pathways that would decrease; map/grid sites devoted to paretic muscles would increase, and excitability of interneuronal circuits within ipsilesional M1 would increase [38–43]. Therefore, the current standard of cortical stimulation emphasizes boosting excitability of ipsilesional M1 and its pathways to the paretic limb to boost benefit from rehabilitative therapies.

2.2. Evidence That Contralesional Cortices Oppose Recovery. While evidence favoring the significance of ipsilesional M1 was becoming prominent, evidence for the negative influence of contralesional cortices was also emerging. Classical studies of functional imaging demonstrated that activation of contralesional motor cortices accompanied movement of the paretic limb in patients with incomplete recovery [35, 37, 44–46]. Landmark neurophysiologic studies validated the claims. In a study that employed bihemispheric TMS, where TMS to contralesional M1 was applied a few milliseconds prior to TMS to ipsilesional M1, Murase et al. explained how contralesional M1 inhibited output from the ipsilesional M1 via transcallosal effects [24]. Conditioning pulses to contralesional M1 suppressed activity evoked in paretic muscles with TMS to ipsilesional M1. Greater suppression was associated with poorer recovery of the paretic limb. While it should be remembered that Murase et al. studied patients who were recovered enough to perform distal finger motor task, their study of interhemispheric inhibition set one of the strongest bases for present-day brain stimulation therapy. Evidence that

in a group of relatively well-recovered patients the contralesional M1 levies strong, persistent inhibition upon ipsilesional M1 via callosal interactions has shaped our current philosophy of stroke motor recovery and underlying neurophysiology. As such, the current standard of cortical stimulation emphasizes inhibiting excitability of contralesional M1 to disinhibit and boost output of weak, ipsilesional M1.

Taken together, several lines of evidence from animal and human studies, based on neurophysiology and neuroimaging, have informed the basis of current standard for cortical stimulation therapy. The current standard is based on the model of interhemispheric inhibition, the idea that ipsilesional M1 is central to most impactful plasticity while its homologue opposes recovery via transcallosal interactions in relatively well-recovered patients. Therefore, the current standard seeks to restore interhemispheric balance to maximize recovery by boosting excitability of ipsilesional M1 and inhibiting excitability of contralesional M1.

3. When and Why Does the Existing Approach Fail?

If ipsilesional M1 is a critical resource for plasticity and contralesional M1 opposes recovery, then why does the current standard of stimulation fail to benefit many? The answer we believe lies in the nature of stroke-related injury and consequent effects on physiology that deviate from classical tenets of the model of interhemispheric inhibition.

3.1. The Nature of Stroke-Related Injury. Ipsilesional M1 or its corticospinal pathways are damaged in ~96% of patients experiencing a typical middle cerebral artery stroke [15, 16, 47–50]. In fact, damage is so extensive in 58–83% of patients that stimulating ipsilesional M1 fails to evoke a response in muscles of the paretic upper limb [6, 16, 50]. It is thus not surprising that patients with extensive damage and deficit respond poorly to stimulation of ipsilesional M1, whereas outcomes are fairly homogenous and promising in those with minimal damage and impairment [23, 38, 46, 51–54]. This discrepancy may also explain why stimulating ipsilesional M1 is found to be frequently effective in smaller pilot studies [25, 55] than in large-scale pivotal trials [6, 17]. For instance, invasive stimulation of ipsilesional M1 was witnessed to be advantageous for rehabilitative outcomes in phase I/II studies [48, 49, 55], but benefits failed to translate into later phase III pivotal trial [6]. It was reasoned that a majority of patients in the early trials had preserved pathways where stimulation of ipsilesional M1 could evoke movements in the paretic limb, but the phase III study enrolled a majority without evidence of such sparing [16, 50]. Along similar lines, when damage to the territory of ipsilesional M1 is considered in different studies, benefits become weak and variable with cortical lesions affecting the ipsilesional territory [56, 57]. As such, since large-scale studies include larger number of patients with heterogeneous damage and disability, variability in lesions and degree of injury to ipsilesional M1 and pathways weakens the effectiveness standard stimulation. Since the presumed substrate for plasticity, and the target for current stimulation therapies, ipsilesional M1, is affected most commonly in typical injuries, a singular approach to stimulation would inevitably be variable in affecting recovery [16, 22].

3.2. Challenges to the Classical Model of Interhemispheric Inhibition. The current standard also varies because its underlying model, the model of interhemispheric inhibition, deviates under many circumstances. For example, recovery in subacute, subcortical stroke is associated with gains in ipsilesional excitability, but interhemispheric inhibition remains stable and symmetric. Stinear et al. studied patients with subcortical stroke who had experienced no damage to the cortical territory of ipsilesional M1; in such cases, the most notable contribution to recovery came from gains in ipsilesional excitability [58], while interhemispheric balance was not disrupted, nor did it evolve with recovery. The model also fails to explain why inhibiting excitability of affected motor cortices reduces hypertonicity and improves function of the paretic upper limb, when according to the model facilitating excitability would be expected to have such an effect [59]. The model also does not explain why inhibiting excitability of contralesional M1 reinstates deficits of the paretic upper limb in patients with greater impairment [60]. It becomes conceivable that contrary to the model's premise, which originated in relatively well-recovered patients, interhemispheric inhibition from contralesional motor cortices is not significant in patients with greater impairment of the paretic limb. The model also appears to deviate based on the extent and nature of injury and behavioral influences. For instance, learned "nonuse" of the paretic limb and injury to cortical γ-amino butyric acid (GABA) interneurons that interact with callosal neurons affects interhemispheric inhibition and alleviation of inhibition with recovery. After stroke, patients typically learn to rely on use of their nonparetic limb in order to compensate for failures they experience with the use of the paretic limb, which exaggerates "learned nonuse" of the paretic limb and hampers recovery. Blicher et al. offered rehabilitative therapy, where they required patients to focus on using their paretic upper limb during restraint of the nonparetic limb [61]. They found that GABA levels and interhemispheric inhibition decreased after therapy, in association with functional improvement, but changes were individual-specific. Patients with greatest nonuse and those with high interhemispheric inhibition experienced greatest decreases in GABA and tremendous gains in therapy. Patients with damage to GABA neurons in the ipsilesional cortices did not show gains with therapy.

Therefore, the current standard of stimulation fails to benefit many patients likely because ipsilesional M1 and its pathways are commonly injured, which affects the ability to facilitate ipsilesional excitability. Additionally, the model of interhemispheric inhibition deviates in the presence of subcortical injuries, learned nonuse of the paretic limb, and loss of GABAergic interneurons, which weakens the basis of standard stimulation therapy.

4. What Are the Likely Alternate Sources That Could Support Recovery?

Even though M1 is considered critical to the executive motor system [30, 31], scope for its plasticity is remarkable only

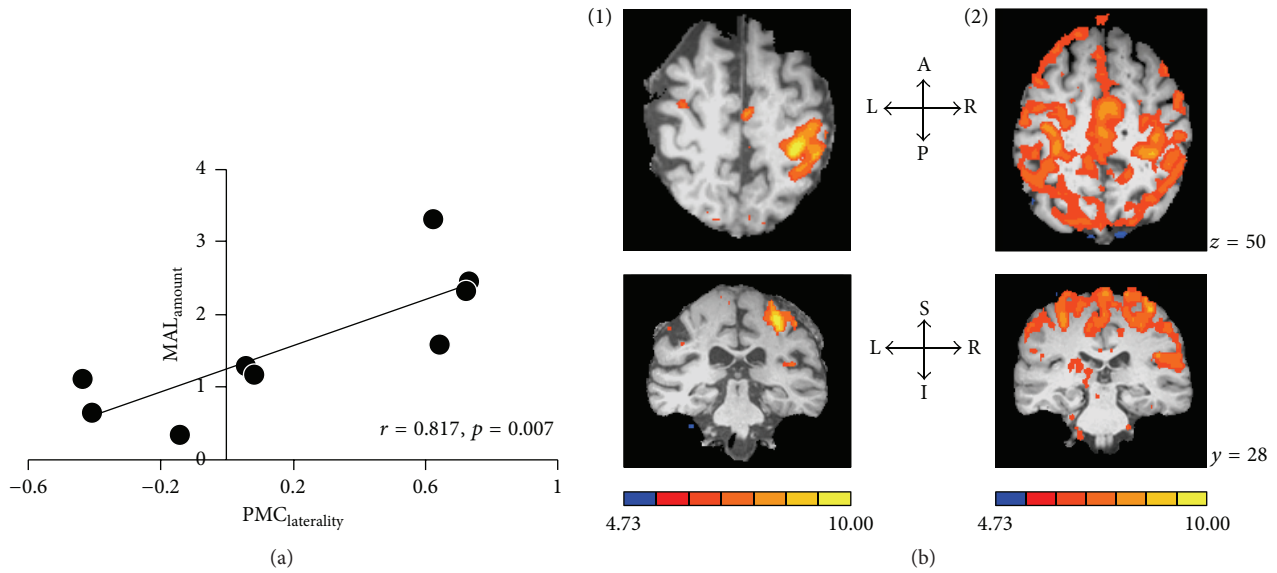

Figure 1: Role of ipsilesional premotor areas: from our work in Cunningham et al. [38]. PMC: premotor cortex (synonymous with PMd here); MAL: motor activity log. The figure explains the potential of ipsilesional higher motor areas including ipsilesional PMd in recovery. Patients with wide-ranging baseline impairments undergo functional MRI during movement of the paretic hand. Activation of ipsilesional versus contralesional cortices is computed using a laterality index, where a higher positive value suggests cortices contralateral to the paretic limb are activated. (a) demonstrates that patients who show better laterality for PMd, that is, greater activation of ipsilesional versus contralesional PMd (x-axis), perceive less disability in using their paretic hand (y-axis). Perception of disability is signified using a popular scale, known as MAL. Values on MAL range anywhere from 0 to 5, where 5 signifies no disability in the use of the paretic hand. (b) presents an illustration of subjective examples. Two patients, labeled 1 and 2, underwent fMRI during movement of their paretic hand. Images show fMRI activation in transverse (top) and coronal (bottom) planes. For simplicity, the lesioned hemisphere is shown to the right of each image. Patient 1 demonstrates focused activation of ipsilesional PMd that coincides with greater laterality, while patient 2 shows weaker laterality because activation of most regions is bilateral. MAL scores for patients 1 and 2, respectively, are 2.3 and 0.66. Therefore, patient 1 who perceived lesser disability in using the paretic hand showed greater activation of ipsilesional PMd, though patient 2 with extreme perception of disability activated multiple other regions. Patients who recover, albeit incompletely, can rely on plasticity of their ipsilesional premotor areas.

in patients without significant injury, while, in patients with damaged M1 or pathways, alternate sources can express plasticity to contribute to recovery. Since motor cortical areas can act in parallel to generate and control distal limb movements [30], it becomes conceivable that they have the ability to substitute for each other in cases of injury. As such, when standard stimulation fails, alternate areas may serve as new sources of recovery. These areas include the following.

4.1. Ipsilesional Premotor Areas. Alternate substrates for plasticity typically include higher-order ipsilesional regions, like premotor and supplementary motor cortices (PMC and SMA) [51], known collectively as premotor areas. Their plasticity can be meaningful [62–64] because they constitute more than 60% of the frontal cortex projecting to the spinal cord [65]. Although originally it was believed that they do not contribute to corticospinal pathways [26], Dum and Strick [65] showed these areas contribute ~40% of pathways to the hand, independently of M1. And even though only a small number of premotor pathways are actually connected to spinal interneurons for finger muscles and their cortical cells have smaller muscle field size, their contribution still matches or exceeds contribution from M1 [65, 66] and can undergo structural plasticity like better myelination [67, 68]. As such, ipsilesional premotor areas form direct, parallel modules for control of distal forelimb independent of M1.

Not only do they offer alternate motor output, but their cortical territories can remap to assume functions typically served by damaged M1. For instance, when majority of distal forelimb representation in M1 is destroyed, premotor areas can show remapping of the corresponding representation by up to ~50% [69, 70]. Similarly, with damage to M1 and its corticospinal pathways, patients can exhibit task-related fMRI activation within ipsilesional premotor areas that increases proportionally with the degree of the injury [46, 62, 71–73]. We have found as well that activation increases linearly with better perception of disability of the paretic limb [46] (Figure 1). Premotor cortices can also pair with associative posterior parietal cortices as in the case of learning to control a brain-computer interface with a completely paralyzed extremity [74]. With long-term learning, intensity of activating PMC but not ipsilesional M1 changes suggesting premotor networks improve in efficiency over the course of recovery [46, 75]. Such remapping is causal, not just epiphenomenal; inactivating premotor areas but not the ipsilesional M1 [76] reinstates motor deficits in recovered animals and humans [76–79].

The ability of ipsilesional premotor areas to remap can be ascribed to their flexible organization and connectivity. For instance, we find SMA possesses integrated representations just like M1, but PMC presents differentiation in distal and proximal representations like sensory cortices [82]. Ipsilesional premotor areas also share strong connectivity with ipsilesional M1. Wu et al. recently employed dense-array EEG to study coherence of activity between these regions, finding that ipsilesional premotor-M1 connectivity was the strongest predictor of chronic motor status, and the change in their connectivity evolved with gains in therapy [83]. Therefore, though, in most cases of mild damage, recovery can rely on ipsilesional M1 and its residual pathways, with greater damage to large-diameter fibers from M1, small diameter fibers from PMC and SMA that are more resistant to ischemia can offer independent parallel nonprimary motor loops [84]. This is not to say that recruitment of ipsilesional premotor areas can help achieve complete recovery (Figure 1). Yet, these instances suggest that clinical improvement can occur in patients with (near) complete damage to M1 and its corticospinal pathways via "reorganized" albeit limited pathways from ipsilesional premotor territories.

An important caveat needs to be considered, however. The potential of ipsilesional premotor areas is evident more consistently in animal models with homogenous focal infarcts [77, 85, 86] or in humans with focal injuries that spare PMC and SMA [62, 79, 87] and/or posterior portions of the posterior limb of the internal capsule where their corticospinal tracts converge. But, in a typical middle cerebral artery stroke, where 96% of patients experience white matter damage at the level of periventricular and internal capsular regions [47], it is less likely that a lesion affecting pathways from ipsilesional M1 would spare pathways from PMC and SMA. Injury to tracts from ipsilesional M1 and ipsilesional PMC or SMA is not remarkably different [88, 89]. With damage limited to pathways from ipsilesional M1, one can anticipate other ipsilesional areas could become meaningful for recovery, but given that lesions are heterogeneous, the potential for plasticity offered by alternate ipsilesional substrates would theoretically remain uncertain and inconsistent. As such, in one of our most recent clinical studies, patients receiving stimulation to facilitate ipsilesional premotor areas during rehabilitation recovered more than patients receiving rehabilitation alone, but benefits were variable to a certain degree [90].

4.2. Contralesional Motor and Higher Motor Areas. Liu and Rouiller have proposed a gradient of plasticity, which varies with the extent of stroke-related injury. When damage is small and pathways are partially spared, it is possible for perilesional M1 and ipsilesional premotor areas, like PMC and SMA, to reorganize in a way that supports recovery. But, with larger lesions affecting most of frontal cortices and pathways, there is little option but to rely on plasticity of intact, contralesional cortices [76, 91, 92]. For instance, in a randomized clinical study involving patients with little function (Upper Extremity Fugl-Meyer = 9–12), improvements with 12 weeks of training were associated with activation in contralesional premotor areas rather than ipsilesional M1 [63]. Such contralesional plasticity has a causal influence and is not simply a characteristic of patients with greater disability. For example, when excitability of contralesional hemisphere is suppressed with traditional brain stimulation, deficits become reinstated in patients with greater disabilities. This too serves as a deviation from the classical notion of interhemispheric inhibition suggesting contralesional motor cortices are adaptive for recovery at least in patients with greater damage and disability [60, 93–96].

Of all the contralesional cortices, contralesional dorsal premotor cortex (PMd) has greatest likelihood to support recovery because of the following.

(a) With greater impairment, cPMd can exert more causal influence upon recovery than other contralesional motor cortices. During performance of a reaction time task at the paretic upper limb, Johansen-Berg et al. and Bestmann et al. separately suppressed cPMd, cM1, and other cortices using TMS. Suppression of cPMd significantly slowed movement of the paretic limb. Slowness was more prominent in patients with greater impairment of the paretic limb [94, 95]. Therefore, Johansen-Berg et al. and Bestmann et al. concluded that cPMd exerts a more causal influence than other cortices in the recovery of patients with greater impairment of the paretic limb.

(b) cPMd can exert a causal influence by limiting inhibition it imposes upon the paretic limb. Bestmann et al. sought to understand what constituted a causal influence from cPMd. They conducted two sets of experiments. In one set of experiments, they tested neurophysiologic inhibition imposed from cPMd upon ipsilesional M1 using bihemispheric TMS. In the second experiment, they applied TMS to cPMd during grip tasks involving the paretic limb as they acquired fMRI. Using bihemispheric TMS, Bestmann et al. found that interactions between cPMd and ipsilesional M1 were predominantly inhibitory in patients with minimal impairment, which aligned with the traditional model of interhemispheric inhibition. But, in patients with greater impairment, TMS to cPMd led to less inhibition and even facilitation of output from ipsilesional M1. When Bestmann et al. repeated TMS during fMRI, they found that TMS to cPMd facilitated activation with ipsilesional M1 in patients with greater impairment of the paretic limb. Therefore, cPMd could exert a causal influence upon ipsilesional M1 via physiologic interhemispheric interactions; cPMd could lessen its inhibition on ipsilesional M1 to support recovery especially in patients with greater impairment of the paretic limb.

cPMd could likely modulate its inhibition upon ipsilesional M1 because it shares strong callossal connectivity with homologous as well as heterologous cortices. Unlike M1 that shares some of the weakest callossal connections, PMd is densely connected with opposite PMd and opposite M1 [97, 98]. PMd shares extensive callossal connectivity potentially since it is involved in mediating abstract higher-order movement planning for bilateral movements [98, 99].

(c) cPMd can also have a causal role by offering ipsilateral pathways to the paretic limb in case of extreme damage to corticospinal pathways. With increasing damage to corticospinal pathways from ipsilesional M1, it is likely that contralesional motor cortices, including cPMd, can increase physiologic output of their *ipsilateral* pathways to the paretic limb [80, 81, 94, 100–108] (Figure 2). Ipsilateral pathways mainly support proximal and axial flexion [106, 109–111],

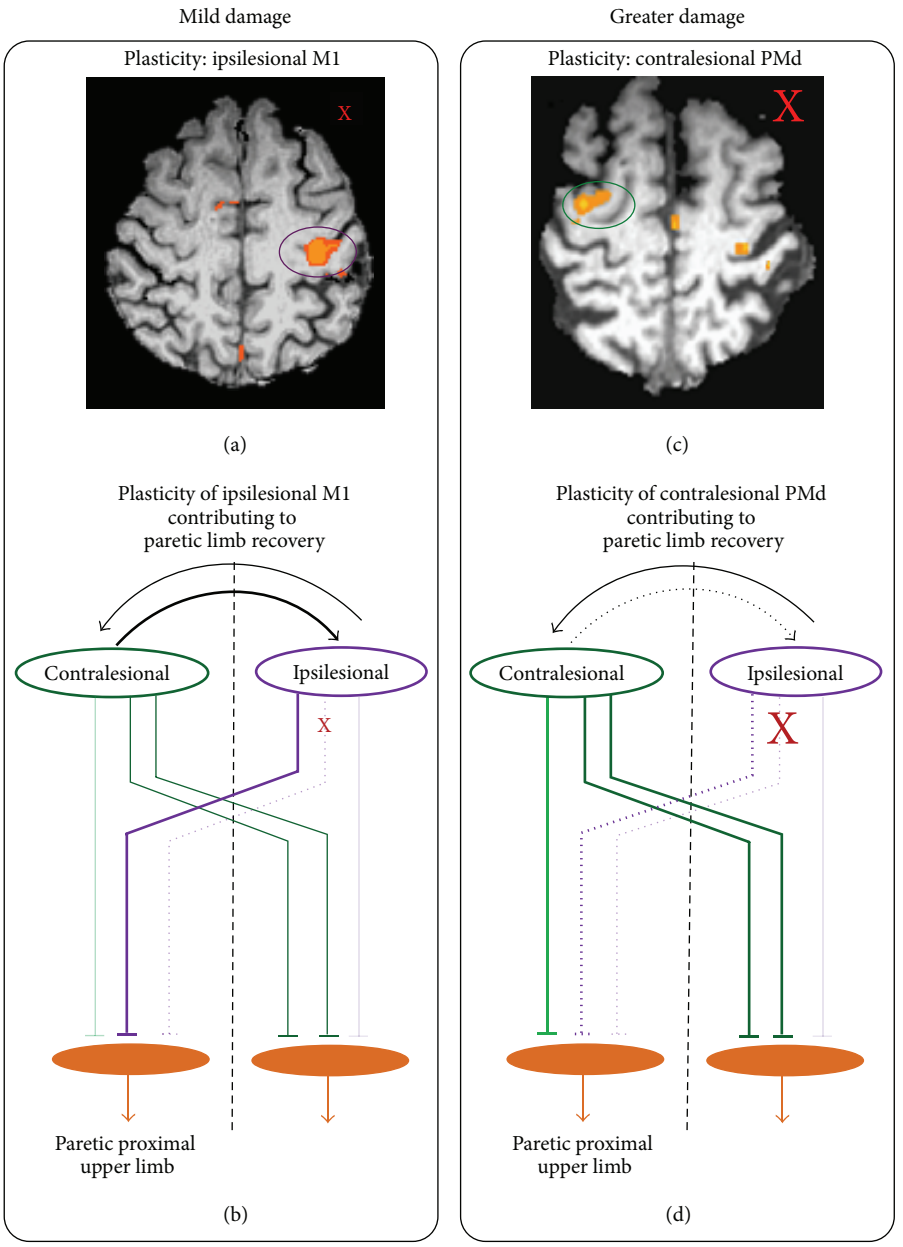

Figure 2: How contralesional PMD contributes to recovery of the paretic upper limb. Plasticity of ipsilesional M1 (iM1) is best evident in patients who are mildly impaired and have little damage to iM1 and corticospinal pathways because (a) they can feasibly recruit ipsilesional M1 in movement of the paretic upper limb in functional MRI (fMRI) and (b) can increase output of spared ipsilesional pathways (bold purple lines) to support the paretic limb. (c) Since, with greater damage, plasticity of ipsilesional M1 or any ipsilesional substrates is less likely, these patients recruit contralesional PMd in movement of the paretic limb. (d) Contralesional PMd reduces its inhibition on weak ipsilesional M1 (dotted black lines) so it partially supports paretic limb recovery (bolder, dotted purple lines). Also, contralesional PMd offers ipsilateral pathways (green) (uncrossed corticospinal and brainstem-mediated reticulospinal) to the proximal paretic limb to help recover [38, 80].

so patients can at least recover functions like shrugging, elevation, and reaching, even if they cannot recover any distal control [106, 111–113]. cPMd gives more ipsilateral pathways than other contralesional cortices; these pathways are comprised of uncrossed corticospinal [114–117] and brainstem-mediated reticulospinal and rubrospinal connections [106, 111]. Therefore, with greater damage to corticospinal pathways from iM1, cPMd would be more likely to support recovery of the proximal paretic upper limb than other motor cortices.

Thus, in patients with substantial and variable damage and greater disability, contralesional areas especially the contralesional PMd could serve as more intact, consistent sources for plasticity to support recovery.

4.3. Other Substrates. Although the focus in clinical studies has been on stimulation of cortices, alternate substrates may be meaningful to consider for future studies. For instance, the contralateral cerebellum may play a key role in poststroke

recovery. Cortical insult such as stroke is associated with rapid decreases in metabolic activity of the contralateral cerebellum, a phenomenon that is called crossed cerebellar diaschisis [118, 119]. Patients with severe crossed cerebellar diaschisis present with worse outcomes [120, 121] likely due to lack of excitatory input to cortical perilesional areas. Reversing crossed cerebellar diaschisis, as our group has proposed, presents a unique opportunity for promoting stroke recovery. For example, we have demonstrated that potentiating activity of cerebello-thalamo-cortical pathways via chronic stimulation of the dentate (lateral cerebellar) nucleus can reverse crossed cerebellar diaschisis in an animal model of middle cerebral artery occlusion [122]. Compared to sham-treated animals, animals that receive five weeks of chronic stimulation demonstrate a modest but significant improvement in motor outcomes [123]. When stimulation is paired with forelimb training in a model of focal infarct localized to M1, recovery is more favorable [124]. Benefits are associated with perilesional plasticity [125] and significant remapping, where representations of affected forepaw reemerge in perilesional cortical territories. Markers of long-term potentiation are significantly expressed and number of perilesional synapses increases. While results to date indicate that chronic stimulation of the dentate nucleus may become a viable therapy to promote recovery after stroke, the therapy has not yet been tested in humans. Findings here represent an opportunity for cerebellar stimulation as an emerging therapy in stroke rehabilitation.

Cortical plasticity has largely been related to structural integrity and physiologic excitability of corticospinal tracts from ipsilesional M1 and premotor areas. However, integrity of the extrapyramidal descending tracts is important to consider as well [126]. The extrapyramidal descending tracts include the rubrospinal tract originating from the red nucleus. In primates, the rubrospinal tract has monosynaptic connections with motor neurons located in the cervical spinal cord [127–131] for control of both proximal and distal muscles of the forelimb [31, 132]. Following damage to corticospinal tracts, the red nucleus can undergo synaptic reorganization to offer alternate output to paretic forelimb via the rubrospinal tract [111]. Despite a prominent presence in the primate model, rubrospinal tract does not appear to have a key role in normal motor control in humans. In instances of stroke, however, where corticospinal tracts become substantially damaged, rubrospinal tracts can offer compensatory support. Using diffusion tensor imaging (DTI), Rüber et al. [133] reveal a shift in microstructural properties of bilateral red nuclei and rubrospinal tract in relation to motor function in patients with chronic stroke who otherwise have experienced damage to corticospinal tracts. In a more recent study, Zheng and Schlaug [134] demonstrate plastic changes in the rubrospinal tract but not in the corticospinal tract following 2 weeks of concurrent cortical stimulation and physical/occupational therapy for the paretic upper limb. Therefore, while corticospinal tracts are prime in predicting recovery, in patients with substantial damage, the otherwise latent rubrospinal tracts and parent red nucleus can express structural and physiologic plasticity to help mediate recovery of the paretic upper limb.

When discussing brainstem-mediated pathways, one cannot overlook the contribution of medial brainstem systems including the reticulospinal tracts. In primates, neurons of the reticular formation are primarily involved in reaching and gross upper limb movements. They can participate in movements of fingers even though only 30% as often as corticospinal tracts and with 20% the amplitude. But, in those with lesions to the corticospinal tracts, the reticulospinal neurons become the most important candidates for recovery. Recovered hand movements however are often incomplete and appear poorly fractionated [105, 135].

5. How to Determine the Alternate Substrate That Would Most Likely Benefit an Individual's Recovery?

Since the original promise of cortical stimulation therapies has become faint in light of contradictory findings [17, 20, 136, 137], it is now more important than ever to tailor the technique rather than offer it as a generic therapy. While several substrates other than ipsilesional M1 can express plasticity as explained above, the greatest challenge lies in determining which alternate substrate could maximize individual's potential for recovery. Here, we summarize several theoretical models that are proposed to explain how to personalize or tailor stimulation therapies.

5.1. Model Based on Individual's Response to Stimulation. *The essential premise* of such models is that stimulation should be individualized to targets that patients are most responsive to in systematic comparisons. Shah-Basak et al. [138] proposed and tested one such model in the treatment of aphasia. As in upper limb recovery, the theory of interhemispheric inhibition dominates the application of brain stimulation in aphasia. It is typically believed that left-hemispheric frontal-temporal activity should be enhanced while right-hemispheric activity should be suppressed [139]. However, influence of the right hemisphere is more complex and variable and cannot always be considered inhibitory [140, 141]. Given the complexity, Shah-Basak et al. [138] designed a systematic study to individualize stimulation. Patients received facilitation of left frontotemporal regions, inhibition of homologues on the right, facilitation of regions on the right, and inhibition of frontotemporal regions on the left in a repeated measures crossover study. Seven out of 12 patients responded to at least one form of stimulation. But, as anticipated, response varied. Three individuals responded to the traditional left-hemispheric facilitation, and 3 individuals responded to left-hemispheric inhibition, while one responded to right-sided inhibition. *Post hoc* analysis explained why these differences emerged; patients who benefitted from left-hemispheric inhibition had experienced more extensive lesions in the frontal cortices than patients who responded to the typical paradigm of left-hemispheric facilitation. Overall, remapping of hemispheric specialization of language subfunctions served as a better guide to identify an alternate approach for recovery in aphasia than the traditional approach based on a generic model of interhemispheric inhibition.

While the sample was small, we discuss Hamilton et al.'s model [138] here because it can be exemplary for individualizing stimulation for upper limb recovery. Still, provisions would have to include a triage process that involves crossover comparisons, where one would have to identify which application best suits each individual. Larger number of patients would be required so best responses are discerned across larger samples. Models such as this, however, could forego systematic triage if it were possible to predict *a priori* who would respond to which type of stimulation. Models discussed below offer such opportunities. Regardless, individualizing stimulation based on patients' own response to different types of stimulation is systematic and patient-driven.

5.2. Unimodal Models Predicting Recovery Based on Patient Characteristics. Perhaps, the most common models are models predicting recovery. There has been a growing interest to predict who recovers and who does not recover after a stroke. One might further argue that these existing models can be extrapolated to explain who recovers from stimulation of ipsilesional M1 and who does not recover. Models prognosticating chronic recovery like those by Stinear et al. [81, 142, 143], Crafton et al. [144], O' Shea et al. [145], and Quinlan et al. [146] are based on a simple yet powerful *premise*. Knowing baseline characteristics that govern recovery can potentially help stratify patients for stimulation of ipsilesional M1. In separate studies, investigators examined patients who underwent motor therapies for the paretic upper limb [81, 142–144, 146] or traditional stimulation therapy [145]. Assessment of baseline characteristics included clinical scales of motor impairment, functional activation (fMRI) and functional connectivity, damage to corticospinal integrity studied with DTI, and excitability of descending pathways studied with TMS. Other variables included demographics (age, sex, and handedness), nature of stroke (lesion volume (cc); damage to motor cortices; location, i.e., cortical/subcortical/mixed; ischemic/hemorrhagic; side of stroke), neurologic status (chronicity, paresis of dominant side, cognitive function, depression, neglect, and aphasia), and comorbidities (hypertension, diabetes, hyperlipidemia, and smoking) [46, 56, 146, 147]. Bivariate and multivariate analyses explained which baseline characteristics predicted recovery with motor therapies [81, 142–144, 146] or with stimulation of ipsilesional M1 [145]. Overall, models showed that potential for recovery decreases with incrementally greater damage (Figure 3). Crafton et al. [144] recommended that patients showing >37% loss of fMRI activation in ipsilesional M1 experience greater motor impairment. Quinlan et al. [146] extended these findings, suggesting that patients experiencing >63% injury to corticospinal tracts (studied with DTI) cannot achieve significant gains with motor therapy. O'Shea et al. reported only patients with better baseline function and greater chronicity most respond to typical stimulation where contralesional cortices are suppressed (R^2 = 52.8%) [145]. In a separate study, Stinear et al. [81, 142, 143] used a similar multivariate model, but with a multilayered scheme. In patients who could evoke potentials in paretic muscles with TMS, they found excitability of descending pathways

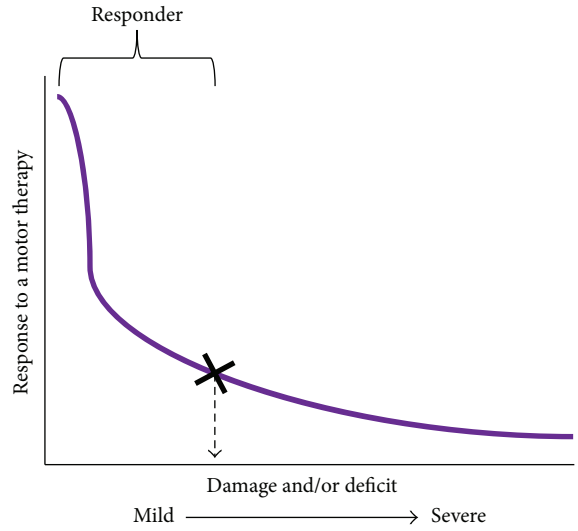

Figure 3: Presenting a schematic of unimodal models of recovery. Typically, unimodal models show how recovery following a motor therapy varies as a function of patient's individual characteristics, like damage to ipsilesional pathways, or impairment of the paretic limb. When characteristics are plotted against patient's response to motor therapy, one can understand who achieves criterion level of recovery (marked by X). Patients who achieve at least the criterion level or greater recovery are known as "responders." Others are considered to have hit the "point of no return" (see Stinear et al. [81]). Degree of damage or deficit (or any other patient characteristic) that separates responders from nonresponders is deemed as cut-off to stratify patients for said therapy. It is important to note that criterion level of recovery, hence the cut-off, can vary from one therapy to another therapy and from study of one characteristic to another. If extrapolated, such recovery models can be effective at predicting who would respond to stimulation of ipsilesional M1.

predicted recovery (R^2 = 58%), but, in patients who did not show any response to TMS, residual integrity of corticospinal pathways captured with DTI predicted recovery (R^2 = 67%). Patients with the worst levels of residual integrity however (worse than a cut-off of DTI value of 0.25) were considered to have hit a "point of no return"; that is, they showed very little prospect for gain with unilateral motor therapies (R^2 = 71%). Stinear et al. utilized a decision-tree to explain how such models could be extrapolated to predict who would respond to stimulation of ipsilesional M1. Overall, patients with spared ipsilesional M1 and pathways, that is, those below a "point of no return" (or those who have suffered <37% loss of activation of ipsilesional M1 or lost <63% of corticospinal tracts), are candidates for stimulation of ipsilesional M1.

Recovery-based models are powerful because by showing how recovery decreases exponentially at a set level of damage (or threshold or cut-off level of another characteristic), they can stratify patients for stimulation of ipsilesional M1. According to these models, patients below the cut-off or the threshold of injury recover best from motor therapies. Therefore, these models are unimodal because the peak (mode) of recovery lies below the threshold. As such, recovery-based models are superior to cross-sectional studies or studies requiring systematic comparison of differing stimulation

therapies [139] because thresholds derived in a single study can help stratify candidates in future studies.

Important caveats need to be considered, however. We have, for instance, witnessed that patients with wide-ranging corticospinal injury respond to intensive motor therapies; intensive therapies likely have an equalizing effect across patients with mild as well as substantial corticospinal injury [67, 68]. Cut-offs or thresholds of injury derived in unimodal recovery models therefore may vary with the nature and intensity of therapy. Further, unimodal models are unable to directly test what alternate options exist for patients who suffer from greater-than-threshold level of injury. Finally, in multivariate models, it is important to derive weights for predictors, in this case, weights for the different characteristics. This would explain how to stratify patients based on not just one, but a combination of baseline characteristics, including corticospinal tract injury [81, 142, 143, 146], loss of fMRI activation [144], baseline function and chronicity [145], cortical/subcortical nature of stroke [56, 57], and excitability of contralesional cortices [57] to name a few.

5.3. Bimodal Model Predicting Recovery Based on Patient Characteristics. Bimodal models, such as one recently proposed in a landmark study by Di Pino et al., best complement unimodal recovery models [148]. Bimodal models differ from unimodal models because not only do they hypothesize how peak (mode) of recovery with a therapy will lie below a certain threshold of injury, but they also explain how patients above the threshold could benefit from an alternate therapy. The *essential premise* of the most recent bimodal model, called the bimodal balance-recovery hypothesis, is that the *structural reserve* is the most important patient characteristic dictating individual expressions of plasticity. If ipsilesional corticospinal pathways are structurally viable or spared, then patients could recruit ipsilesional M1 and its pathways and benefit from the standard stimulation of ipsilesional M1 and suppression of "inhibitory" contralesional M1. But, if the ipsilesional pathways are damaged substantially, then contralesional cortices would become adaptive rather than becoming inhibitive and could be stimulated to support recovery. Partial support for Di Pino et al.'s bimodal model comes from studies suppressing contralesional cortices. Patients experiencing lesser damage respond well to typical suppression of contralesional cortices, but patients with excessive damage instead experience deterioration of function, suggesting that contralesional cortices support their recovery against tenets of classical model of interhemispheric inhibition [93–95]. As such, the bimodal view helps clarify long-standing speculations about the variable role of contralesional cortices. A bimodal model also extends knowledge beyond recovery-based hypotheses explaining how traditional approaches may benefit patients with reasonable residual integrity but a new approach that involves facilitating contralesional cortices could theoretically benefit patients with greater damage. The latter possibility and as such the bimodal model here remain untested in humans, though a recent study shows promise of facilitating contralesional cortices in animal models with large infarcts [149].

5.4. Bimodal Model Based on Inherent Expressions of Plasticity. Here, we extend the hypothesis proposed by Di Pino et al. Specifically, we explain how to derive the cut-off or structural reserve or neural threshold of injury that differentiates between ipsilesional and contralesional expressions of plasticity. Our *premise* is that stimulation would be most effective if it boosts patient's mechanism of plasticity. To derive a robust model, we anticipate requiring a series of 2 studies, which are paired. The first study will adopt a crossover design, where patients receive stimulation of the standard target-ipsilesional M1 and stimulation of an alternate target in the contralesional cortices, besides sham. Stimulation will be offered for a single session each, where adequate time is allotted between sessions for washout of effects. The choice for alternate target in the contralesional cortices is described in detail in previous sections; for instance, cPMd would potentially be an ideal region to target based on evidence from other studies and the theoretical framework established in Figure 2 [94, 95]. Patients will be tested upon improvement of timed functional activities of the paretic upper limb, activities that are responsive to change within a single session in patients with mild as well as severe disability. Improvement with standard stimulation of ipsilesional M1 will be studied as a function of baseline damage and impairment. Improvement with stimulation of cPMd too will be studied as a function of baseline damage and impairment. If Di Pino et al.'s hypothesis is accurate, then we would anticipate improvements with standard stimulation of ipsilesional M1 will reduce with greater damage and impairment, whereas improvements with stimulation of cPMd will increase. Based on their opposing variances, we would be able to identify the intersection (Figure 4) that would serve as the cut-off level of damage and impairment that stratifies patients for tailored therapies.

The second study in our series will advance significantly beyond Di Pino et al.'s hypothesis to generate a more robust model to tailor brain stimulation therapies. Patients from the first study will participate in a second study after a period of washout. In the second study, they will receive rehabilitation for the paretic upper extremity. No stimulation will be provided. The goal will be to observe processes of plasticity elicited in recovery. We would observe pre- to-postchanges in excitability of ipsilesional M1 and ipsilesional pathways and changes in excitability of cPMd and changes in its inhibition on ipsilesional M1. We will study if plasticity of iM1 and ipsilesional pathways reduces with greater damage and impairment of the paretic limb. Similarly, we will study whether plasticity of cPMd potentiates with greater damage and impairment. Based on their opposing variances, we will be able to identify the intersection between plasticity of ipsilesional M1 and cPMd. This cut-off of plasticity, derived from the second study, will be compared to the cut-off derived from the first study. We will examine whether responders to stimulation of ipsilesional M1 in the first study express greater plasticity of ipsilesional M1 than plasticity of cPMd. We will also study whether responders to stimulation of cPMd express greater plasticity of cPMd than ipsilesional M1 in their recovery. Therefore, the second study will help us confirm whether plasticity witnessed in individual recovery over several sessions of rehabilitation validates cut-offs derived

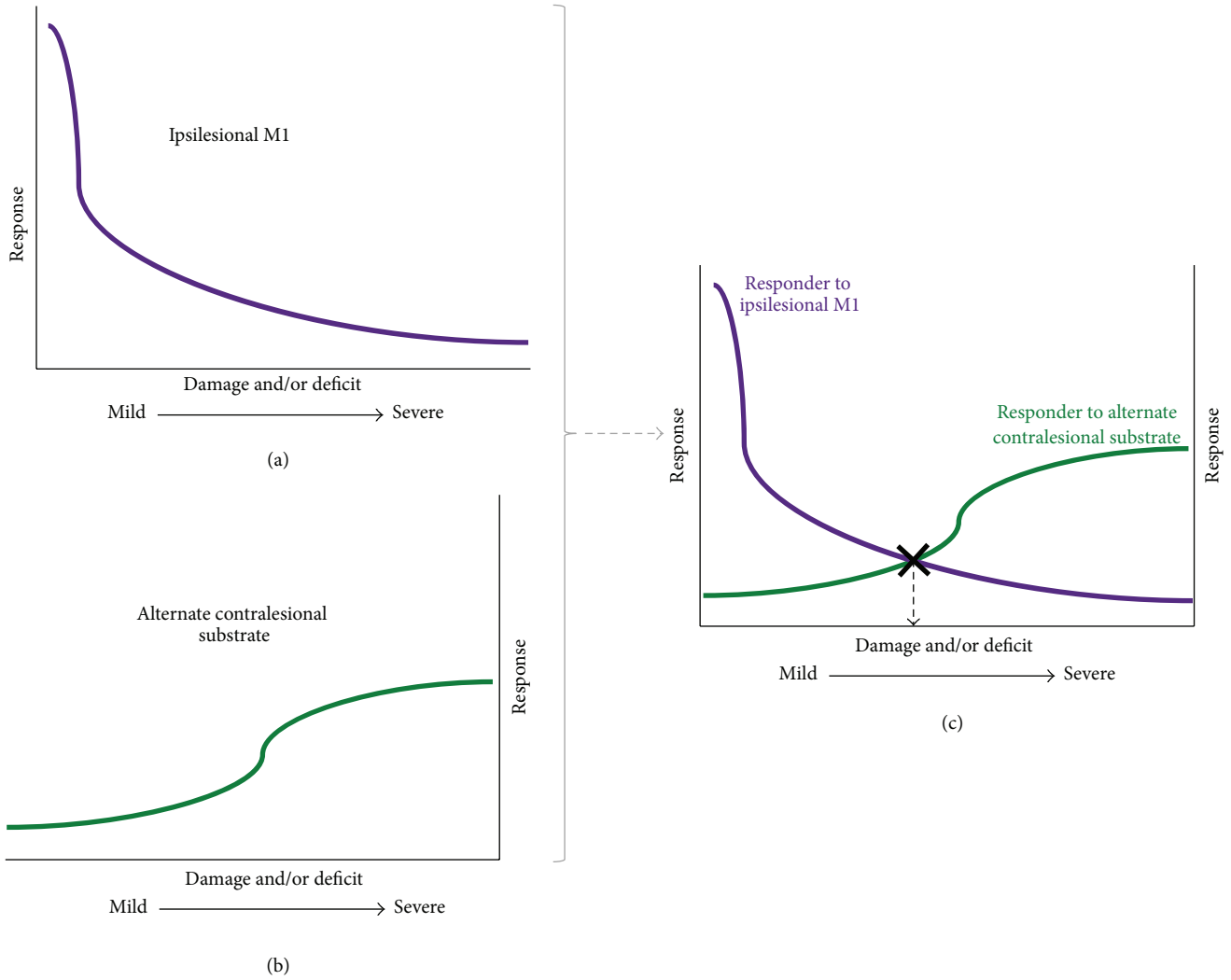

Figure 4: Bimodal model based on inherent expressions of plasticity. We propose a bimodal model that explains how to empirically derive a cut-off that separates responders for stimulation of the traditional substrate-ipsilesional M1 (a) versus stimulation of an alternate substrate in the contralesional cortices (b). Our proposed bimodal model of paretic upper limb recovery: cut-off derived empirically (c).

from single sessions of stimulation in the first study. As such, the second study will help confirm the model for tailored stimulation derived from the first study. More importantly, the second study will allow us to modify cut-offs derived from the first study. Therefore, our series will stratify candidates for standard stimulation of ipsilesional M1 versus novel stimulation of cPMd based on evidence of their plasticity observed in long-term recovery. Once the series is complete, then future studies can simply follow our stratification guide to test tailored stimulation. Thus, our series will not need to be repeated in subsequent studies.

Our model that stratifies patients based on a bimodal model of ipsilesional versus contralesional plasticity is conceptually different still from Di Pino et al.'s model because of the following.

(i) While we will validate Di Pino et al.'s hypothesis in the first study of our series, our series will be unique because it will empirically derive the cut-off or "structural reserve" to stratify patients for different therapies.

(ii) Compared to Di Pino et al.'s model, our model is validated by expressions of plasticity. We propose a model derived from paired studies, where we will confirm that patients who recover with stimulation of the standard ipsilesional M1 recover via plasticity of ipsilesional M1 and patients who recover with stimulation of cPMd recover via plasticity of cPMd.

(iii) A model that is based on both response to stimulation and long-term plasticity will likely be more robust to tailor stimulation therapies.

Because bimodel models, like Di Pino et al.'s model and our own model, compare two alternate therapies unlike unimodal models, they help validate the role of contralesional cortices in recovery. For instance, we typically suppress excitability of contralesional cortices assuming they compete

with ipsilesional M1 [13, 24, 25]. But, it is likely that they support recovery in patients with greater damage [38, 80, 94, 95, 148]. Bimodal models are set up to clarify these theories. In patients ranging from mild to severe damage, if patients with greater severity benefit from stimulation of contralesional cortices but fail to benefit from their typical suppression, then it would confirm that contralesional cortices are supportive and not inhibitive in patients with greater severity.

According to the models discussed here, response to individual treatments can be predicted on the basis of measurable "parameters" or characteristics that differentiate between patients. These models collectively propose that defining heterogeneity in terms of characteristics allows one to understand who would potentially express which mechanism of plasticity in recovery. Such knowledge of individual mechanisms could guide personalization of stimulation. A key drawback however lies in the assumptions of plasticity. What if the treatment tested in unimodal models or two alternate treatments tested in bimodal models are not relevant to a patient's recovery? The model below developed in the context of depression could help address the caveats of existing models in upper limb recovery.

5.5. Models Based on Network-Based Connectivity. Even though recovery-based models and the bimodal hypotheses can empirically explain how to identify who would respond to stimulation of one region versus another, there is still a degree of uncertainty. Can patients be reasonably and clearly considered to fall into one or the other categories? Here is where a model recently employed in depression can be particularly informative. This *model considers* that neurological diseases like stroke, Parkinson's disease, and so forth can be conceptualized as diseases of networks rather than of unitary brain regions [150]. Interactions across networks can be witnessed using techniques like resting state functional connectivity MRI (rs-fMRI) that study polysynaptic connectivity across immediate and remote networks. The model has been studied more extensively in depression [151, 152]. The usual suggestion is to target the region of dorsolateral prefrontal cortex (DLPFC) commonly believed to be located 5 cm anterior to the site in M1. But, such an unvarying approach can evoke variability. This issue plagues the field of depression. A possible remedy is to study group-level hypometabolism in the region of DLPFC. But, targeting such regions has been ineffective as well. Based on previous studies suggesting that sites in DLPFC that are most effective are functionally connected with subgenual activity, Fox and Pascual-Leone et al. [150, 151, 153] have proposed an elaborate model to individualize stimulation to the DLPFC. Subgenual connectivity is used as a guide to target stimulation to DLPFC.

One can extrapolate this concept to the development of better strategies to improve upper limb recovery in stroke. It can be envisioned that regions showing highest connectivity to ipsilesional M1 would potentially be well positioned to support recovery. Since the investigation would be network-wide, it would decrease our reliance on one or another substrate of recovery and create opportunities for individualizing stimulation across many.

The key points to remember, however, are the potential limitations of the model if it is directly applied to stroke. Challenges presented in stroke are unique compared to depression and neurocognitive diseases [150, 151, 153]. For instance, relying on a perfusion-based contrast alone can be problematic in stroke since localization of activation is contorted in areas of vascular compromise [154, 155] and can shift inconsistently in recovery [154]. Most importantly, recovery-based unimodal models have taught us that structural integrity of corticospinal tracts is key for stroke recovery [81, 142, 146]; fMRI activation is generally epiphenomenal to their integrity [23, 156–158]. As such, one may have to be cautious in interpreting the exact location of rs-fMRI activity and may have to factor in residual integrity and baseline abilities.

6. Conclusions

A great challenge facing stroke rehabilitation is the lack of information on how to derive targeted therapies. As such, techniques once considered promising, such as brain stimulation, have demonstrated mixed efficacy across heterogeneous samples in clinical studies. Here, we explain reasons, citing its unvarying assumption and a one-type-suits-all approach as the primary cause of variable efficacy. We present evidence supporting the role of alternate substrates, which can be targeted instead in patients with greater damage and deficit. A significant roadblock, however, is the lack of information on how to tailor brain stimulation therapies and how to stratify patients for stimulation of traditional versus an alternate substrate for recovery. To this end, we discuss different frameworks. To the best of our knowledge, our report is the first instance that enumerates and compares across theoretical models from upper limb recovery and conditions like aphasia and depression. In agreement with Ward et al. [23], we explain how different models capture heterogeneity across patients and how they use heterogeneous patient characteristics to predict which patients would best respond to what treatments to develop targeted, individualized brain stimulation therapies. Our intent is to weigh pros and cons of testing each type of model so brain stimulation is successfully tailored to maximize upper limb recovery in stroke.

Conflict of Interests

A. G. Machado has the following conflict of interests to disclose: being a consultant of functional modulation at St Jude; having distribution rights at Enspire, ATI, and Cardionomics; having fellowship support from Medtronic. Unrelated to present work, A. B. Conforto has the following conflict of interests to disclose: as a consultant at BMS/Pfizer and Bayer. Other authors have no conflict of interests to disclose.

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Research Article

Interhemispheric Plasticity following Intermittent Theta Burst Stimulation in Chronic Poststroke Aphasia

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The effects of noninvasive neurostimulation on brain structure and function in chronic poststroke aphasia are poorly understood. We investigated the effects of intermittent theta burst stimulation (iTBS) applied to residual language-responsive cortex in chronic patients using functional and anatomical MRI data acquired before and after iTBS. Lateralization index (LI) analyses, along with comparisons of inferior frontal gyrus (IFG) activation and connectivity during covert verb generation, were used to assess changes in cortical language function. Voxel-based morphometry (VBM) was used to assess effects on regional grey matter (GM). LI analyses revealed a leftward shift in IFG activity after treatment. While left IFG activation increased, right IFG activation decreased. Changes in right to left IFG connectivity during covert verb generation also decreased after iTBS. Behavioral correlations revealed a negative relationship between changes in right IFG activation and improvements in fluency. While anatomical analyses did not reveal statistically significant changes in grey matter volume, the fMRI results provide evidence for changes in right and left IFG function after iTBS. The negative relationship between post-iTBS changes in right IFG activity during covert verb generation and improvements in fluency suggests that iTBS applied to residual left-hemispheric language areas may reduce contralateral responses related to language production and facilitate recruitment of residual language areas after stroke.

1. Introduction

Strokes of the left middle cerebral artery (LMCA) territory often lead to impairments in language function that are collectively referred to as aphasias [1]. Language recovery after LMCA stroke is highly variable, and many patients remain chronically aphasic despite optimal rehabilitative approaches [2, 3]. Aphasia following LMCA stroke typically results from lesions affecting frontal and/or temporal language regions in the left hemisphere and also often involves damage to white matter pathways connecting these regions [4–11].

Functional neuroimaging studies indicate that the recovery of language abilities after LMCA stroke involves the restoration of language-related processing in the remaining tissues near affected language areas as well as the compensatory recruitment of unaffected areas for language-related processing [12–14]. While downregulated responses in affected left-hemisphere language areas and upregulated responses in unaffected right-hemisphere homologues are commonly observed during language task performance in acute patients [12, 13, 15], the restoration of typical language-related responses in residual left-hemisphere language areas (which is thought to be marked by a restoration of left-hemisphere dominance for language-related processing) is likely critical for the successful long-term recovery of language functions [12, 15–20]. Thus, while the upregulation of right-hemisphere responses during language task performance might reflect a form of compensatory reorganization, it is likely less effective than the reinstatement of left-hemisphere processing for accomplishing language task performance [13, 16, 20–23].

Studies investigating how changes in cortical function relate to language recovery following stroke provide strong evidence indicating that the preservation and/or restoration of language-related processing in the residual left inferior frontal gyrus (IFG), a region that has been strongly implicated

in various language processes such as word processing and word generation [24–26], is strongly related to the recovery of language functions in both the acute and chronic stages of recovery. For example, adult patients with acute injury who show preserved dominance of the residual left IFG for language task performance have less severe language impairments than patients who depend on the compensatory recruitment of the right IFG to accomplish the same task, indicating that the preservation of language-related processing in this region after LMCA stroke is an important factor in determining initial aphasia severity [21, 22]. In addition, adult patients that receive early poststroke aphasia rehabilitation show enhanced language-related responses in the residual left IFG compared to patients that do not receive early rehabilitation, and the magnitude of treatment-related increases in left IFG responses during language task performance is correlated with improvements in language function after treatment [23]. Similarly, increases in the left-lateralization of IFG activity related to language task performance from early to chronic recovery phases correlate with improvements in naming ability in adult patients with poststroke aphasia [17], and the level of language-related activity in left frontal areas correlates with improvements in naming ability subsequent to behavioral treatments in chronic patients [27]. The development of treatments that can facilitate the restoration of language-related processing in residual frontal language areas may, therefore, be an important step in improving both spontaneous and treatment-induced recovery in patients with poststroke aphasia.

Techniques such as transcranial magnetic stimulation (TMS) enable the noninvasive manipulation of cortical excitability in specific parts of cortex and may provide a means for facilitating beneficial cortical plasticity in patients with poststroke aphasia [28, 29]. Experimental interventions utilizing these techniques typically attempt to induce changes in cortical function that mirror those observed in successfully recovered patients by transiently enhancing the excitability of residual left-hemisphere language areas or suppressing responses in their right-hemisphere homologues [29–31]. High-frequency TMS stimulation protocols (e.g., >5 Hz) such as intermittent theta burst stimulation (iTBS) are delivered in short intervals to produce a rapid facilitation of synaptic transmission in the stimulated cortex that can persist for over an hour after the initial stimulation session [32]. In addition to facilitating changes in local synaptic transmission and evoked potential amplitude, iTBS may also alter the temporal characteristics of ongoing oscillatory activity, suggesting that it may lead to changes in ongoing neural dynamics at larger spatial scales that reflect changes in the functional organization of distributed functional networks [33].

Excitatory stimulation protocols are typically applied to the residual left IFG in order to facilitate language-related processing [34–36]. In contrast, low-frequency stimulation protocols (e.g., <1 Hz) that are delivered in continuous trains for longer periods of time have predominantly inhibitory effects on synaptic transmission and are typically applied to the right IFG in order to reduce contralateral compensation and/or interference during language-related processing [36–40]. Studies investigating the efficacy of these paradigms for restoring language function after stroke have provided consistent evidence for improvements in language function subsequent to stimulation [34, 36–38]. Studies assessing the general effects of excitatory [34] and inhibitory [40] stimulation paradigms on neuroimaging measures of language-related responses in aphasic patients suggest that improvements in language function are accompanied by changes in the responses of both the residual left-hemisphere language network and homologous areas in the right hemisphere, although research in this area remains limited.

A previous behavioral and functional MRI (fMRI) study conducted by our laboratory found that after 10 sessions of iTBS applied to residual language-responsive left frontal cortex identified with a semantic decision/tone decision task, patients with chronic poststroke aphasia showed significant improvements in word generation as well as changes in fMRI responses during a semantic decision task that included a significant leftward shift in the lateralization of activity in the IFG [34]. In addition, a previous analysis of concurrently collected diffusion tensor imaging (DTI) data from the same patients found evidence for changes in white matter integrity in multiple regions including the left IFG following iTBS treatment [41]. However, a major limitation of our previous fMRI study is that it was restricted to changes in activation associated with the same task that was used to define language-responsive cortex for targeting with iTBS [34], and this limits inferences regarding whether or not similar effects might be observed for activation during other language tasks. Our previous fMRI analysis was also limited in that it only assessed changes in fMRI measures of activation, and it is increasingly recognized that the characterization of changes in measures of interregional connectivity is important for developing a full understanding of how changes in interregional interactions relate to the recovery of function after stroke [42, 43]. In addition, our previous structural analysis was restricted to investigating changes in white matter integrity after iTBS, although changes in cortical grey matter morphology might also be expected since excitatory TMS protocols have been found to result in measureable changes in cortical grey matter volume after as little as 5 days of treatment in individuals without stroke [44].

Here, we first analyzed the pre-/postintervention fMRI data to assess whether or not iTBS might have similar effects on fMRI responses elicited by a covert verb generation (VG) paradigm that was not used to define iTBS targets. Notably, while both the semantic decision paradigm used in our previous study and the VG paradigm used in the current study reliably evoke strong responses in the left IFG in healthy individuals [45] and in patients with poststroke aphasia [46], they target different functional domains (word comprehension versus word generation) and there is typically little overlap between the activations attained with these tasks beyond the left inferior frontal cortex [46]. We hypothesized that if iTBS has a general facilitatory effect on language-related processing in the residual left IFG (i.e., by modulating synaptic transmission to facilitate communication with other language-relevant areas or to suppress interference from language-irrelevant interactions with other areas), then patients should show increased responses in the left IFG

during covert verb generation after treatment with iTBS and increased left-lateralization of IFG activity associated with covert verb generation. Because language lateralization in frontal cortex is associated with both higher levels of activity in the left hemisphere and lower levels of activity in the right hemisphere for language-related versus non-language-related tasks [47] and because our previous study also found evidence for decreased activity in the right IFG related to semantic decisions following iTBS [34], we expected that patients would also show reductions in right IFG activity during covert verb generation after iTBS. In addition, because studies of healthy individuals indicate that the presence of left-lateralized IFG activation during language tasks may be in part due to a task-dependent reduction in connectivity between left and right IFG [48] and because we are unaware of any studies that have investigated changes in functional MRI measures of connectivity in patients with poststroke aphasia subsequent to iTBS treatment, we also investigated whether or not interhemispheric connectivity between right and left IFG during covert verb generation was affected by iTBS. Finally, in order to fully characterize the structural effects of iTBS in these patients, we also tested whether or not patients showed changes in regional grey matter volume after iTBS treatment.

2. Materials and Methods

2.1. Patient Demographics and Language Testing. Eight prospectively identified patients (4 females; mean age = 54.4, SD = 12.7) with chronic aphasia resulting from LMCA stroke were recruited as described previously [34, 41]. The mean time since stroke for all patients included was 5.25 years (SD = 3.62). Aphasia types were determined by a linguistics expert following language testing. Four patients presented with anomic aphasias; of these subjects, two also presented with dysarthria and one also presented with conduction aphasia. The remaining four patients all presented with nonfluent Broca's type aphasias. Aphasia diagnoses and lesion characteristics are shown for each patient in Table 1. None of the patients had contraindications to MRI scanning, none had history of seizures, and all were right-handed prior to the stroke. The study was approved by the University of Cincinnati, Cincinnati Children's Hospital Medical Center, and University of Alabama at Birmingham Institutional Review Boards and adhered to the Declaration of Helsinki regarding human subject research. Each patient provided signed informed consent prior to inclusion in the study. Neuropsychological measures of language function were acquired before and after iTBS treatment as described in previous publications [34, 41]. Briefly, naming and word-finding abilities were evaluated using the Boston Naming Test (BNT) [49], receptive vocabulary was evaluated using the Peabody Picture Vocabulary Test (PPVT) [50], verbal fluency was evaluated using the Semantic Fluency Test (SFT) [51] and Controlled Oral Word Association Test (COWAT) [52], and comprehension was evaluated using the Complex Ideation Subtest of the Boston Diagnostic Aphasia Examination (BDAE CompId) [53]. Patients also completed the min-Communicative Abilities Log in order to provide subjective measurements of progress in verbal communication [54]. Pre- and posttreatment testing used different versions of the assessments in order to reduce the potential for learning-related effects.

Table 1: Patient characteristics.

Patient	Aphasia diagnosis	Total lesion volume (voxels)
P1	Anomia, mild dysarthria	29,243
P2	Nonfluent (Broca-type)	32,744
P3	Anomia, mild dysarthria	1,436
P4	Anomia	20,195
P5	Nonfluent (Broca-type)	52,452
P6	Anomia, conduction	13,208
P7	Anomia	36,479
P8	Nonfluent (Broca-type)	7,269

2.2. Intermittent Theta Burst Stimulation Protocol. Detailed descriptions of all iTBS and neuronavigation protocols performed on these patients can be found in our previous publication [34]. Briefly, all patients received iTBS to residual language-responsive cortex in or near the left IFG as identified using an fMRI semantic decision/tone decision language localizer task described in our previous publication [34]. Stimulation intensities used for each patient were set at 80% of the active motor threshold obtained from stimulation of the right motor cortex. Stimulation sessions occurred each day for five consecutive weekdays over the course of two weeks, resulting in a total of 10 stimulation sessions. Each session consisted of 600 total pulses, with three pulses at 50 Hz given every 200 milliseconds in 2-second trains at 10-second intervals over a 200-second period. fMRI-guided neuronavigation using BrainSight2 (Rogue Research Inc., Montreal Canada) enabled the targeting of residual language-responsive cortex in the left frontal lobe near the IFG (frontal targets were used for 7 patients; language-responsive cortex in the left temporal lobe was targeted for one patient; see Figure 1 in [34]) that was identified using the fMRI localizer task, and allowed for reliable and precise localization of the same location at each session. A schematic illustrating the experimental timeline is shown in Figure 1.

2.3. MRI Data Acquisition. MRI data were acquired before and after the treatment sessions. The functional and anatomical MRI data presented in this study were acquired using a Varian 4 Tesla Unity INOVA whole body MRI/MRS scanner (Varian, Inc., Palo Alto, CA). For each patient, a high-resolution T1-weighted 3D-MDEFT (Modified Driven Equilibrium Fourier Transform) anatomical volume (scan parameters: repetition time/echo time = 13.1/6 ms, field of view = 25.6 × 19.2 × 19.2 cm, flip angle = 22°, and voxel dimensions = 1 × 1 × 1 mm) and $T2^*$-weighted blood oxygen-level dependent (BOLD) volumes (scan parameters: repetition time/echo time = 3000/30 ms, FOV = 25.6 × 25.6 cm, matrix = 64 × 64 pixels, number of slices = 30, slice thickness = 4 mm, and flip angle = 75°) were obtained at both pretreatment and posttreatment sessions.

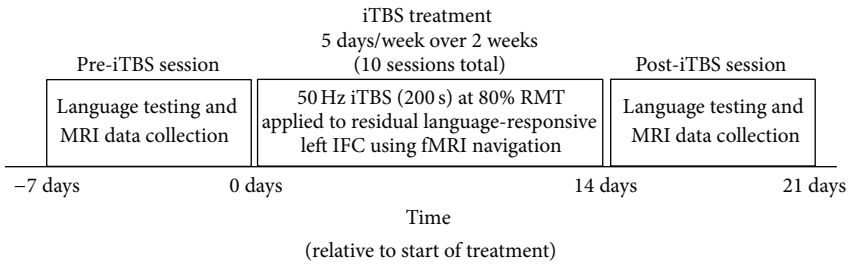

Figure 1: Experimental timeline. Patients underwent language testing and MRI scans during the week prior to treatment. Patients then received one session of iTBS each on weekday over a two-week period and underwent language testing and MRI scans again during the week following treatment.

FMRI data were collected while patients performed an alternating block-design covert verb generation (VG) task that consisted of alternating 30 s blocks of an active condition involving silent verb generation in response to binaurally presented nouns and a control condition involving bilateral sequential finger tapping (FT) in response to a frequency modulated tone centered on 400 Hz that was modulated by 25% every 5 s. This task was chosen because previous studies indicate that it reliably produces left-lateralized activation patterns [45] and because it has excellent test-retest (across time points) reliability for evoked activity patterns in patients with aphasia due to LMCA stroke [46]. The control condition served to control for the auditory stimulation during the noun presentation in the active condition and to distract patients from continuing to generate verbs outside of the active condition blocks while maintaining a task state. Each condition was performed 7 times. Each patient's understanding of and ability to perform the task were assessed prior to scanning by having the patients perform the task outside of the scanner. Patients had to be able to generate at least one verb in response to each noun prior to proceeding to scanning. Following each scan session, patients performed a forced-choice recognition test involving the nouns that were presented during the covert verb generation task, and the percentage of correctly remembered nouns was utilized as an indirect measurement of task performance.

2.4. MRI Data Preprocessing. All MRI data were preprocessed using MATLAB scripts implementing functions from the most recent release version of Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB r2014B (The MathWorks Inc., Natick, MA). All statistical analyses were performed using statistical functions provided in MATLAB.

Functional MRI data from the baseline and follow-up scans were slice-time corrected, realigned and resliced, and coregistered to the structural image obtained during the same scan. Deformation fields containing the deformation differences between across-session average anatomical volume and the anatomical scan from each session were used to warp the coregistered functional volumes to the across-session average anatomical volume. The average anatomical scan was then normalized to Montreal Neurological Institute (MNI) template using unified normalization-segmentation as implemented in the New Segment tool in SPM. The deformation parameters obtained from the warping of the anatomical volume were used to normalize the functional volumes to MNI template space. The functional volumes were resampled to $2 \times 2 \times 2$ millimeter isometric voxels and spatially smoothed with a 6-millimeter full-width half maximum (FWHM) Gaussian kernel. Functional volumes in which participants moved more than 0.5 mm in one frame (3 s) were replaced with a volume interpolated from adjacent time points. Volumes were to be rejected if they contained >3 mm of motion, but no volumes met criteria for rejection.

Individual patient lesion delineations were created from the pre-iTBS anatomical scans using an automated voxel-based Bayesian classification algorithm developed by our lab and implemented in the lesion_gnb toolbox for SPM12 [55]. The resulting lesion delineations were used to create a group-level lesion frequency map. The group-level lesion frequency map is provided in Figure 2 and illustrates the number of patients with lesioning at each voxel. The greatest across-patient lesion overlap was observed in the left insula, left putamen, and left precentral gyrus (Figure 2).

Anatomical data utilized in the voxel-based morphometry (VBM) analysis were preprocessed according to a recently described longitudinal preprocessing pipeline for VBM analyses [56]. First, probabilistic tissue segmentation implementing the New Segment + DARTEL (diffeomorphic automatic registration through exponentiated lie algebra) approach with an additional tissue prior (mean of white matter and CSF tissue probability maps) and medium bias regularization was used to obtain DARTEL-compatible tissue probabilistic maps (TPMs) encoding the grey matter (GM) and white matter (WM) probabilities for each voxel. The additional tissue prior and medium bias regularization were used since this has been shown to improve template-space normalization using the New Segment + DARTEL approach [57]. Next, patient-specific anatomical templates were created with DARTEL using the GM and WM tissue maps from the baseline and follow-up scans. For each patient, the baseline and follow-up TPMs were then warped to the subject-specific templates and modulated using the Jacobian determinant of the transformation to increase sensitivity to absolute differences in GM volume [58, 59]. The creation of the patient-specific templates was performed in order to enable more precise between-session spatial alignment of TPMs

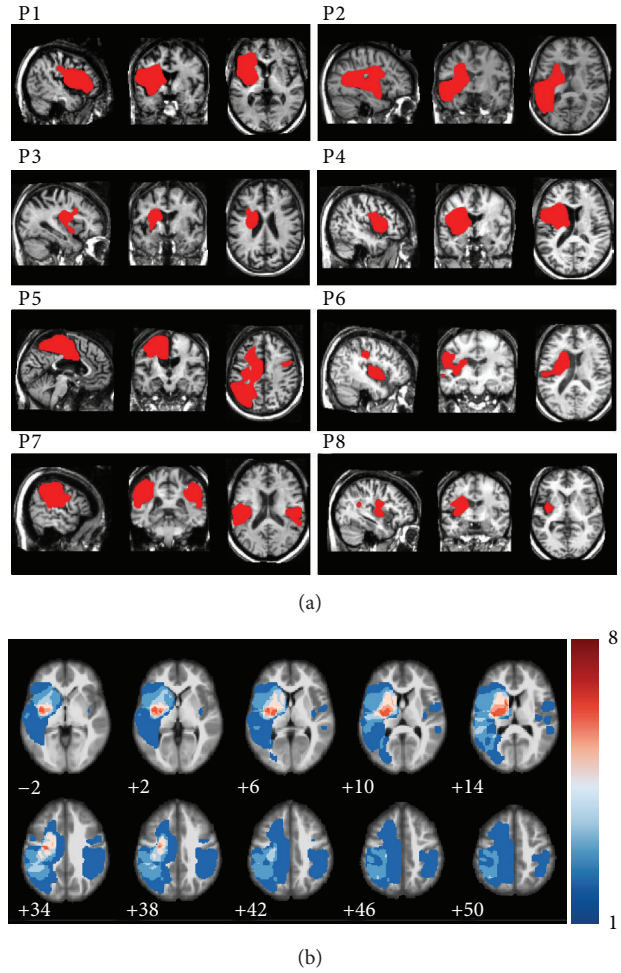

Figure 2: (a) Representative images from the normalized T1-weighted anatomical scans are shown for each patient; lesion delineations are shown in red. (b) A lesion frequency overlay for all 8 participants shown as a color-map overlaid on a template anatomical image. Colors represent the number of patients with a lesion at each voxel as indicated by the color bar.

[56]. A group template was then created by nonlinearly registering all of the patient-specific templates simultaneously using DARTEL. The modulated/warped GM and WM TPMs obtained from each patient were then nonlinearly normalized to the population template and modulated with the Jacobian determinant of the transformation. Finally, the population template was then registered to MNI space using an affine transformation, and each TPM was then coregistered to MNI space using an identical transformation and smoothed using an 8 mm FWHM Gaussian kernel.

2.5. Functional MRI Data Analyses. Functional MRI activity related to the covert verb generation task was quantified by contrasting the active condition blocks (VG) against the control condition blocks (FT). For each patient, the fMRI data were fit to a general linear model (GLM) [60] where each active block was modeled as a boxcar regressor convolved with a canonical hemodynamic response function. To account for temporal variability in the hemodynamic response, time and dispersion derivatives were modeled as basis functions in the first-level analyses [61]. Single-patient statistical maps containing contrast estimates quantifying differences between the active and control conditions were computed for both pre- and post-iTBS scans. Statistical comparisons of the contrast estimate maps were used to evaluate changes in activation between the pre- and post-iTBS sessions.

FMRI data were first analyzed using a region of interest (ROI) approach in order to directly test our hypotheses regarding changes in IFG activity and connectivity between pre- and post-iTBS sessions. ROI masks were created using the marsbar toolbox for SPM (http://marsbar.sourceforge.net/), and ROIs in the left and right IFG were defined using peak activation coordinates obtained from an independent analysis of activation related to covert verb generation in healthy individuals [45]. 8 mm radius spherical ROIs were centered on voxels in the left IFG (MNI coordinates: $x = -50$, $y = 16$, and $z = 16$) and on mirrored coordinates in the right IFG (MNI coordinates: $x = 50$, $y = 16$, and $z = 16$). Only two patients (P1 and P4) had overlap between the left IFG ROI and their lesion delineation. P1's lesion encompassed nearly the entire left lateral prefrontal cortex and the left IFG ROI

fell directly onto the perilesional rim, resulting in 100% lesion overlap with the left IFG ROI. P4's lesion was primarily localized to the left ventral IFG and the ROI overlapped by 60.2% with the perilesional rim. Nonetheless, for both patients, the 1st principal component of the signal extracted from the ROI showed phasic responses consistent with the design of the task. While anatomical overlap was noted, functional analyses indicated BOLD signal changes aligned with the box-car function of the fMRI task design indicating that the fMRI responses reflected the responses of perilesional cortex rather than CSF. Additionally, signal from the left IFG ROI was more strongly correlated with signal from the right IFG ROI than with the CSF signal, and this was only marginally influenced by partialling out variability accounted for by the CSF signal (Supplemental S1) (see Supplementary Material available online at http://dx.doi.org/10.1155/2016/4796906). Nonetheless, control analyses indicated that excluding these patients did not substantially change the statistical significance of results for any analysis involving the left IFG ROI, indicating that the presence of lesion-ROI overlaps for these patients did not strongly influence the outcome of the ROI analyses.

To test our hypothesis about whether patients showed changes in fMRI activity during covert verb generation in the left and right IFG ROIs after iTBS, we extracted the mean parameter estimates for the active versus control condition contrast and compared the estimates obtained for each ROI between the pre- and post-iTBS sessions. This analysis provided information about the mean level of activity in the IFG ROIs for each session, with positive values indicating stronger activation during the active condition and negative values indicating stronger activation during the control condition. To test our hypothesis that patients would show more strongly left-lateralized IFG activation following iTBS, laterality index (LI) analyses were performed to quantify the lateralization of activity related to covert verb generation. For each patient, changes in LI were evaluated using an adaptive threshold determination approach [62]. LI values range from −1 (complete right-lateralization) to 1 (complete left-lateralization), and LIs for each session were calculated according to the formula shown in

$$\mathrm{LI} = \frac{\left(\sum \mathrm{activation}_{\mathrm{left}}/\mathrm{mwf}\right) - \sum \mathrm{activation}_{\mathrm{right}}}{\left(\sum \mathrm{activation}_{\mathrm{left}}/\mathrm{mwf}\right) + \sum \mathrm{activation}_{\mathrm{right}}}. \quad (1)$$

Using adaptive threshold determination, the term activation is defined as the values of voxels with intensities that are greater than the within-ROI average intensity for the contrast of interest. This method was chosen because it has been shown to provide reliable LI estimates that are more robust against interindividual variability in signal-to-noise ratio than approaches that employ arbitrary/fixed cut-off thresholds that are applied to all subjects (e.g., corrected P value thresholds); this method does not substantially increase susceptibility to false positives [62]. The mask weighting factor (mwf term in (1)) is used to adjust the LI estimates to account for differences in the volume of each ROI and is defined by the proportion of the volumes of the left- and right-hemisphere ROIs [62].

To test our hypothesis regarding the effects of iTBS on interhemispheric connectivity, we conducted a generalized psychophysiological interaction (gPPI) analysis using the gPPI toolbox for SPM [63]. gPPI enables the modeling of context-specific changes in the relationship of activity in one brain region, referred to as a seed region, to activity in other brain regions by including a term specifying an interaction effect between the seed region time series and the task time series in each first-level GLM [64]. gPPI effects are interpreted as changes in interregional connectivity which are driven by psychological states related to factors such as the task being performed [63, 65], making gPPI an appropriate tool for testing our hypothesis that iTBS would lead to changes in interhemispheric connectivity during covert verb generation. For each patient, the first principal component of the BOLD time series from each scan was extracted from the right IFG ROI and entered as a seed time series for the gPPI analysis. The right IFG ROI, rather than the left IFG ROI, was chosen in order to reduce potential confounds in the extracted time series related to lesion proximity since two patients showed substantial lesion overlap with the left IFG ROI. Cerebrospinal fluid (CSF) and WM signals were also included as nuisance variables in the gPPI model in order to reduce the influence of nonneural signals on estimates of task-dependent connectivity [66]. For each patient, gPPI estimates quantifying the level of condition-dependent connectivity from right to left IFG during each session were then extracted from the gPPI model using the marsbar tool for SPM and compared from pre- to post-iTBS sessions.

All between-session comparisons were tested for statistical significance using two-tailed dependent samples t-tests. Correlations between changes in fMRI measures of IFG function and behavioral measures were assessed using linear correlation analyses. Multiple-comparisons correction for all ROI-driven comparisons between pre-iTBS and post-iTBS scans was performed using the Benjamini-Hochberg procedure to control the false-discovery rate (FDR) at 0.05 [67, 68], and all associated P values presented are FDR-adjusted. Exploratory whole-brain GLM and gPPI analyses were also performed in order to provide a more thorough characterization of functional MRI measures of activity and right IFG connectivity related to the VG task at the pre-iTBS and post-iTBS sessions. Statistical tests for these analyses were performed using dependent samples t-contrasts. Exploratory and ad hoc partial correlational analyses were performed to further characterize the data and are presented with uncorrected P values.

2.6. Voxel-Based Morphometry Analyses. VBM is a technique that allows for the measurement of grey matter (GM) volume in T1-weighted MRI data [58, 69]. Here, we used VBM to address the question of whether or not patients showed changes in GM volume after iTBS treatment. The DARTEL-processed subject-level grey matter maps from baseline and follow-up scans were entered into a dependent samples t-contrast that also included each patient's lesion volume as a nuisance covariate. Changes in GM volume were assessed at the whole-brain level using dependent samples t-contrasts.

3. Results

3.1. Behavioral Results. Analyses evaluating performance on the out-of-scanner forced-choice noun recognition task revealed good performance for both pre-iTBS (mean % correct = 94.13; SEM = 1.63) and post-iTBS (mean % correct = 95.13; SEM = 2.05) sessions. Dependent samples t-test comparing pre-iTBS and post-iTBS evaluations did not reveal a significant change in noun recognition performance (t_7 = 0.415, P = 0.69). These results are consistent with previous studies that have reported good out-of-scanner noun recognition performance on this task in patients with poststroke aphasia [46, 70].

The effects of iTBS on neuropsychological measures of language function have been previously reported [34, 41] and will briefly be described here to provide details relevant to the current study. Our previous analysis revealed that patients showed a statistically significant (at $P < 0.05$) improvement on the Semantic Fluency Test, statistically nonsignificant (at $P < 0.05$) improvements in performance on the Boston Naming Test (Boston Diagnostic Aphasia Examination, Peabody Picture Vocabulary Test, and the Communicative Abilities Log), and a statistically nonsignificant (at $P < 0.05$) decrease in performance on the Controlled Oral Word Association Test (see Table 1 in [34]). Since statistically significant improvements were only observed for performance on the Semantic Fluency Test, exploratory analyses investigating the relationship between changes in functional MRI measures of IFG activation/connectivity and the behavioral effects of iTBS were restricted to this test. While ideally behavioral correlations would have been performed on the out-of-scanner noun recognition task, the miniscule change between sessions and globally good performance precluded this approach. Importantly, the Semantic Fluency Test, like the covert verb generation task, required patients to generate words in response to a prompt. For the Semantic Fluency Test, patients generated as many words as they could think of that were congruent with category prompt (e.g., animals) with a 1-minute time limit, and performance on the Semantic Fluency test was measured by the number of congruent words produced within the 1-minute time limit. Thus, whereas the covert verb generation task required patients to silently generate verbs in response to presented nouns, the Semantic Fluency Test required patients to generate words in response to a given category.

3.2. Functional MRI Results. To test our hypotheses regarding the effects of iTBS on the magnitudes of activity in left and right IFG during covert verb generation, we compared activation magnitudes at each ROI between pre- and post-iTBS sessions. It is worth noting that the ROIs used for these analyses were chosen *a priori* in order to avoid the introduction of bias by defining ROIs based on the GLM results. Our analyses revealed increased activation magnitudes in the left IFG (t_7 = 3.32; FDR P = 0.02; mean change = 0.54, SEM = 0.18) and decreased activation magnitudes in right IFG (t_7 = −2.3; FDR P = 0.05; mean change = −0.22, SEM = 0.09) related to covert verb generation after iTBS treatment. Left and right IFG activation magnitudes for each patient are shown in Figures 3(b) and 3(c). On average, patients showed lower levels of activity in left IFG and higher levels of activity in right IFG during covert verb generation compared to finger tapping pre-iTBS. In contrast, patients showed higher levels of activity in left IFG and similar levels of activity in right IFG during covert verb generation compared to finger tapping post-iTBS. Accordingly, results from the LI analysis indicated that overall IFG responses during covert verb generation were more strongly left-lateralized after iTBS treatment (t_7 = 3.46, FDR P = 0.02; mean change = 0.48, SEM = 0.14). LI estimates for each patient at pre-iTBS and post-iTBS sessions are shown in Figure 3(d). On average, patients showed right-lateralized activation patterns in IFG pre-iTBS. In contrast, patients showed left-lateralized activation patterns in IFG post-iTBS.

To allow for a more thorough characterization of the data, whole-brain GLM analyses were also performed. Although no regions showed significant effects at a whole-brain FDR-corrected threshold of 0.05, the uncorrected statistical maps provide evidence for increased responses related to covert verb generation in left-hemisphere frontal, temporal, and parietal regions after iTBS (Figure 4(a)). While no regions showed changes that were significant after multiple-comparisons correction, the most reliable (voxelwise $P < 0.001$, uncorrected) increases in activity were observed in the left IFG pars opercularis (peak MNI coordinate: −40, 14, 10; 171 voxel clusters), the right thalamus (peak MNI coordinate: 10, −14, 20; 64 voxel clusters), and the right cerebellum VI (peak MNI coordinate: 30, −62, −30; 3 voxel clusters), and the most reliable (voxelwise $P < 0.001$, uncorrected) decreases in activity were observed in the right cerebellum crus 2 (peak MNI coordinate: 48, −52, −42; 12 voxel clusters), the right cerebellum VIII (peak MNI coordinate: 34, −44, −40; 6 voxel clusters), and the right inferior temporal gyrus (peak MNI coordinate: 54, −6, −30; 4 voxel clusters).

To test our hypothesis regarding the effects of iTBS on effective connectivity between the right and left IFG, we compared gPPI estimates between the right IFG seed region and the left IFG target region between pre- and post-iTBS sessions. It is important to note that gPPI estimates reflect the magnitude of condition-dependent changes in the relationship between activity in the seed region and activity in the target region [63]. Thus, the connectivity estimates for each session quantify how the relationship between responses in the right IFG and responses in the left IFG differed between conditions. These analyses revealed that compared to the pre-iTBS session, patients showed reductions in gPPI estimates between the right IFG seed region and the left IFG target region for the active condition contrast at the post-iTBS session (t_7 = −2.97; FDR P = 0.03; mean change = −0.24, SE = 0.09). The gPPI estimates for the active condition contrast for each patient are shown in Figure 3(e).

Since the gPPI measurement quantifies differences in the relationship between activity in the seed region (R IFG) and the target region (L IFG) that are moderated by task condition (VG-FT), a reduction in the gPPI estimate between right IFG and left IFG would indicate that the effect of right IFG activity on left IFG activity for covert verb generation relative to finger tapping was reduced after iTBS. Patients showed a small but positive mean effect of covert verb generation on connectivity

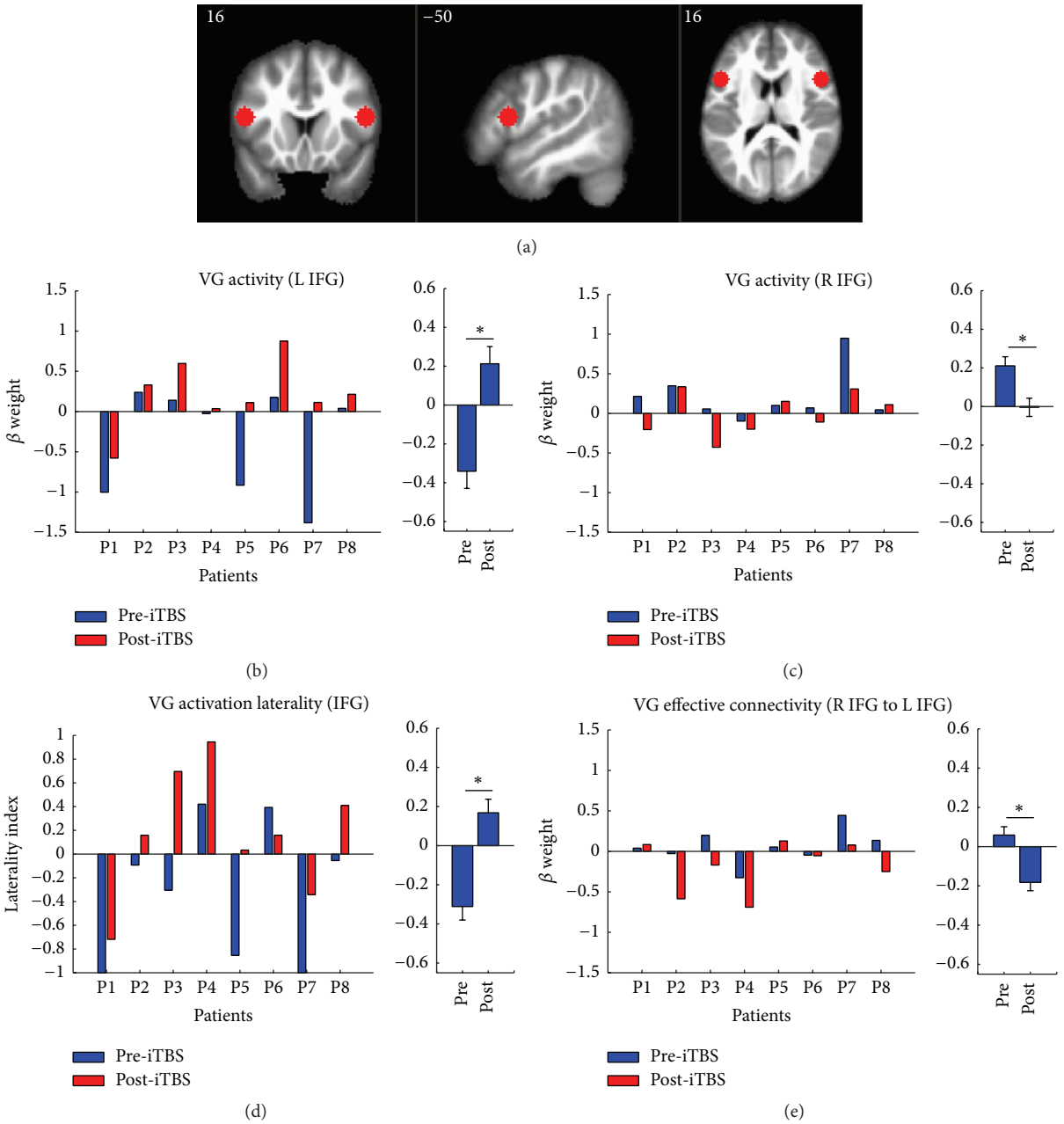

Figure 3: Results from ROI analyses. The left and right IFG ROIs are shown overlaid on slices from an anatomical template brain. The estimates of left (b) and right (c) IFG activation magnitudes, laterality indices (d), and effective connectivity from right to left IFG (e) are shown for the pre-iTBS (blue) and post-iTBS (red) sessions of each patient. For each plot in (b–e), bar graphs are shown on the right side that illustrate the mean and within-subjects standard error of the effect at pre-iTBS and post-iTBS sessions. *Significant at FDR $P = 0.05$.

between the right IFG and left IFG pre-iTBS, indicating that right IFG activity was more positively associated with left IFG activity during covert verb generation than during finger tapping. In contrast, patients showed a negative mean effect of covert verb generation on connectivity between the right IFG and left IFG post-iTBS, indicating that right IFG activity was more negatively associated with left IFG activity during covert verb generation than during finger tapping. Thus, the direction of the effect of task condition on the relationship between right IFG activity and left IFG activity changed between pre-iTBS and post-iTBS sessions, with right IFG activity being more negatively associated with left IFG activity during covert verb generation than during finger tapping.

To allow for a more thorough characterization of the data, whole-brain gPPI analyses were also performed. Although no regions showed significant effects at a whole-brain FDR-corrected threshold of 0.05, the uncorrected statistical maps provide evidence for reduced connectivity between the right IFG and left-hemisphere frontal, temporal, and parietal regions after iTBS (Figure 4(b)). While no regions showed

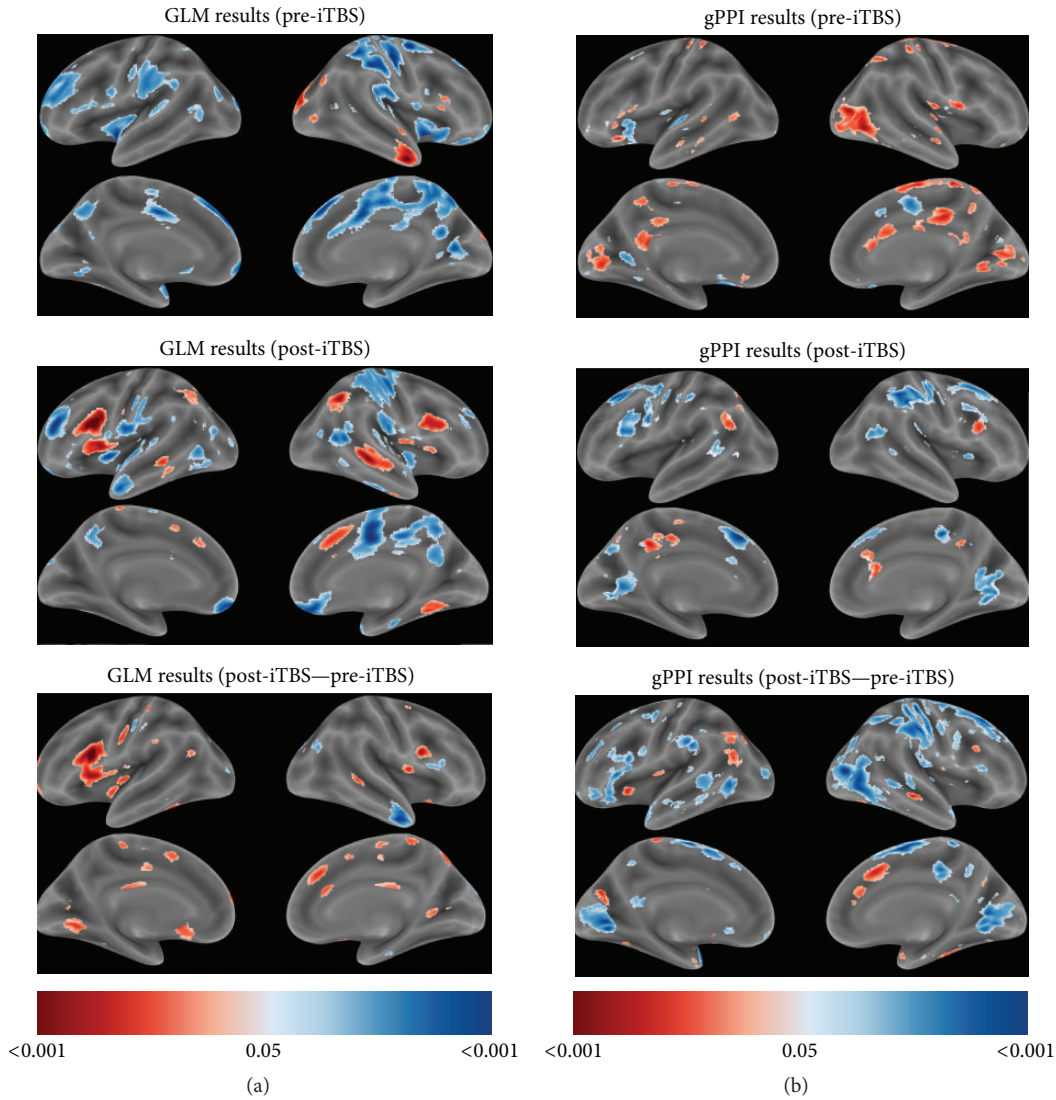

Figure 4: Whole-brain statistical maps for GLM and gPPI analyses. (a) Statistical parametric maps (SPMs) illustrating whole-brain activation for the VG > FT (red) and VG < FT (blue) contrasts from the pre-iTBS (top) and post-iTBS (middle) scan sessions are shown to illustrate overall activation patterns for each scan session (left, middle). An SPM illustrating changes in VG activation is also shown (bottom). (b) SPMs illustrating whole-brain gPPI results for the R IFG seed region for the VG > FT (red) and VG < FT (blue) contrasts from the pre-iTBS (top) and post-iTBS (bottom) scan sessions are shown to illustrate overall task-dependent connectivity patterns for each scan session. An SPM illustrating changes in task-dependent connectivity is also shown (bottom). Color bar values for all SPMs indicate uncorrected P values ranging from 0.05 to <0.001.

changes that were significant after multiple-comparisons correction, the most reliable (voxelwise $P < 0.001$, uncorrected) reductions in right IFG connectivity associated with the VG task were observed in the right middle temporal gyrus (peak MNI coordinate: 36, −74, 6; 65 voxel clusters), the right superior frontal gyrus (peak MNI coordinate: 16, −2, 60; 32 voxel clusters), the left IFG pars opercularis (peak MNI coordinate: −50, 8, 22; 8 voxel clusters), the right postcentral gyrus (peak MNI coordinate: 36, −32, 56; 7 voxel clusters), the left lingual gyrus (peak MNI coordinate: −14, −70, 0; 6 voxel clusters), the right cerebellum VI (peak MNI coordinate: 24, −60, −24; 4 voxel clusters), the left caudate (peak MNI coordinate: −12, −4, 10; 4 voxel clusters), and the left temporal pole (peak MNI coordinate: −32, 10, −30; 1 voxel cluster). Interestingly, comparable (voxelwise $P < 0.001$, uncorrected) increases in right IFG connectivity associated with the VG task were not observed after iTBS.

3.3. Exploratory Behavioral Correlation Results. Prior to assessing behavioral correlations with fMRI measures of IFG function, correlations between total lesion volume and each measure were assessed. This revealed moderate but nonsignificant correlations between total lesion volume and changes in L IFG activity ($r = 0.5$, $P = 0.2$) and changes in connectivity ($r = 0.33$, $P = 0.43$) and weak but nonsignificant correlations between total lesion volume and right IFG

activity ($r = 0.11$, $P = 0.79$). Thus, partial linear correlations were computed to investigate the relationship between the changes in functional MRI measurements of IFG function during covert verb generation and changes in performance on the Semantic Fluency Test following iTBS that were not attributable to total lesion volume. These analyses did not reveal significant correlations between overall changes in LI and changes in performance (partial $r = -0.03$, $P = 0.96$), changes in the magnitude of left IFG activity and changes in performance (partial $r = 0.16$, $P = 0.74$), or changes in the effects of covert verb generation on interhemispheric connectivity and changes performance (partial $r = 0.15$, $P = 0.76$). These analyses did reveal a strong negative correlation between changes in the magnitude of right IFG activity and changes in performance (partial $r = -0.82$, $P = 0.01$), indicating that decreases in right IFG activity during covert verb generation between pre/post-iTBS sessions were associated with concurrent improvements on the Semantic Fluency Test.

3.4. Ad Hoc Functional MRI Analysis Results. To further explore the effects of iTBS on IFG function, additional analyses were performed on the fMRI data. Our *a priori* analyses indicated that iTBS was associated with changes in the responses of both the left IFG and right IFG during covert verb generation and also indicated that iTBS was associated with reduced connectivity from right IFG to left IFG during covert verb generation. The exploratory behavioral correlation analyses also revealed the somewhat surprising result that post-iTBS improvements in performance on the Semantic Fluency Test were most strongly related to reductions in the responses of right IFG during covert verb generation. These findings led us to question whether the relationship between post-iTBS changes in the responses of left and right IFG during covert verb generation showed a consistent pattern across patients. They also led us to question whether the effects of iTBS on the responses of left and right IFG during covert verb generation might relate to the pretreatment levels of effective connectivity from right IFG to left IFG during covert verb generation. It might be expected, for example, that preexisting interhemispheric dynamics might influence the effects of high-frequency iTBS on the function of left and right IFG. These questions were addressed using additional exploratory partial correlation analyses that, while not related to our initial hypotheses, were included to more fully characterize the data.

First, we addressed the question of whether or not changes in left IFG activity after iTBS were correlated with changes in right IFG activity after iTBS while controlling for total lesion volume. This revealed a nonsignificant negative correlation between post-iTBS changes in left and right IFG activity (partial $r = -0.65$, $P = 0.12$). Second, we addressed the question of whether or not the effects of iTBS on left and right IFG activation magnitudes were correlated with the effects of covert verb generation on interhemispheric connectivity prior to iTBS treatment. This revealed a positive correlation between pre-iTBS effects of verb generation on interhemispheric connectivity and changes in left IFG activation magnitude after iTBS treatment (partial $r = 0.75$, $P = 0.05$). A nonsignificant negative correlation was found between pre-iTBS connectivity and changes in right IFG activation magnitude after iTBS (partial $r = -0.60$, $P = 0.15$).

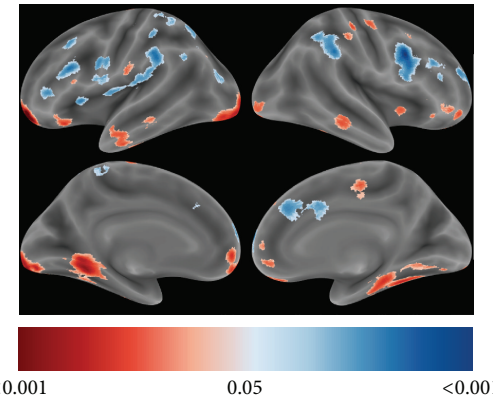

Figure 5: Whole-brain statistical maps VBM analyses. Statistical parametric maps (SPMs) illustrating increases (red) and decreases (blue) in GM volume following iTBS. Color bar values for all SPMs indicate uncorrected P values ranging from 0.05 to 0.001.

3.5. Voxel-Based Morphometry Analyses. VBM was used to test our hypothesis that patients would show changes in GM volume between pre- and post-iTBS sessions. An initial analysis using a voxelwise FDR threshold of 0.05 did not reveal any effects of iTBS on GM volume. An evaluation of the unthresholded statistical maps (Figure 5) revealed that the most reliable ($P < 0.001$, uncorrected) increases in GM volume occurred in the left medial orbital gyrus (peak MNI coordinates: −22, 52, −14; 123 voxel clusters) and in the left lingual gyrus (peak MNI coordinates: −20, −94, −14), and the most reliable ($P < 0.001$, uncorrected) decreases in GM volume occurred in the right superior frontal gyrus (peak MNI coordinates: 18, 66, 12; 8 voxel clusters) and in the right IFG pars opercularis (peak MNI coordinates: 36, 6, 30; 6 voxel clusters).

4. Discussion

Growing evidence supports the use of techniques that utilize the noninvasive modulation of cortical excitability to improve language functions in patients poststroke aphasia [28, 29, 34, 37, 40, 71–73]. However, the development and optimization of future treatment protocols that harness the full potential of these techniques are limited by a rudimentary understanding of the changes in neural function that enable their therapeutic effects [74]. The present study provides insights into this issue by characterizing changes in cortical function and structure following 10 sessions of iTBS applied to residual language-responsive cortex in a group of chronic poststroke aphasia patients. Our results show evidence for changes in language task-related responses in both the stimulated and unstimulated hemispheres following iTBS treatment that are characterized by a general shift from right-lateralized to left-lateralized responses. Moreover, we show evidence for

changes in the language task-related connectivity of right-hemisphere homologues of residual left-hemisphere language areas subsequent to iTBS treatment. These findings both replicate our previously reported observations of post-iTBS changes in left- and right-hemisphere responses related to semantic decisions [34] and extend them by demonstrating that similar changes in activation as well as additional changes in interhemispheric connectivity are observed during a covert verb generation task. Importantly, the current study utilized a language task (covert verb generation) that targets different aspects of language function from our previous study, which focused on semantic decisions, and that is independent of the stimulation targeting paradigm [34]. In addition, behavioral partial correlation analyses revealed that post-iTBS changes in the function of contralesional cortex showed a strong relationship to improvements in neuropsychological measures of language function after treatment that could not be explained by interindividual differences in lesion extents. Although we only found preliminary evidence for changes in regional grey matter volume following treatment with iTBS, our results nonetheless provide evidence of structural and functional neuroplasticity subsequent to a short-duration iTBS treatment in patients with poststroke aphasia. While preliminary, these results provide important insights into the changes in cortical function that enable improvements in language abilities following iTBS treatment.

The rerecruitment of residual left-hemisphere cortex for language processes is likely an important factor for the optimal long-term recovery of language functions following LMCA stroke [12, 14–17, 19, 21, 23]. Noninvasive techniques such as iTBS may facilitate the reintegration of residual cortex into cortical language networks by promoting beneficial neuroplasticity [29, 40]. While the mechanisms underlying the neuroplastic effects of iTBS in stroke patients are not fully understood, they likely involve multiple factors including modulations of gene expression, growth factor production, neurotransmitter release, and the facilitation of synaptic plasticity [74]. Our findings provide support for the conclusion that iTBS can induce plastic changes in the function of both the stimulated and unstimulated hemispheres in patients with chronic poststroke aphasia. Indeed, our ROI results suggest that the application of iTBS to residual language-responsive cortex in the left hemisphere has the potential to reduce contralesional compensation, increase residual left-hemisphere recruitment for language task performance, and alter task-dependent interhemispheric connectivity (Figure 3). While exploratory in nature, the results from our whole-brain analyses support these conclusions. Our GLM analysis found evidence for distinct patterns of left versus right-hemisphere activity during pre-iTBS and post-iTBS sessions, with left-hemisphere frontotemporal areas showing increased activity related to covert verb generation post-iTBS (Figure 4(a)). Similarly, our gPPI analysis found evidence for large-scale changes in the connectivity of right IFG during covert verb generation between pre-iTBS and post-iTBS sessions, with widespread reductions in right IFG connectivity being observed after iTBS (Figure 4(b)).

A speculative explanation for the observed effects is that the changes in left versus right IFG activity and connectivity during covert verb generation reflect the reinstatement of balanced inhibitory interactions between left and right IFC [13, 75]. Disproportionate influences of right-hemisphere homologues on left-hemisphere language areas have been previously documented in patients with aphasia resulting from LMCA stroke [76], and it is possible that heightened right IFG activation during language tasks reflects the release of transcallosal inhibitory outputs from left to right IFG following left-hemisphere damage [14, 75]. While not reaching our threshold for statistical significance, the results of our post hoc analyses suggested that increases in left IFG activation were related to decreases in right IFG activation regardless of lesion extent. This suggests that changes in right IFG activation depended in part on changes in the function of the left IFG, although this result is preliminary and should be interpreted as such. More highly powered analyses of larger samples are therefore necessary before conclusions about this relationship can be definitively drawn.

Additionally, results from our post hoc analyses indicated that the effects of iTBS on left and right IFG function had opposite relationships with the pre-iTBS strength of right IFG to left IFG connectivity during covert verb generation. While exploratory and requiring additional validation, these results have important implications, as they suggest that preexisting interhemispheric dynamics contribute to the effects of iTBS on the function of both the stimulated and unstimulated hemispheres. This interpretation is consistent with results from a recent study that indicated that the preservation of frontal white matter tracts, specifically the left arcuate fasciculus, explains substantial interindividual variability in behavioral improvements following cathodal TDCS applied to right IFG in patients with left IFG lesions [77]. Our results indicate that patients that showed stronger right to left IFG connectivity during covert verb generation at the pre-iTBS session also showed the most pronounced effects of iTBS on both left and right IFG activation magnitudes at the post-iTBS session. While future studies comparing connectivity between stroke patients in healthy controls are necessary to fully understand the implications of these findings, the general implications are that iTBS treatment can lead to increased left IFG activity/reduced right IFG activity and reduced right IFG to left IFG connectivity during language task performance and that the effects of high-frequency iTBS on both left and right IFG activation likely depend on the preexisting interhemispheric state prior to treatment.

Nevertheless, it is pertinent to address the question of how such large-scale changes in cortical function might result from the passive stimulation of residual left-hemisphere areas. After stroke, the loss of large-scale neural populations is thought to result in an acute breakdown of function in large-scale cortical networks that enable complex cognitive functions such as language [78] and attention [79]. This abrupt disruption of neural communication and regulation might be conceptualized as a large-scale perturbation of the brain's functional state that alters the trajectory of ongoing neural signaling [42]. During recovery, adaptive changes in the residual neural populations are thought to allow for the restoration of interregional communication and regulation, and it has been proposed that successful

recovery of function after stroke may reflect the restoration of a near-normal functional state, whereas poor recovery may reflect ineffective reorganization that results in an aberrant functional state that is maladapted to generating normal cognitive/behavioral outputs [42]. Thus, it might be speculated that by passively stimulating the residual left-hemisphere cortex iTBS might induce changes in the state of local neural populations that facilitate the restoration of a closer-to-normal functional brain state. An expected outcome in such a scenario would be that following iTBS patients would show task/stimulus-evoked responses that more closely resemble those observed in healthy individuals. While preliminary, the observed changes in language-related responses and interhemispheric connectivity resemble the patterns of language-related responses [24, 47] and task-dependent connectivity [48] that are observed in healthy individuals with typical language function.

While the combination of iTBS with active language therapy might also be expected to lead to an enhancement of beneficial neuroplasticity, the expectation that passive stimulation can lead to changes in task-driven responses and connectivity is not unfounded. Indeed, the cortical/subcortical networks that underlie cognitive and behavioral functions such as language and attention maintain ongoing interregional signaling even when tasks are not being performed [80–83]. Importantly, disruptions in resting state cortical networks are observed in stroke patients [43], and the structure of residual resting state networks is also altered by treatment [84]. Thus, it might be expected that passive high-frequency stimulation of a residual but dysfunctional language network node might lead to the strengthening of synaptic connections with other language network nodes and that this may facilitate the eventual reintegration of the stimulated node to the residual language network. Such an effect would be consistent with the capabilities of iTBS to induce LTP-like changes in synaptic transmission that persist beyond the stimulation period [32] and with reports that these effects are paralleled by changes in the temporal coordination of large-scale, low-frequency oscillatory activity [33].

4.1. Limitations. The present study has limitations that must be acknowledged and considered in interpreting the results and in designing future studies. Primarily, the lack of a sham-stimulation group precludes the ability to make definitive statements about whether the observed effects are specific to iTBS treatment. It is worth noting that activation patterns during the covert verb generation task have been found to be remarkably consistent across time in patients with chronic poststroke aphasia [46], and the presence of reliable effects across chronic stroke patients in the present study indicates that the observed effects are not likely due to spontaneous changes in IFG function. Nonetheless, future studies that employ a sham-stimulation control are necessary to make definitive statements regarding the neuroplastic effects of iTBS in patients with chronic poststroke aphasia.

While sham-controlled studies investigating the effects of neurostimulation on language function in patients with chronic poststroke aphasia have consistently reported behavioral improvements that are specific to real stimulation [36, 71, 73, 85], most of these have used stimulation protocols involving the application of low-frequency rTMS to the unaffected right IFG. This does make our finding that behavioral improvements subsequent to high-frequency stimulation of left IFG negatively correlated with changes in right IFG activation particularly noteworthy, as this finding supports the use of paradigms such as these that aim to suppress dysfunctional activity in right IFG. While it is possible that both approaches may be manipulating similar mechanisms to achieve improvements in behavior, it is important for future studies to characterize the similarities and differences in the neuroplastic effects induced by each approach and to identify the mechanisms by which beneficial behavioral effects are achieved. However, since iTBS increases local cortical excitability and potentiates cortical evoked responses [32, 33], it might potentiate language-related responses in residual IFG or lead to changes in LI estimates even in the absence of beneficial neuroplastic effects. For example, in the absence of some preserved interactions between left and right IFG, high-frequency stimulation of left IFG (or low-frequency stimulation of right IFG) might lead to unilateral changes in activation during language tasks that could present as a transient overall shift in LI estimates. This might provide an explanation for the absence of a relationship between overall changes in LI and improvements in SFT in the current study and for the absent [71] or weak [40] relationships between changes in LI and behavioral improvements reported by other studies that have applied low-frequency rTMS to right IFG. Indeed, while measurements such as LI provide useful summary statistics, they face intrinsic limitations that likely limit their utility in assessing the specific effects of iTBS [86]. Thus, future studies investigating the effects of iTBS in this population should consider independently the changes in left versus right-hemisphere function in addition to assessing changes in summary statistics such as LI.

A second limitation to this study is the relatively small sample size. Although some would argue that this property makes the observed significant effects more compelling since the likelihood of finding significant-but-trivial effects increases with sample size, our limited sample likely also led to the obscuration of real effects due to relatively low power [87]. Indeed, in the current study, the detrimental effects of having a small sample size would most likely manifest as insufficient power to detect real effects, especially for the whole-brain GLM, gPPI, and VBM analyses at multiple-comparisons corrected thresholds. As we did not find any significant effects at corrected P value thresholds for the whole-brain analyses, the results from these analyses should be interpreted with caution. As such, we have refrained from drawing strong conclusions about the effects of iTBS on GM volume or on activity/connectivity beyond those examined with our ROI analyses.

While the whole-brain results are exploratory and thus should not be used to draw strong conclusions about the effects of iTBS, they do merit discussion. Regarding the observed effects of iTBS on regional GM volume, it would not be surprising if iTBS did have an effect on GM morphology in these patients, as detectable changes following rTMS have been reported after in as little as five days by studies investigating the effects of rTMS on cortical morphology in healthy

individuals [44]. It is also worth noting that the previously reported effects of iTBS on white matter integrity in these patients were obtained using similarly lenient thresholds [41], and given the large variability in lesion etiologies for the patients in this study, it is thus perhaps not surprising that stronger effects were not observed here. While the direction and locations of some of the most reliable VBM effects (increased GM in left prefrontal areas/decreased GM in right IFG) are in line with our expected results, the current results do not provide basis for strong conclusions but do provide support for future investigations into these effects. Similarly, as noted earlier in the discussion, the whole-brain GLM and gPPI results do show effects consistent with larger-scale changes in the responses and interactions of the residual language network during covert verb generation. Thus, future studies with larger sample sizes are necessary to provide a full characterization of the effects of iTBS in this population.

In conclusion, we investigated the effects of iTBS applied to residual language-responsive cortex in the left hemisphere on MRI measurements of cortical function and structure in eight patients with chronic poststroke aphasia. We found that iTBS was associated with increased left-lateralization of IFG activity during covert verb generation. Changes in lateralization were characterized by increases in left IFG activation magnitudes and decreases in right IFG activation magnitudes that presented as an overall shift in the lateralization of IFG activity during covert verb generation. iTBS also led to reduced right to left IFG connectivity during covert verb generation, consistent with our interpretation that the effects of iTBS are related in part to changes in context-dependent interhemispheric interactions. Interestingly, our post hoc analyses suggest that the effects of iTBS on left and right IFG function were negatively correlated across patients (increased left IFG activity was associated with decreased right IFG activity), and the changes in left versus right IFG responses had opposite relationships to pre-iTBS levels of right IFG to left IFG connectivity during covert verb generation. These data provide insights into the neuroplastic changes associated with iTBS applied to residual left-hemisphere language areas in the treatment of chronic poststroke aphasia and provide support for future research in this area. Randomized, blinded, and sham-controlled studies in a larger sample of patients are necessary and are currently in progress (e.g., NCT01512264) in order to better clarify the neuroplastic effects of iTBS in this population.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Is the Frequency in Somatosensory Electrical Stimulation the *Key* Parameter in Modulating the Corticospinal Excitability of Healthy Volunteers and Stroke Patients with Spasticity?

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Somatosensory electrical stimulation (SES) has been proposed as an approach to treat patients with sensory-motor impairment such as spasticity. However, there is still no consensus regarding which would be the adequate SES parameters to treat those deficits. Therefore, the aim of this study was to evaluate the effects of applying SES over the forearm muscles at four different frequencies of stimulation (3, 30, 150, and 300 Hz) and in two intervals of time (5′ and 30′) by means of transcranial magnetic stimulation and Hoffmann's reflex (H-reflex) in healthy volunteers (Experiments I and II). A group of stroke patients (Experiment III) was also preliminary evaluated to ascertain SES effects at a low frequency (3 Hz) applied for 30′ over the forearm spastic flexors muscles by measuring the wrist joint passive torque. Motor evoked potentials and the H-reflex were collected from different forearm and hand muscles immediately before and after SES and up to 5′ (Experiment I) and 10′ (Experiments I and II) later. None of the investigated frequencies of SES was able to operate as a *key* in switching modulatory effects in the central nervous system of healthy volunteers and stroke patients with spasticity.

1. Introduction

On the recent years, an approach known as somatosensory electrical stimulation (SES), which consists in applying peripheral electrical stimulation below or at the motor threshold (MT) level [1–3], has been employed to treat patients with sensory-motor impairments such as spasticity [4–8]. Although there are encouraging clinical results observed in stroke [3, 9] and spinal cord lesioned [10, 11] patients, several methodological aspects of using SES therapeutically remain unresolved [12]. Chipchase et al. [13] and Veldman et al. [14] performed systematic reviews of SES parameters upon the primary motor cortex (M1) and suggest that there is insufficient evidence to determine their effects. Additionally, there also seems to be a lack of consensus regarding the effects of SES over spinal circuits mainly due to methodological constraints, which are described in more details elsewhere [15].

Table 1: Main characteristics of the stroke patients.

Patient	Age	Sex	Months after stroke	Prestroke hand dominant hemisphere	Lesioned hemisphere	Lesion type	Modified Ashworth scale
P1	59	M	37	Left	Left	Ischemic	2.0
P2	69	M	18	Left	Left	Ischemic	1.0
P3	45	M	48	Left	Left	Hemorrhagic	2.0
P4	63	F	24	Left	Left	Ischemic	1.0+
P5	70	M	51	Left	Left	Hemorrhagic	2.0

Among SES underlying mechanisms, Ward [16] proposed that an increase in the frequency of stimulation upon the stimulated nerve would allow the ionic current to flow more deeply, leading to the recruitment of a larger pool of somatosensory receptors from different tissues adjacent to the SES stimulation site. Thus, distinct effects upon excitability in M1 and/or spinal circuitries would be expected depending on the average output of recruited sensory fibers. However, to our knowledge, no previous studies have compared the effects of more than two SES frequencies upon corticospinal and spinal excitability.

Therefore, the aim of this study was to evaluate by means of transcranial magnetic stimulation (TMS) and Hoffmann's reflex (H-reflex) in normal volunteers the effect of applying SES over the hand and forearm muscles at four different stimulation frequencies, conducted in two experiments. Moreover, a group of stroke patients was also preliminary evaluated to ascertain SES effects at a low frequency over the forearm spastic flexors muscles on the wrist joint passive torque.

2. Materials and Methods

2.1. Subjects. The first two experiments were performed with two groups of right-handed volunteers without neurological disorders. The first was composed of fourteen volunteers (seven males and seven females; age: 19.0–39.0 years; height: 1.54–1.92 m; body weight: 53.3–97.0 kg; Edinburgh Handedness Inventory [17]: +30.0–+90.0) and the second comprised six volunteers (five males and one female; age: 20.0–37.0 years; height: 1.54–1.92 m; body weight: 56.0–97.0 kg; Edinburgh Handedness Inventory [17]: +40.0–+95.0). The criteria of inclusion and exclusion were based on Rossi et al. [18]. The first and second groups were subjected to $5'$ and $30'$ SES protocols, respectively, hereafter called Experiments I and II. Both application times were arbitrarily defined.

A third group composed of five chronic stroke patients (one female and four males; age: 45–70 years; height: 1.56–1.70 m; body weight: 61.0–89.0 kg) with spasticity, all right-handed (Edinburgh Handedness Inventory [17]: before stroke [+86.67–+100.0]; after stroke [−100.0–+23.33]), was also recruited for a pilot study concerning SES effects on spastic muscles (Experiment III). Among the adopted criteria of inclusion [18], the main one was to present spasticity on the right forearm limiting wrist movements with a maximum score of "2" ("More marked increase in muscle tone through most of the ranges of motion (ROM), but affected part(s) easily moved") based on the modified Ashworth scale [19]. Furthermore, cognition and skin sensitivity should be normal, which were evaluated by means of the *Mini Mental State Examination* [20] and *Pain and Light Touch Sensation* tests [21], respectively. All the stroke patients were independently evaluated by two experienced physical therapists. Individual characteristics of all stroke patients are summarized in Table 1.

The entire experimental protocols were submitted to the local ethical committee (process number: 082/08) and were conducted after each volunteer gave informed consent.

2.2. Experimental Designs. The first and the second groups (Experiments I and II) were subjected to four different frequencies of SES: 3, 30, 150, and 300 Hz. The frequencies were chosen based on previous reports in which they resulted in motor control improvement and/or neuromodulation [2, 22–24] by using SES and other therapeutic modalities of electrical stimulation. The frequencies of stimulation were applied in a random manner in both experiments. In Experiment I, the effects of the four frequencies of SES upon corticospinal and spinal excitability were evaluated in the same experimental session. Each frequency of SES was applied for $5'$ and was followed by a rest interval of $10'$. Motor evoked potentials (MEPs) and H-reflex were collected immediately before (baseline) and after ($0'$) SES application and then $5'$ later ($5'$). In contrast, in Experiment II, the volunteers were subjected to $30'$ of SES for each frequency and the protocol was conducted on four different days separated by a minimum interval of 72 hours. Similarly to Experiment I, MEPs and H-reflex were collected immediately before (baseline) and after ($0'$) SES application and then $5'$ ($5'$) and $10'$ ($10'$) later. Each single experimental session lasted for approximately 4 h.

In Experiment III, the stroke patients were submitted to SES therapy only at 3 Hz that was also applied for $30'$ in one single session, similarly to Experiment II. We justify such decision due to the time consumption (~4 h) of Experiments I and II and because previous authors [14] report interesting M1 modulatory effects when SES was applied below 10 Hz. Additionally, the passive mechanical resistance of the right wrist joint in the extension movement was evaluated by means of an isokinetic system [25] only before (baseline) and immediately after ($0'$) SES therapy.

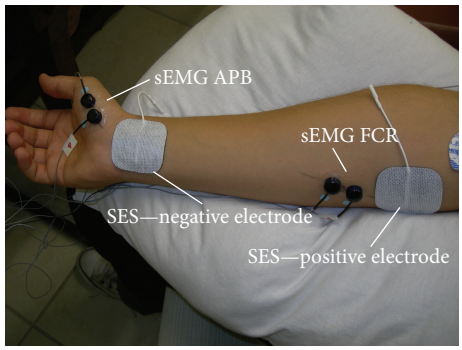

Figure 1: Surface electrode placement for SES. The positive electrode was placed near the elbow joint while the negative electrode was placed near the wrist joint. Surface electromyographic electrodes (in black) can be observed over the *flexor carpi radialis* (FCR) and *abductor pollicis brevis* (APB) muscle bellies.

2.3. SES Application. The SES pulse was a constant amplitude current waveform (an unbalanced asymmetrical biphasic pulse) with duration of 500 μs [26, 27]. SES was delivered using a custom electrical stimulator (FES-PEB) built by Velloso and Souza [27]. Pulse intensity was set below the MT and was determined based on the volunteers' reports of a tingling sensation in the stimulated area (forearm flexor muscles) without any pain or visible movement of the wrist and fingers. Surface self-adhesive electrodes (5 × 5 cm; model: CF5050, Axelgaard Manufacturing Co., Ltd., Denmark) were used for SES. SES intensities were set between 2–7 mA (Experiment I), 3–8 mA (Experiment II), and 3–5 mA (Experiment III). The surface electrodes were positioned over the right forearm, between the wrist (negative electrode) and the elbow (positive electrode) joints, parallel to the FCR muscle in the longitudinal direction (Figure 1).

Because it has been suggested that forearm rotation around its longitudinal axis may modulate spinal reflexes [28], the volunteers remained seated in a comfortable chair with the right forearm maintained in a prone position throughout the experiments.

2.4. TMS and H-Reflex Data Acquisition. A BIOPAC system (model: MP150; A/D converter: 16 bits; dynamic range: ±10 V; sampling frequency: 15 kHz; band pass filter: 4th order and 100–5000 Hz; gain: 2000; BIOPAC Systems, Inc., USA) was used to collect the MEPs and H-reflex. Surface BIOPAC reusable electrodes (Ag/AgCl; diameter: 8 mm) were placed following SENIAM recommendations [29] over the following muscle bellies: the *flexor* (FCR) and *extensor* (ECR) *carpi radialis* and *abductor pollicis brevis* (APB). The ECR and APB muscles were defined as controls in Experiments I and II. In Experiment III, we monitored one more muscle: the contralateral *flexor carpi radialis* (FCRc) from the nonaffected left forearm. Therefore, in this particular experiment, the FCRc, ECR, and APB muscles were defined as controls.

A TMS *butterfly* coil (model: MagPro; MagVenture, Denmark) was positioned over the left M1 in the optimal scalp position (*hot-spot*) to elicit FCR motor responses in the contralateral hemibody. The *hot-spot* position was achieved using a cap with marks (grid: 1 × 1 cm) according to the international 10-20 system for electroencephalography. The FCR *hot-spot* was defined as the site in M1 in which a single magnetic pulse set at a minimum intensity produced a MEP response (amplitudes with more than 50 μV in three out of six trials) in the relaxed muscle [30–32]. Then, the magnetic stimulus intensity was adjusted to 20% above the FCR resting MT.

As previously mentioned, MEPs were collected from all the muscles studied immediately before (baseline) and immediately after ($0'$) SES and up to $5'$ (Experiment I) and $10'$ (Experiments II and III) later after each session of SES and for each frequency. In each measurement, at least six (Experiment I) and ten (Experiments II and III) single TMS pulses were delivered with an interpulse interval of 5–10 s. The surface electromyographic (sEMG) data acquisition was triggered by a hardware pulse provided by the TMS system. Changes in spinal excitability were monitored through the evaluation of the mean value between the maximum and the minimum FCR H-reflex responses obtained by means of a curve of recruitment collected before the beginning of each SES session. To elicit the H-reflex from the FCR, a rectangular monophasic pulse of 800 μs was applied to a pair of surface electrodes, where one of the electrodes was placed over the median nerve (cathode: Ag/AgCl; 4 mm diameter), ~4 cm above the elbow joint, and the other on the opposite limb (anode: Ag/AgCl; 47.5 cm^2). The sEMG signal acquisition was started by a hardware pulse trigger provided by the stimulator. Once the electrical pulse was applied, a data window of 100 ms was collected and saved. The interpulse intervals varied between 5 and 10 s [33]. At least four sEMG signal data windows were obtained for further analysis due to the robustness of the collected H-reflex data. Regarding the FCR H-reflex, Experiment I provided suitable data only from seven volunteers (one man and six women; age: 19.0–31.0 years; height: 1.55–1.73 m; body mass: 53.3–82.6 kg; Edinburgh Handedness Inventory [17]: +60.0–+90.0) due to methodological constraints in recording it. Similarly, also due to methodological constraints, it was possible to collect the FCR H-reflex only from two stroke patients and, therefore, we decided not to present these data in this study.

Visual feedback of the sEMG signals was provided throughout all the experimental sessions to certify that all the volunteers were relaxed.

2.5. The Passive Wrist Torque Measurement. A custom-made device was built to evaluate the passive resistance of the wrist joint while being moved (Figure 2). It consisted of a stepper motor of 100 kgf·cm static torque controlled by a micro-step driver to make small steps of 0.036° that smoothed the movement. Attached to the stepper motor, a load cell allowed measuring the torque applied to the wrist. The data was recorded using a Spider 8 (HBM, Hottinger Baldwin Messtechnik) system with 16 bits, 4800 Hz sample rate, and an antialiasing filter set at 960 Hz.

The root mean square (RMS) value of the force measured by a load cell was calculated and used as an estimate of the

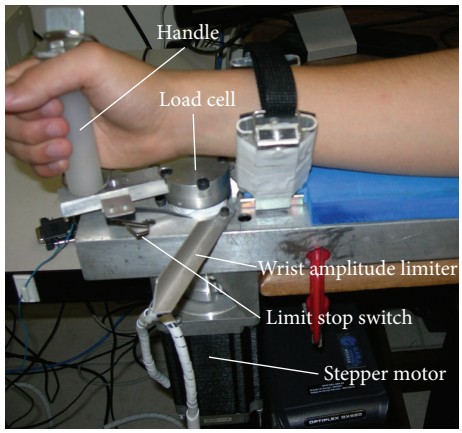

FIGURE 2: The isokinetic system that was built for measuring the passive mechanical resistance in the wrist joint. It provides the torque and angle data from cyclical wrist extensions with constant angular speed and range of movement.

torque (gf·cm) during 5 cycles of 35 degrees of wrist extension set at an angular velocity of 10 degrees per second to avoid the stretch reflex [34].

2.6. Data and Statistical Analyses. Surface EMG signals collected from each muscle during Experiments I, II, and III and at each interval of time (baseline, $0'$ and $5'$ or $10'$) were analyzed using an algorithm built in Matlab 6.5 (Mathworks, USA). This algorithm measured MEP and H-reflex peak-to-peak (P-P) values, which represents corticospinal [35] and spinal [36] excitability. MEP and H-reflex median values were then obtained from each six (Experiment I) and ten (Experiments II and III) sEMG signal data windows were from the muscles previously mentioned for each group, resulting in one value for each interval of time, that is, before (baseline) and after ($0'$) SES application, as well as $5'$ (Experiment I) and $10'$ (Experiments II and III) later for each SES frequency and for each volunteer. The medians from $MEP_{P\text{-}P}$ and $H\text{-}reflex_{P\text{-}P}$ values were then normalized by computing the ratio between the data for each interval of time ($0'$, $5'$, and $10'$) and the corresponding baseline value achieved before SES multiplied by 100 [2, 37–39].

All normalized MEP data values were analyzed using a two-way repeated measures ANOVA (factors: *interval of time* × *frequency*) for each muscle individually. For the H-reflex data, a two-way repeated measures ANOVA (factors: *interval of time* × *frequency*) was used, as all measures were taken only from the FCR muscle. For Experiment III (TMS and H-reflex), the analysis was performed using a two-way repeated measures ANOVA (factors: *interval of time* × *muscle*) while the isokinetic data evaluated by means of Student's paired t-test. The level of significance (α) was set at 5%. The statistical analysis was performed using R, version 3.1. The results are presented in terms of means and standard deviations.

3. Results

3.1. Experiment I. Figure 3 depicts the results obtained for normalized $MEP_{P\text{-}P}$ and FCR $H\text{-}reflex_{P\text{-}P}$ values, respectively, immediately after ($0'$) SES and up to $5'$ later for the four frequencies of SES applied during $5'$ and for the three muscles (FCR, ECR, and APB). The results obtained after SES set at all the investigated frequencies did not reveal any significant difference among *frequencies* ($P > 0.155$) and *intervals of time* ($P > 0.087$) in $MEP_{P\text{-}P}$ data as compared to the baseline for all the muscles (Figures 3(a), 3(b), and 3(c)).

Concerning the normalized FCR $H\text{-}reflex_{P\text{-}P}$ values (Figure 3(d)), it also did not show any significant difference among *frequencies* ($P = 0.469$) and *intervals of time* ($P = 0.177$) from the baseline.

3.2. Experiment II. Figure 4 depicts the results obtained for normalized $MEP_{P\text{-}P}$ and FCR $H\text{-}reflex_{P\text{-}P}$ values, respectively, immediately after ($0'$) SES and up to $5'$ and $10'$ later for the four frequencies of SES applied during $30'$ and for the three muscles (FCR, ECR, and APB). The results obtained after SES set at all the investigated frequencies did not reveal any significant difference among *frequencies* for FCR ($P = 0.443$) and APB ($P = 0.524$) muscles. Although there was a significant difference among frequencies for ECR ($P = 0.006$), they were not statistically different from baseline ($P > 0.05$). Similarly to Experiment I, there was also no significant difference among *intervals of time* ($P > 0.235$) in $MEP_{P\text{-}P}$ data from the baseline for all the muscles (Figures 4(a), 4(b), and 4(c)).

Our results did not also show any significant difference among *frequencies* ($P = 0.638$), *intervals of time* ($P = 0.563$), and interaction of *interval of time* × *frequency* ($P = 0.112$) concerning normalized FCR $H\text{-}reflex_{P\text{-}P}$ values from the baseline.

3.3. Experiment III. Figures 5 and 6 depict the results obtained for the normalized $MEP_{P\text{-}P}$ values and latency, respectively, for SES set at 3 Hz and during $30'$. There were no significant differences among *intervals of time* in normalized $MEP_{P\text{-}P}$ relative values from the baseline for all the three muscles, that is, the FCR ($P = 0.092$), FCRc ($P = 0.172$), ECR ($P = 0.814$), and APB ($P = 0.864$). Latency measures also did not show any significant difference ($P > 0.150$) concerning baseline values.

The resistance to passive extension (Figure 7(a); $P = 0.094$) and flexion (Figure 7(b); $P = 0.774$) movements of the wrist joint, evaluated by means of the isokinetic system, also did not show any significant difference for the comparison of measurements collected immediately after ($0'$) (Post) SES and the baseline (Pre).

4. Discussion

It has been proposed that the use of SES in the clinical field can provide improvements similar to those obtained with intensive training [40]. For instance, Conforto et al. [41] observed an increase in the force level of pinch movements in stroke patients after two hours of SES. Dos Santos-Fontes et al. [9] also suggested that SES might lead to long-lasting improvements of paretic arm performance in chronic stroke

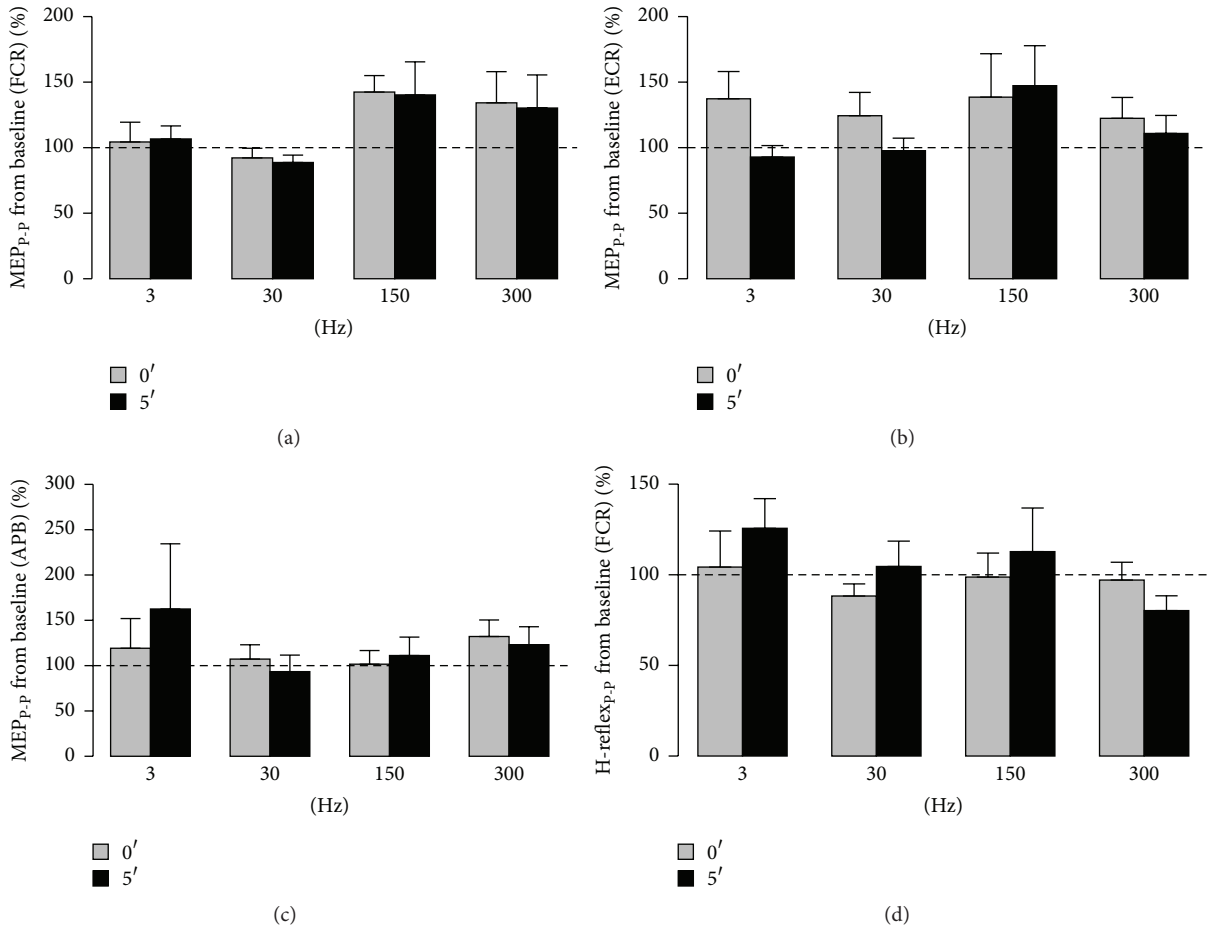

Figure 3: Normalized MEP$_{P-P}$ values collected immediately after (0′) SES and up to 5′ later at the four frequencies (3, 30, 150, and 300 Hz) for the *flexor* (FCR) (a) and *extensor* (ECR) (b) *carpi radialis* and the *abductor pollicis brevis* (APB) (c). (d) depicts the results obtained for normalized FCR H-reflex$_{P-P}$ values immediately after (0′) SES and up to 5′ later for the four frequencies of SES. The dotted line provides a reference from the baseline (before SES) and relative deviations of the results obtained after SES.

patients. Furthermore, SES has been proposed as an alternative approach in minimizing spasticity [6, 7, 42], although there is also no clarity concerning its underlying mechanisms. Hence, despite the above-mentioned examples concerning the positive effects of SES in a clinical setting, there is still no consensus regarding how some of the parameters used in SES (e.g., application time, frequency, intensity, waveform, and pulse width) are taken into account by the central nervous system (CNS) [14, 43]. Therefore, we decided to evaluate the effect of different frequencies of SES in the spinal and corticospinal excitability of healthy volunteers. In addition, we also performed a pilot study to evaluate the effect of SES applied for 30′, in line with clinical practice, and chose a frequency of 3 Hz applied over the spastic forearm flexor muscles of five stroke patients by means of TMS and passive wrist movement assessment.

Nevertheless, what does the literature tell us about different frequencies of SES in the corticospinal modulation and spasticity? Excitatory as well as inhibitory effects in M1 were shown to be maintained from minutes to hours after SES therapy [4, 13, 37, 44, 45]. Even though some authors have suggested that an increase in the stimulation frequency might lead preferentially to an increase in M1 excitability [13, 22, 38, 46, 47], others reported an opposite effect at the spinal level [48]. We hypothesized that an increase in frequency would allow the ionic current to flow more deeply over the full forearm extent and around the median nerve, which innervates the skin of the palmar side of the thumb, the index, the middle finger, and the APB muscle [49]. As a result, we expected to induce changes in corticospinal excitability of the FCR and APB muscles. However, we also considered the hypothesis of observing some effect in the ECR muscle given that type II afferent fibers (nonadapting sensory fibers) in muscles are able to facilitate or inhibit antagonist muscles [50], although Pierrot-Deseilligny and Burke [36] state that the effect of this interaction on the upper limb is not well understood.

Nevertheless, in the present study, both short (5′) and long (30′) durations of SES applied at different frequencies did not lead to changes in spinal and corticospinal excitability of the muscle under stimulation nor at the muscles that share any kinesiologic property with the stimulated one.

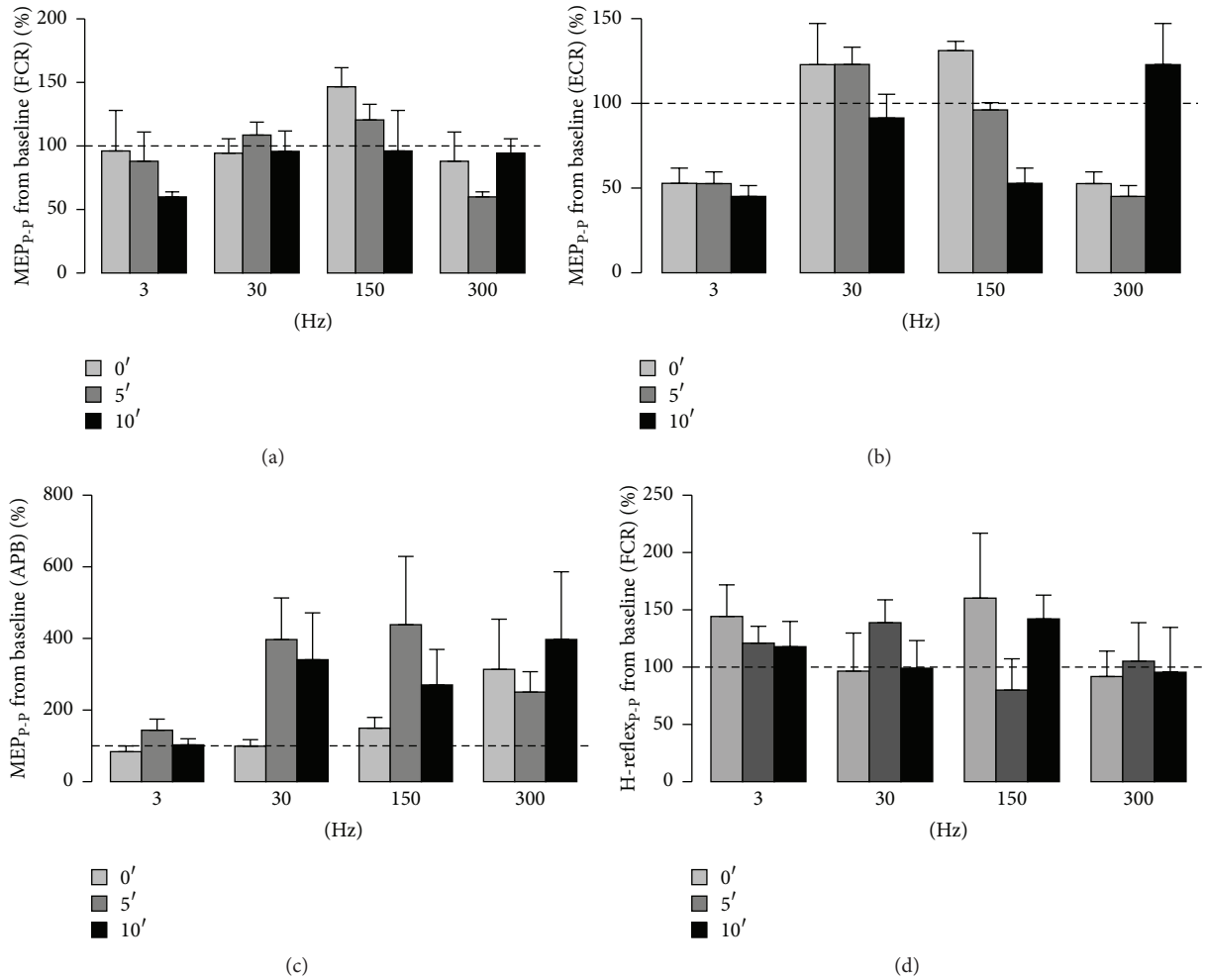

Figure 4: Normalized MEP$_{P\text{-}P}$ values collected immediately after (0′) SES and up to 5′ and 10′ later at the four frequencies (3, 30, 150, and 300 Hz) and for the *flexor* (FCR) (a) and *extensor* (ECR) (b) *carpi radialis* and the *abductor pollicis brevis* (APB) (c). (d) depicts the results obtained for normalized FCR H-reflex$_{P\text{-}P}$ values immediately after (0′) SES and up to 5′ and 10′ later for the four frequencies of SES. The dotted line provides a reference from the baseline (before SES) and relative deviations of the results obtained after SES.

Despite the discouraging results, some issues in addition to the frequency of stimulation must be taken in account and they are discussed as follows.

4.1. Pulse Width. We used a longer pulse width (500 μs) than have other authors (100 to 300 μs) [2, 6, 22], which are more selective [26]. We decided on this pulse width due to the need of recruiting a wide range of diameters and modalities of sensory afferents fibers. As our main aim was to evaluate the effect of different frequencies of SES, an increase in the selectivity of recruitment could mask a possible source of a corticospinal excitability modulation derived from this parameter only.

Similar negative and divergent results to ours have also been reported in the literature. For instance, Tinazzi et al. [2] observed an increase and a decrease in the corticospinal excitability of ECR and FCR, respectively, after applying SES at 150 Hz over the FCR muscle for 30′. On the other hand, Fernandez-del-Olmo et al. [49] performed a similar protocol and did not observe any facilitation or inhibition of both muscles. Curiously, both studies used a narrower pulse (100 μs), which is expected to be more selective for larger diameter fibers [16].

A shorter pulse width is expected to achieve higher selectivity in discriminating between somatosensory, motor, and pain sensory nerves. A pulse width of 500 μs may result in a greater summation of responses from receptors distributed close to the site of SES, which will be integrated and processed at different levels of the CNS and likely transmitted to M1 as an "averaged" signal. Thus, as a first hypothesis to explain the lack of SES modulation we suggest that this averaged input might not be able to induce any spinal or corticospinal modulation.

4.2. The Intensity of SES Stimulation. Another important issue concerns the intensity of the stimulation. Some studies report divergent effects of SES set at different intensity levels in corticospinal excitability but also including paired associated stimulation (PAS) protocols. In this context, Pitcher et al. [22] applied electrical stimulation above the MT and

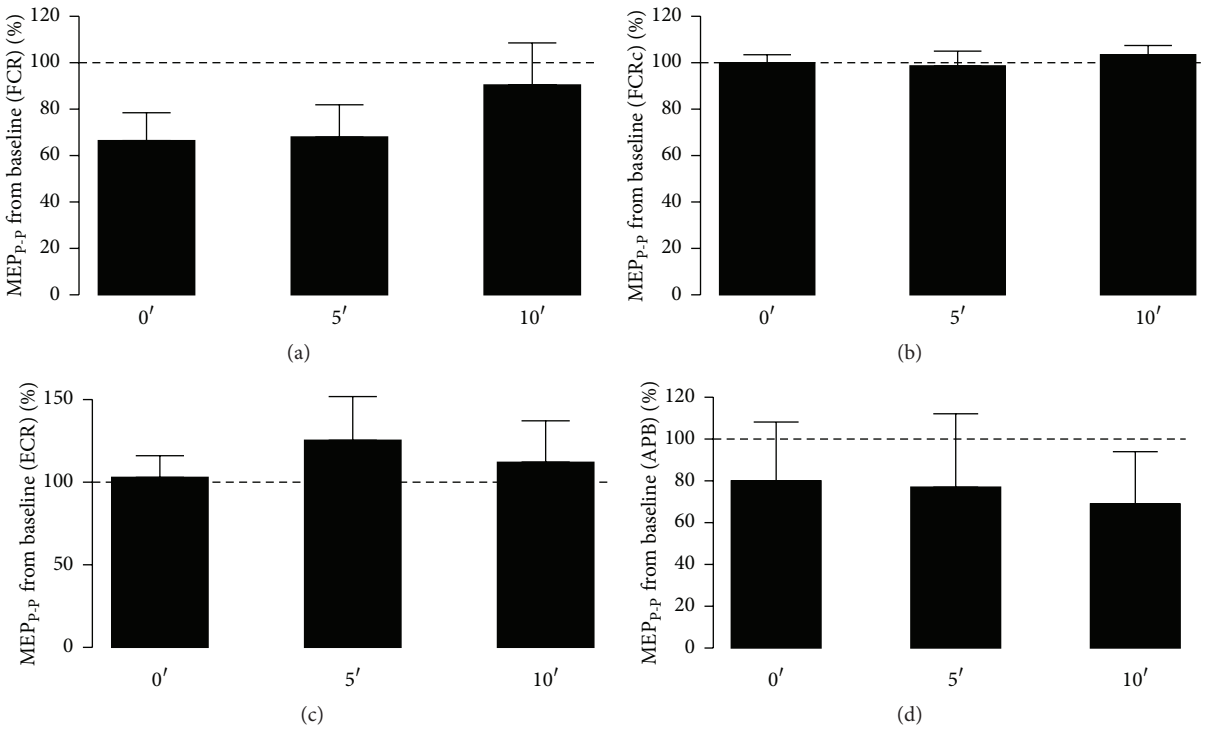

FIGURE 5: Normalized MEP$_{P\text{-}P}$ values collected immediately after (0′) SES and up to 5′ and 10′ later at 3 Hz for the ipsi (FCR (a)) and contralateral (FCRc (b)) *flexor carpi radialis*, the *extensor carpi radialis* (ECR), (c) and the *abductor pollicis brevis* (APB) (d). The dotted line provides a reference from the baseline (before SES) and relative deviations of the results obtained after SES.

set at 3 Hz over the *first dorsal interosseous* (FDI) muscle during 30′ while pulses of TMS were synchronized over the FDI *hot-spot* in a PAS protocol. They observed a decrease in MEP$_{P\text{-}P}$ for approximately 40–50′, suggesting that peripheral electrical stimulation at such low frequency mediates the recruitment of neural circuits that induce long-term depression (LTD). Alternatively, Aimonetti and Nielsen [51] showed that applying a conditioning electrical stimulus just below the MT over the median nerve, which supplies the FCR, produced a facilitation of the ECR for a very short term. In contrast, Bertolasi et al. [52] also showed that applying a conditioning electrical stimulus just above the MT over the median nerve produced an ECR inhibition. Veldman et al. [14] considered that the corticospinal excitability level appears to be modulated by a fine-tuning of SES intensity, which can vary from the perceptual to the motor threshold and be explained by the wide range and directions of neuronal responses obtained from the MEPs in TMS experiments. Moreover, their findings suggest that a stimulation intensity set at the perceptual threshold would not be capable of inducing any modulation in the corticospinal excitability. Based on these remarks and on the methodological approach adopted in the present study to tune the SES intensity (see details above in Section 2), as a second hypothesis we conjecture that, being provided at or very near the perceptual threshold for most of the volunteers, SES did not induce any measurable physiological effect for all the tested muscles, frequencies, and intervals of time.

4.3. The Maintenance of SES Intensity. Another important aspect concerns the maintenance of the stimulation intensity. Different authors adjust the intensity of SES during their experiments to avoid habituation [3, 41, 53, 54]. Unlike most of authors, we decided to maintain the same stimulation intensity to avoid a *bias* in the evaluation of corticospinal modulation after SES. Moreover, we evaluated two different application times of SES: a very short (5′) and a long (30′) one. Therefore, habituation mechanisms must be taken into account even in the SES protocol of short duration. In line with this third hypothesis, the works of Dobkin [55] and Dimitrijević et al. [56] supported the idea that a regular and constant pattern of SES can lead either to habituation/accommodation very quickly or to a failure in producing any change in M1 excitability, although this process does not seem to be rigid. Thus, we suggest as a third hypothesis that a habituation effect induced by the maintenance of the stimulation intensity could be an additional variable of not inducing any spinal or corticospinal modulation from SES in the present study.

4.4. The H-Reflexes$_{P\text{-}P}$ Evaluation. Even though we have faced methodological constraints to record the H-reflex from some healthy volunteers, SES seemed to fail to induce changes in the excitability of such measurement in FCR in Experiments I and II. Despite the fact that the H-reflex is generally considered a monosynaptic response, it may be also modulated

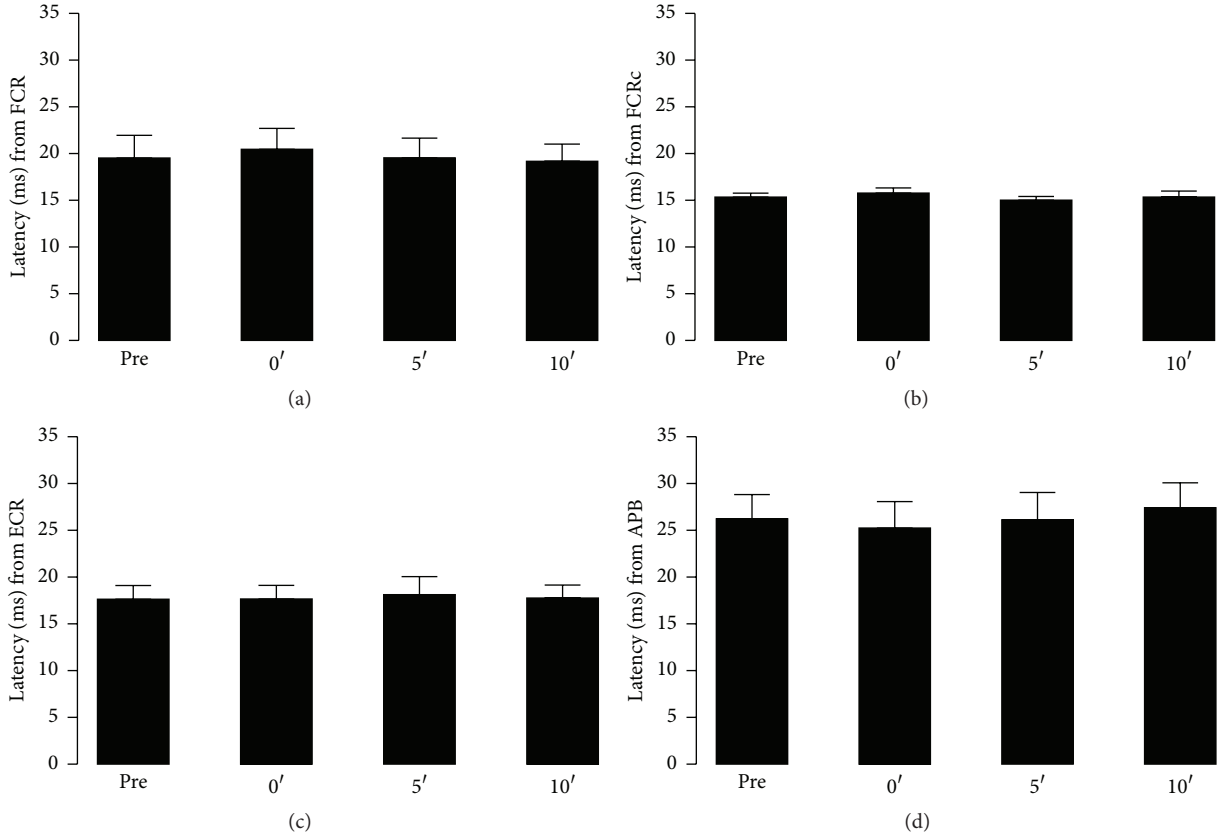

Figure 6: Latency (ms) collected before (Pre) and immediately after (0′) SES and up to 5′ and 10′ later at 3 Hz for the ipsi (FCR (a)) and contralateral (FCRc—nonaffected side (b)) *flexor carpi radialis*, the *extensor carpi radialis* (ECR (c)), and the *abductor pollicis brevis* (APB) (d).

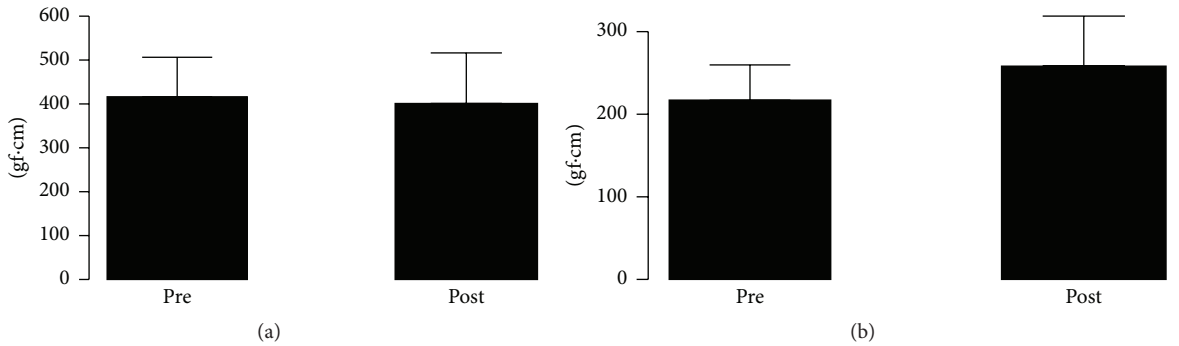

Figure 7: The torque (gf·cm) values from the resistance to the passive extension ((a) $P = 0.094$) and flexion ((b) $P = 0.774$) movements of the wrist joint collected before (Pre) and immediately after (0′) (Post) SES for the five stroke patients diagnosed with spasticity.

by other inputs which converge to common interneurons and that may receive inputs from spinal and supraspinal sources [7, 15]. Therefore, SES seems to stimulate differently specific receptors which might cancel themselves reciprocally and produce a mixture of excitation and inhibition [7], which was previously assumed as one of our hypotheses of not observing any significant difference in corticospinal excitability.

Departing from the herein shown lack of SES effect upon the FCR H-reflex, some studies [57] have shown that functional electrical stimulation (FES), which allows recruiting Ia muscle spindle sensory neurons, is able to induce modulation of the H-reflex in neurological patients and healthy subjects as well. Thus, it may be suggested that Ia afferents, not likely recruited under the SES protocol adopted in this study, could be able to evoke a FCR H-reflex modulation. Hence, the intensity of stimulation might also be a "key-point" in the modulation of spinal reflexes.

4.5. Stroke Spastic Patients. The purpose of this preliminary study was to evaluate for the first time, to our knowledge, the effects of SES set at a low frequency (3 Hz) over the

spastic forearm flexor muscles at the corticospinal level in chronic stroke patients. Moreover, we intended to evaluate the carryover effects of SES in the passive mechanical resistance of the impaired wrist joint. Although we did not observe any significant spinal and corticospinal modulation in Experiments I and II, we firstly hypothesized that a decrease in the corticospinal response provided by SES at a low frequency (3 Hz) [22] would be capable of contributing to decreasing temporarily such muscle overactivity. However, despite the negative results, different authors have provided some interesting arguments and results that preliminarily reinforce our previous hypothesis. As already cited, Pitcher et al. [22] observed that peripheral electrical stimulation at a low frequency results in a decrease in corticospinal excitability, although the hypotheses concerning the likely mechanisms under the effects of this electrical stimulation pattern in spasticity are still lacking. Notwithstanding, Liepert et al. [58] suggested that the intracortical inhibition might be reduced in stroke patients, due to a decreased GABAergic (inhibitory) and/or an increased glutamatergic (excitatory) activity, respectively. The unbalance of those neurotransmitters might contribute to the manifestation of spasticity of supraspinal origin although its physiopathology is still under investigation [59]. Likewise, long-term (>30′) SES at low frequencies might be able to conduct to an increase in the recruitment of GABAergic circuitries and conduct to a depression in corticospinal excitability. Pitcher et al. [22] also support that the modulation of those neural circuitries may be frequency-dependent and might be optimized by 3 Hz stimulation. Sonde et al. [60] also investigated SES set at a low frequency (1.7 Hz) in the treatment of spasticity in individuals with stroke and despite the improvements in the motor pattern, they did not also observe any significant decrease in spasticity, as evaluated by means of the Ashworth scale.

Even though the MEPs and wrist torque data did not reach statistically significant levels, the evaluation of the mechanical resistance by means of an isokinetic system, that is, a more accurate and sensible approach, four out of six patients presented relative decreases (5.5 to 14.3%) in passive wrist torque (flexion and extension), which might be seen as clinically significant. It is important to highlight that the Ashworth scale does not provide sensitivity to minimal variations on the level of spasticity.

A hyperexcitability of H-reflex has been considered as an index of spasticity [48, 61]. Therefore, the lack of change in H-reflex measurements does not allow implying spinal instead of corticospinal excitability as the likely portion of the CNS suitable to SES effects in stroke patients with spasticity.

In summary, as we expected to observe a covariation between the MEP behavior with a decrease in resistance to the passive extension movement of the wrist joint, we may also assume that a low frequency of SES set at 3 Hz and the perceptual threshold might be unable to induce any neuromodulation in these patients.

5. Conclusion

Based on the work of Ward [16], we proposed that an increase in the frequency of SES stimulation would allow the ionic current to flow more deeply and so a larger pool of somatosensory receptors from different tissues adjacent to the SES would be recruited. However, even though we must recognize small participant size samples in Experiments II and III, the results provided by our experiments suggest that none of the investigated frequencies (3, 30, 150, and 300 Hz) of SES along with all the other chosen parameters seem to be able to operate as a *key* in switching modulatory effects in the CNS of healthy volunteers and stroke patients with spasticity.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Review Article

Upper Limb Immobilisation: A Neural Plasticity Model with Relevance to Poststroke Motor Rehabilitation

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Advances in our understanding of the neural plasticity that occurs after hemiparetic stroke have contributed to the formulation of theories of poststroke motor recovery. These theories, in turn, have underpinned contemporary motor rehabilitation strategies for treating motor deficits after stroke, such as upper limb hemiparesis. However, a relative drawback has been that, in general, these strategies are most compatible with the recovery profiles of relatively high-functioning stroke survivors and therefore do not easily translate into benefit to those individuals sustaining low-functioning upper limb hemiparesis, who otherwise have poorer residual function. For these individuals, alternative motor rehabilitation strategies are currently needed. In this paper, we will review upper limb immobilisation studies that have been conducted with healthy adult humans and animals. Then, we will discuss how the findings from these studies could inspire the creation of a neural plasticity model that is likely to be of particular relevance to the context of motor rehabilitation after stroke. For instance, as will be elaborated, such model could contribute to the development of alternative motor rehabilitation strategies for treating poststroke upper limb hemiparesis. The implications of the findings from those immobilisation studies for contemporary motor rehabilitation strategies will also be discussed and perspectives for future research in this arena will be provided as well.

1. Introduction

The human brain changes itself in response to different types of experience through the reorganisation of its neuronal connections. This phenomenon is known as neural plasticity. It is suggested that it involves firstly a short-term modulation in the strength of existing pathways and that, over time, with prolonged exposure, such modulation might be followed by more stable, longer-term structural changes in brain networks [1]. Neural plasticity manifests itself during brain development [2], motor and perceptual skill learning [3, 4], and also during/after central nervous system (CNS) diseases/disorders [5], to name a few. The reorganisation of neuronal connections in the brain within these and also other contexts is commonly seen as being beneficial to the individual. However, neural plasticity can also be detrimental [6]. When brain changes are associated with improvements in the individual's behavioural capacity, neural plasticity is referred to as being adaptive [7–9]. On the other hand, when brain changes are linked to behavioural deterioration, or adverse consequences to the individual, neural plasticity is referred to as being maladaptive [10, 11].

Thus, it follows from the above that, by identifying neural plasticity and its behavioural correlates, together with an understanding of its mechanisms and likely causal factors, one can develop strategies to enhance adaptive and/or suppress maladaptive brain changes in order to improve the individual's behavioural capacity [12]. This opportunity for intervention is of paramount importance to the clinical context of CNS diseases/disorders, where many different patterns

of neural plasticity have been identified, each of which being associated with either positive or negative behavioural outcomes [5]. This is particularly true for stroke [5].

Stroke is a major cause of acquired physical disability in adults worldwide. Motor deficits affecting the upper limb are a common manifestation of stroke and greatly contribute to decreasing the individual's functional performance and thereby to the level of disability that is achieved [13]. It is widely appreciated that motor rehabilitation after stroke plays an essential role in reducing the individual's physical disability [14–16]. This paper will focus on the motor rehabilitation of the paretic upper limb after stroke.

Until about the late 1980s, neurorehabilitation professionals, despite recognising the importance of motor rehabilitation, had a somewhat restricted therapeutic armamentarium for treating stroke-related motor deficits, such as upper limb hemiparesis [17]. This was in part due to our relatively limited understanding of the neural mechanisms underlying motor deficits/recovery after hemiparetic stroke at that time [18]. By then, neurorehabilitation consisted mostly in teaching patients compensatory behaviours with their preserved body functions and/or in the utilisation of so-called "neurophysiological approaches" that lacked a strong scientific basis and had their therapeutic efficacy questioned [19]. Fortunately, from that time onwards, with the advent of noninvasive neurophysiological and neuroimaging tools for assessing/altering brain activity/function in humans, and the increasingly greater utilisation of such tools in stroke patients, together with major advances in the development and use of animal models of stroke, the scenario began to change. For instance, over the past twenty five years or so, the findings from numerous correlational and experimental studies conducted with brain injured adult humans and animals have substantially enlightened our understanding of the neural plasticity that occurs after hemiparetic stroke [5, 20–26]. Overall, this progress has contributed to the formulation of "theories" of motor recovery after stroke. In short, these theories identify neural plasticity patterns, both adaptive and maladaptive, and delineate their mechanisms and likely causal factors, for example, damage to, or activity changes in, particular brain regions or pathways and the presence or absence of specific behavioural or neural signals, to name a few. Such mechanistic understanding of poststroke motor deficits/recovery has, in turn, allowed for the theoretical conceptualisation and subsequent development of new, science-based motor rehabilitation strategies to treat upper limb hemiparesis, most of which are still under investigation [27–30]. In parallel, other strategies that were being conceptualised and developed from otherwise different, yet complementary scientific perspectives, for example, behavioural psychology and multidisciplinary movement science, have found in those neural plasticity-based theories of motor recovery a strong neuroscientific support. This has further contributed to the establishment of these latter strategies as treatment options for poststroke upper limb hemiparesis [31–34]. In this paper, we will refer to both these and those previously mentioned newly developed strategies as "contemporary motor rehabilitation strategies." Altogether, this has not only represented a major revolution in neurorehabilitation but also nurtured a more optimistic prospect to the field.

1.1. The Problem. Notwithstanding the aforementioned achievements, several challenges have yet to be addressed in the arena of poststroke motor rehabilitation research, and this has consequences to clinical practice worldwide [35–38]. One of these challenges, for instance, is that, in general, contemporary motor rehabilitation strategies for poststroke upper limb hemiparesis are most compatible with the recovery profiles of relatively high-functioning stroke survivors and therefore do not easily translate into benefit to individuals with poorer residual function. This is often in contrast to the day-to-day scenario of real-world rehabilitation settings, where many of the patients in need for motor rehabilitation after a stroke are usually at closer proximity to the lower end of the spectrum of functional recovery. This discrepancy may stem from the fact that most of the investigations performed so far in this field, particularly the studies testing motor rehabilitation strategies, have, for several reasons, focused primarily on well recovered stroke models [39] (but see also [40]). As a consequence, many stroke survivors, such as those sustaining low-functioning upper limb hemiparesis, remain with rather limited rehabilitation options [41].

Therefore, in light of the above, we argue that there is a need for alternative motor rehabilitation strategies for stroke, if clinical practice demands are to be met more widely and effectively. Essentially, these alternative strategies have to fulfill at least two requirements. First, they should be able to promote the adaptive neural plasticity pattern(s) currently identified as instrumental to poststroke motor recovery. Second, and most critically, their ability to do that must not be influenced by the individual's level of residual function. Importantly, such strategies are likely not only to be more compatible with the recovery profiles of stroke survivors with poor residual function, but also to translate into benefit to the entire spectrum of functional recovery. However, in order for this to be achieved, models that more closely resemble a condition of low-functioning upper limb hemiparesis are required. As will be elaborated in the remainder of this paper, upper limb immobilisation is a key candidate for this position.

Below, we will first briefly describe two prevailing theories of motor recovery after stroke and some of the contemporary motor rehabilitation strategies for treating poststroke upper limb hemiparesis that have been largely underpinned by these theories. This will be followed by an overview of upper limb immobilisation studies in healthy adult humans and animals and a discussion as to how the findings from these studies could inspire the creation of a model that, we believe, is likely to be of particular relevance to the context of motor rehabilitation after stroke. Our premise here is that an upper limb immobilisation model, by capitalising on both, current theories of motor recovery after stroke and the shortage of physical or overt movements, which is a hallmark of low-functioning hemiparesis, offers a compelling neurobehavioural framework upon which alternative motor rehabilitation strategies for treating upper limb hemiparesis can be envisioned, firstly developed and tested in healthy

individuals, and then ultimately translated into the clinical context of poststroke motor rehabilitation.

2. Theories of Motor Recovery after Stroke

2.1. Background Information: Cortical Motor Representations, What They Reflect, and What Drives Their Organisation. The motor cortex contains representations of body parts [42, 43]. Throughout this paper, we will refer to such representations as "cortical motor representations." These representations are commonly derived through electrical stimulation of the precentral cortex in the frontal lobe, with either noninvasive or invasive techniques, such as transcranial magnetic stimulation (TMS) and intracortical microstimulation (ICMS), respectively. While TMS is more frequently used with humans, ICMS is typically employed in animal research. The mechanism of action of these two techniques, when they are used for that purpose, usually involves the stimulation of axons from local intracortical circuits that synapse onto corticospinal neurons that then synapse onto contralateral spinal motor neurons innervating skeletal muscles, which, in turn, act upon specific body parts. However, direct activation of corticospinal neurons may also occur under certain conditions with both TMS and ICMS. The response to stimulation is then recorded in the periphery visually, that is, through the visualisation of movement of the corresponding body part(s), and/or by means of surface electromyography of the involved muscle(s). Thus, when derived, cortical motor representations may be considered as being a measure of both the amount of cortical/corticospinal tissue that is being dedicated to the motor control of a particular body part, which can be inferred from the size of the obtained representation over the cortex or scalp, and the strength or efficacy of this control at the time of stimulation, which can be inferred from the intensity of the recorded response in the periphery. The latter, in turn, usually indicates the excitability of the cortical/corticospinal components of the representation that are activated by the stimulation. As Phillips and Porter (1977) commented on the use of electrical stimulation for deriving cortical motor representations, "This leaves us free to concentrate on its merits as a tool for mapping the outputs that are available for selection by the intracortical activities that it cannot itself evoke" (Phillips and Porter 1977, p. 37) ([44], p. 304). In other words, the size and/or excitability of a cortical motor representation corresponding to a particular body part can be thought of as reflecting the individual's motor capacity/skill with that body part [45].

Contrary to what was once held, cortical motor representations are by no means static entities. Instead, numerous neurophysiological studies performed with TMS and ICMS on adult humans and animals in the past years have consistently demonstrated that such representations are rather flexible or dynamic and that one fundamental driver of their organisation, in terms of both their size and excitability, is the amount of use or sensorimotor experience with the corresponding body part(s). In general, conditions of increased use or sensorimotor experience that increase activity in the efferent and/or afferent neural signalling pathways targeting and/or coming from a particular body part, or parts, for example, motor skill learning/acquisition and somatosensory stimulation, induce an increase in the size and/or excitability of the cortical motor representation(s) of the involved body part(s). This is often accompanied by gains in motor capacity with the involved body part(s) and therefore reflects adaptive neural plasticity. Conversely, conditions of decreased use or sensorimotor experience that decrease or even cease activity in those pathways, for example, brain or peripheral nerve lesions, amputation, spinal cord injury, and ischemic nerve block-mediated local anesthesia, lead to a decrease in the size and/or excitability of the cortical motor representation(s) of the affected body part(s). This usually parallels a reduction in motor capacity with the affected body part(s) and therefore reflects maladaptive neural plasticity [46–49]. There is evidence that these changes in the size and/or excitability of cortical motor representations, both adaptive and maladaptive, are mediated by, among other factors, synaptic strength modification processes, such as long-term potentiation (LTP) and long-term depression (LTD), occurring within intracortical circuits in the motor cortex (see [45, 49] for further details).

2.2. Theories of Poststroke Motor Recovery. Findings collated from several neurophysiological and neuroimaging investigations performed with brain injured adult humans and animals have contributed so far to the formulation of at least two complementary theories of motor recovery after hemiparetic stroke. In the following sections, we will refer to these theories as the "*reactivation*" and "*rebalancing*" theories. It might be worth mentioning that what we call theories here has actually appeared more frequently in the literature as "concepts," "models," or "neural strategies" for motor recovery, rather than as theories per se. Also, other names rather than "reactivation" and "rebalancing" have been more commonly used. Nevertheless, the underlying principles/mechanisms have been fully preserved and the terms employed here were chosen simply for the purposes of this paper.

The "*reactivation*" theory makes three main assumptions. First, in the healthy brain, increased use or sensorimotor experience in the form of motor skill acquisition promotes adaptive neural plasticity, that is, increases in the size and/or excitability, of the cortical motor representation(s) of the involved body part(s). Second, motor deficits after hemiparetic stroke are due not only to the structural lesion itself, but, critically, also to maladaptive neural plasticity occurring in structurally intact, residual brain areas connected to the damaged region(s). Of special interest here is the adjacent, perilesional tissue surrounding the stroke core. After the stroke, this region may still contain some residual cortical/corticospinal components of the cortical motor representations corresponding to the paretic body parts. When this is the case, it follows that, over time, these spared representations often undergo a substantial reduction in their size and/or excitability. This condition of perilesional depression is usually the combined result of phenomena that are initially triggered by the stroke lesion, such as diaschisis and learned nonuse, and that are subsequently aggravated by a state of substantially reduced usage of, and hence reduced sensorimotor experience with, the paretic body parts. Third,

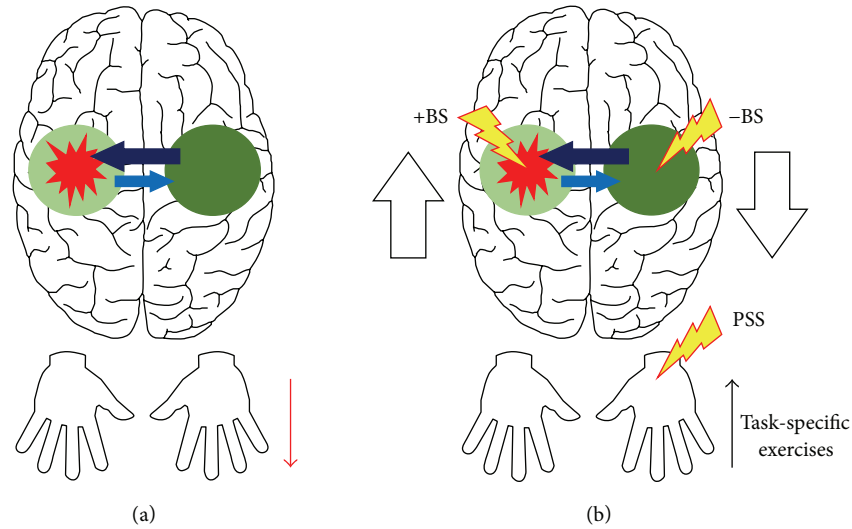

Figure 1: This figure illustrates the interaction between two prevailing theories of motor recovery after stroke, named here as the "reactivation" and "rebalancing" theories (a), and some of the contemporary motor rehabilitation strategies for treating poststroke upper limb hemiparesis that have been largely underpinned by these theories (b). *Red explosion-like balloon*: hemiparetic stroke. *Light green circle*: depression, that is, decreased size and/or excitability, of residual cortical motor representations in the adjacent, perilesional tissue. *Dark green circle*: overactivity of homologous cortical motor representations in the opposite, undamaged cerebral hemisphere. *Light blue arrow*: decreased transcallosal inhibition. *Dark blue arrow*: increased transcallosal inhibition. *Red thin downward arrow*: reduced use of the paretic upper limb contralateral to the stroke side. *Black thin upward arrow*: increased skilled use of the paretic upper limb through physiotherapy in the form of task-specific exercises. *Red-yellow bolts*: adjunctive therapies, such as excitatory and inhibitory brain stimulation (+BS and −BS, resp.) and peripheral somatosensory stimulation (PSS), to be combined with physiotherapy exercises. *White tick upward arrow*: increase activity in the ipsilesional motor cortex. *White tick downward arrow*: decrease activity in the contralesional motor cortex. See text for further details.

the mechanisms of the above can interact so that after hemiparetic stroke, increased use or sensorimotor experience with the paretic body parts in the form of motor skill (re)acquisition may adaptively modulate perilesional neural plasticity. Therefore, this theory predicts that, by increasing use of the paretic body parts in a skill (re)acquisition-like manner, the cortical motor representations corresponding to these body parts, which may still have some residual components available in the perilesional tissue, are *reactivated* and adaptively stimulated; that is, they increase their size and/or excitability and thereby improve the individual's motor function [50, 51] (see also [20, 52, 53] for further discussion).

The "*rebalancing*" theory, on the other hand, suggests that motor deficits after hemiparetic stroke result, apart from the structural lesion itself, from an interaction between depression of the perilesional tissue and further maladaptive neural plasticity involving both the ipsilesional and the contralesional cerebral hemisphere. For instance, a hemiparetic stroke, besides selectively disrupting lateralized motor control networks, often compromises transcallosal circuits that regulate the interhemispheric interactions between cortical areas. Of particular relevance here are the inhibitory transcallosal circuits that connect the cortical motor representations in the motor cortex of one hemisphere to those in the motor cortex of the contralateral hemisphere. The result is a reduction in the inhibition from the motor cortex of the stroke-affected hemisphere to the homologous area in the opposite, unaffected hemisphere. Such disinhibition usually leads to an abnormally increased activity in the contralesional motor cortex, which, in turn, causes excessive transcallosal inhibition from this area towards the homologous region in the ipsilesional hemisphere. This phenomenon is likely to be aggravated by a concomitant compensatory increased use of the less-affected body side, which contributes to further increasing activity in the contralesional motor cortex. Overall, it is suggested that such abnormal interhemispheric inhibition would be superimposed to an already existing condition of reduced perilesional activation in the affected hemisphere and that this could, in turn, contribute to a further decrease in the size and/or excitability of potentially available residual cortical motor representations in that hemisphere. Accordingly, this theory predicts that motor recovery after hemiparetic stroke is facilitated/enhanced if the interhemispheric interactions between the cortical motor representations of the two homologous motor cortices are *rebalanced* and that this can be achieved by increasing activity in the ipsilesional and/or decreasing activity in the contralesional motor cortex [54–56] (see also [20, 21, 57] for further discussion). The two theories of motor recovery are illustrated in Figure 1(a).

3. Contemporary Motor Rehabilitation Strategies for Poststroke Upper Limb Hemiparesis

Overall, those two aforementioned theories of motor recovery currently form the neuroscientific basis of contemporary motor rehabilitation strategies for treating upper limb

hemiparesis after stroke. These strategies might be broadly grouped into two complementary categories of interventions. The first category is primarily supported by the "*reactivation*" theory and currently constitutes the central pillar of modern neurorehabilitation. This category aims to increase skilled use of the paretic upper limb in order to *reactivate* and adaptively stimulate, that is, increase the size and/or excitability of, likely latent cortical motor representations in the damaged cerebral hemisphere. It consists mostly of physiotherapy exercises that are performed with the paretic upper limb and that are delivered in the form of repetitive and increasingly challenging task-specific exercises directed towards the (re)acquisition of motor skills [58, 59]. The second category of interventions, on the other hand, is based on both theories of motor recovery, but particularly on the "*rebalancing*" theory. This category aims to boost the effects of physiotherapy exercises through the use of adjunctive therapies that have the potential to *rebalance* the interhemispheric interactions between the two homologous motor cortices and that can be delivered in combination with task-specific practice. These adjunctive therapies include, but are not limited to, excitatory and inhibitory brain stimulation (+BS and −BS, resp.) [60–70] and peripheral somatosensory stimulation (PSS) [71–75]. The standard approach here is to deliver +BS to the ipsilesional motor cortex to increase its activity and/or −BS to the contralesional motor cortex to decrease its activity. In the case of PSS, the stimuli, which typically consist of low-intensity electric currents, are delivered transcutaneously to the paretic body part(s) in order to increase activity of the contralateral, ipsilesional motor cortex. These adjunctive therapies can be used either separately or in combination with each other. For instance, task-specific exercises can be coupled with both BS and PSS in order to further potentiate practice-induced adaptive neural plasticity (e.g., see [76]). Despite their promise, it is worth noting that these, and also other adjunctive therapies, are still under investigation and therefore are not yet widely used in clinical practice. The two categories of interventions are illustrated in Figure 1(b).

As can be noted, contemporary motor rehabilitation strategies for treating poststroke upper limb hemiparesis are centered in the physical/overt practice of motor tasks. Individuals are required to have a level of residual function that will ultimately allow them not only to actively engage with repetitive task practice, but also to perform increasingly difficult exercises [58, 59]. Therefore, while these rehabilitation strategies may undoubtedly translate into benefit for some stroke survivors, their overreliance on the availability of relatively high levels of residual function to overcome maladaptive and/or promote adaptive neural plasticity, that is, to promote motor recovery, represents a major obstacle. This is particularly true for individuals sustaining low-functioning upper limb hemiparesis who, due to poor residual function, cannot effectively engage with the physical practice of motor tasks in the way that is needed to promote the adaptive neural plasticity driving functional improvements. For these individuals, overt practice-based rehabilitation strategies are of very limited value. At this point, it is worth clarifying that a condition of poor residual function after a hemiparetic stroke, that is, low-functioning hemiparesis, at least in the way this concept is used in this paper, does not necessarily imply a severe neurological lesion completely destroying the cortical and/or corticospinal components of the cortical motor representations corresponding to the paretic body parts. While it stands to reason that such a severe lesion would result in poor residual function, the occurrence of the former is not a sine qua non for the presence of the latter. This is because many factors can influence/determine the level of residual function that is expressed by an individual after a hemiparetic stroke. For instance, it is well recognised that patients often experience substantial cardiorespiratory and skeletal muscle deconditioning after a hemiparetic stroke [77, 78]. As we have discussed elsewhere (e.g., see [79]), such deconditioning status, in turn, might greatly contribute to increasing their fatigue levels. Altogether, this can critically decrease the individual's physical capacity and ability to actively engage with the repetitive overt practice of progressive motor tasks, hence contributing to a low-functioning profile. Moreover, as already mentioned in the previous section, the motor deficits and hence the level of residual function that is shown by an individual after a hemiparetic stroke are currently thought to be largely influenced by maladaptive neural plasticity patterns occurring in structurally intact, residual brain areas/networks that were otherwise spared by the lesion. Therefore, a more holistic view here would be that a condition of low-functioning hemiparesis after stroke likely results from a complex interaction among different compromised body systems, instead of simply from the more direct effects of the neural damage, that is, the selective destruction of motor control pathways in the brain.

Thus, as suggested earlier in this paper, alternative motor rehabilitation strategies for stroke are currently needed. Essentially, in order to overcome the present obstacle, these alternative strategies must not rely on the individual's level of residual function to move from a state of maladaptive to one of adaptive neural plasticity, which may eventually translate into improved motor function. As will be discussed henceforth, an upper limb immobilisation model might be an attractive framework for developing such strategies.

4. Upper Limb Immobilisation and Neural Plasticity: What Do Human and Animal Studies Tell Us?

Given the fundamental role of use or sensorimotor experience in shaping cortical motor representations and thereby the individual's motor capacity/skill with the corresponding body part(s) (see Section 2.1), studies have started to investigate upper limb immobilisation as a paradigm of disuse or sensorimotor deprivation. In such studies, the entire upper limb, or part of it, is prevented to move by means of a bandage, splint, cast, and/or sling, either because of trauma or simply for experimental purposes. Particularly, these investigations have focused not only on the neural but also on the behavioural effects of immobilisation.

For example, in a classical study, Huber et al. (2006) immobilised the left arm and hand of healthy participants for

12 consecutive hours to explore the effects of sensorimotor deprivation on sensorimotor cortex activity, motor performance, and sleep slow wave activity (SWA). After the immobilisation, the authors found a substantial decrease in neuronal activity in the hand representation of the right sensory and motor cortices, as revealed by reduced somatosensory and motor potentials evoked through peripheral nerve stimulation and TMS, respectively. At the same time, the motor performance of the immobilised arm and hand had deteriorated, as indicated by an increase in hand-path area variability while individuals were reaching toward targets placed in front of them. Also, after immobilisation, there was a localised decrease in sleep SWA over the right sensorimotor cortex, which was detected through electroencephalography during subsequent sleep. Of note, a positive correlation was found between the changes in motor performance and the changes in both somatosensory evoked potentials and sleep SWA [80]. Subsequent studies have revealed comparable findings regarding the behavioural effects of immobilisation. In one of these studies, healthy participants had their upper limb immobilised for either 6 or 12 consecutive hours. It was found that after 12 but not 6 hours of immobilisation, motor control of the restricted limb was impaired, which was expressed through abnormalities in both hand trajectories and interjoint coordination during reaching movements [81]. Similarly, in a different study, healthy individuals displayed altered motor performance in a reach-to-grasp task after 10 hours of continuous arm and hand immobilisation. Here, the transport phase of the reach-to-grasp movement was affected, in a way that reaching was slower and its peak velocity time was achieved earlier. An interesting finding from this study was that motor performance on the reach-to-grasp task quickly returned to baseline levels with only a few trials of practice after the immobilisation had been removed [82].

By employing the same immobilisation protocol from the latter study above, Avanzino et al. (2011) explored with TMS the effect of upper limb disuse on the interhemispheric interactions between the two homologous motor cortices. Additionally, they investigated whether this effect was modulated by the amount of use of the nonimmobilised limb. The study consisted of two groups. In one group, participants received no instructions regarding the amount of use of the nonimmobilised arm and hand, "free to move" group, whereas, in the other group, volunteers were instructed to limit contralateral movements, "limited movement" group. After the 10 consecutive hours of right arm and hand immobilisation, both groups showed decreased excitability of the hand representation in the left motor cortex and reduced interhemispheric inhibition from the left to the right hand cortical motor representation, with the latter effect being more pronounced in the "free to move" group. Of note, the excitability of the hand representation in the right motor cortex, as well as the interhemispheric inhibition from the right to the left hand cortical motor representation, increased only in the group that was free to move the left, nonimmobilised arm and hand [83].

In keeping with these latter findings, a longitudinal neuroimaging study by Langer et al. (2012) reported bilateral structural changes in the sensorimotor cortex and corticospinal tract of immobilised individuals recovering from upper limb fractures. After an average of 16 days of right arm and hand immobilisation, cortical thickness and fractional anisotropy (FA) were reduced in the hand representation of the left sensory and motor cortices and over the left corticospinal tract, respectively. In addition, motor abilities with the left arm and hand improved throughout the restriction period, presumably as a consequence of an increased use in order to compensate for the immobilisation of the contralateral limb. Interestingly, this behavioural change was associated with an increase in both cortical thickness and FA of the right motor cortex and corticospinal tract, respectively, and with a decrease in cortical thickness over the left sensorimotor cortex [84].

In another longitudinal study, in this case conducted with healthy adult monkeys, Milliken and colleagues (2013) investigated the effect of distal forelimb immobilisation on the somatotopic organisation of the corresponding cortical motor representation. Here, immobilisation periods varied from 38 to 248 days. Detailed cortical motor representations of the distal forelimb of the animals were obtained through ICMS techniques before, during, and after the immobilisation intervals. The authors found a progressive decrease in the size of the representation of the digits together with an equivalent increase in the size of the representation of more proximal limb parts, such as wrist and forearm. These changes were paralleled by a reduction in general/skilled use of the digits, which, in turn, was followed by a concomitant increase in the use of more proximal limb parts. In general, those cortical changes were reversed to baseline levels after removal of the immobilisation during a period of behavioural recovery, when the animals regained general/skilled use of the digits, either spontaneously or through forced use [85].

Complementing the above findings, Rosenkranz et al. (2014), by recording a variety of TMS-derived measures, recently showed that upper limb immobilisation, besides decreasing the excitability and/or size of the corresponding cortical motor representations in the contralateral motor cortex, also selectively alters neural plasticity and intracortical inhibition mechanisms within the same representations. Specifically, the authors showed that, after 8 consecutive hours of left hand immobilisation, individuals displayed increased responsiveness to paired associative stimulation (PAS) protocols, which are thought to induce long-term potentiation- (LTP-) like and long-term depression- (LTD-) like processes. In other words, both LTP and LTD were facilitated in the hand representation of the contralateral right motor cortex after immobilisation, presumably reflecting homeostatic adjustments that operate to increase the sensitivity of corticospinal neurons to available synaptic inputs and thereby prevent too much of a decrease in motor output capacity. In addition, after immobilisation, short-interval intracortical inhibition (SICI) was reduced in the hand representation of the right motor cortex, and this change was negatively correlated with the changes in excitability over this cortical area. Again, this is likely to reflect compensatory adjustments that act during/after immobilisation to maintain overall motor cortex excitability within a certain range. Finally, a correlation was also found between the reduction

in the excitability of the hand representation over the right motor cortex and the strength of the effect of the PAS protocols. This correlation was positive for the LTP-inducing and negative for the LTD-inducing protocol [86]. The findings from this study, particularly those regarding the changes in neural plasticity and intracortical inhibition mechanisms, might explain, at least in part, the somatotopic reorganisation of cortical motor representations that usually occurs with upper limb immobilisation [86], such as that observed in the monkeys from the study mentioned previously [85].

Interestingly, the neural and behavioural effects that have been reported in immobilisation studies are, to a large extent, similar to those effects reported in investigations employing ischemic nerve block-mediated local anaesthesia, both in healthy individuals and after stroke [87–90]. This similarity emphasises the role of the presence/level of activity in the afferent and efferent neural signalling pathways associated with a particular body part in determining the size and/or excitability of its representation in the motor cortex and thereby the individual's motor capacity/skill with it. This observation, in turn, further corroborates the "*reactivation*" theory that was described previously in this paper (see Section 2.2).

In summary, the studies reviewed in this section provide evidence that upper limb immobilisation

(i) impairs motor performance with the restricted body part(s), even after short periods of restriction ranging from 10 to 12 hours, an effect that is largely reversible;

(ii) induces maladaptive neural plasticity of the cortical motor representation(s) of the immobilised body part(s), which expresses itself in the form of motor behaviour deterioration, and which may vary from a simple reduction in the size and/or excitability of the involved representation(s) to structural changes in the cortical and corticospinal components of the same representation(s), depending on the duration of the immobilisation;

(iii) affects the interhemispheric balance between the two homologous motor cortices in favour of the cortical motor representation(s) from the cerebral hemisphere ipsilateral to the immobilised body part(s), an effect that seems to be largely modulated by the amount of use of the contralateral, nonimmobilised limb;

(iv) modulates neural plasticity and intracortical inhibition mechanisms within the cortical motor representation(s) of the restricted body part(s), a process which is likely to be responsible for the maladaptive neural plasticity of the involved representation(s). More specifically, such modulation occurs in a direction that appears to be predicted by the amount of depression that is induced by the restriction in the involved representation(s); for example, the larger the decrease in excitability, the greater the sensitivity of the representation(s) to subsequent LTP-like processes (with the opposite being true for LTD-like processes) and the smaller the reduction in SICI within the same representation(s).

5. Upper Limb Immobilisation as a Model for Developing Alternative Motor Rehabilitation Strategies for Poststroke Upper Limb Hemiparesis

The proposal presented in this paper is that an upper limb immobilisation model offers a compelling neurobehavioural framework for developing alternative motor rehabilitation strategies for treating upper limb hemiparesis after stroke. As summarized previously, the neural effects of upper limb immobilisation are, to a large extent, similar to the maladaptive neural plasticity patterns that are often seen after hemiparetic stroke and that underpin current theories of motor recovery. To briefly recall, those effects involve both a reduction in the size and/or excitability of the cortical motor representation(s) corresponding to the immobilised body part(s) and changes in interhemispheric balance, with increased activity biased towards the cortical motor representation(s) from the cerebral hemisphere ipsilateral to the restricted limb. Indeed, in terms of maladaptive neural plasticity patterns, an upper limb immobilisation model largely resembles a hemiparetic stroke model, except of course for the absence of a true lesion (Figure 2(a)).

But if this is to be true, then what could be the advantages of using an upper limb immobilisation model as a stroke-like model for developing alternative motor rehabilitation strategies for upper limb hemiparesis, in place of currently used models (see Section 1.1)? Here, we argue that, besides inducing the maladaptive neural plasticity patterns that usually occur after a hemiparetic stroke and that are currently thought to play an important role in mediating the individual's motor deficits, the upper limb immobilisation model essentially promotes a condition of rather decreased, if any, overt use or sensorimotor experience, which in fact characterizes the restriction paradigms themselves. Such condition, in turn, is much more compatible with the recovery profiles of individuals with poor residual function. Thus, an upper limb immobilisation-based stroke-like model, in comparison to current models, more closely resembles a condition of low-functioning upper limb hemiparesis.

Importantly, within this context, if during a paradigm of upper limb immobilisation in healthy individuals interventions could be delivered in order to prevent the maladaptive neural plasticity that is induced by movement restriction, because these interventions would necessarily have to bypass overt movement execution, they could translate into alternative motor rehabilitation strategies for poststroke upper limb hemiparesis with a greater potential for benefiting those with poor residual function. Here, it is at least theoretically plausible that such interventions would be able to promote, for example, in low-functioning stroke survivors, the adaptive neural plasticity patterns currently identified as instrumental to poststroke motor recovery (see the "*reactivation*" and "*rebalancing*" theories in Section 2.2). Furthermore, the behavioural effects of immobilisation would also be of value to this context. For instance, it would be the case that interventions under investigation could aim to prevent not only the induction of maladaptive neural plasticity but also

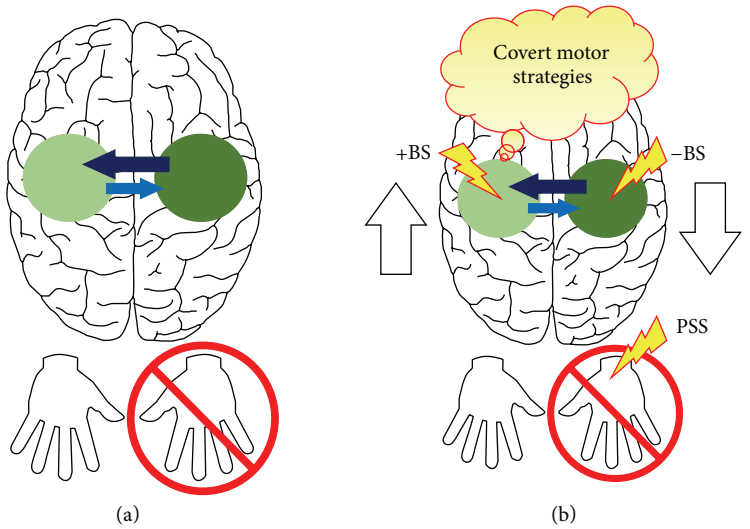

Figure 2: (a) highlights the similarity between the maladaptive neural plasticity patterns that often occur after a hemiparetic stroke and that are currently thought to play an important role in mediating the individual's motor deficits (see Figure 1(a) for comparison) and the neural plasticity patterns that are induced by upper limb immobilisation (*red crossed circle*) in otherwise healthy individuals. *Light green circle*: depression, that is, decreased size and/or excitability, of the cortical motor representation(s) corresponding to the immobilised body part(s). *Dark green circle*: overactivity of the homologous cortical motor representation(s) in the opposite cerebral hemisphere. *Light blue arrow*: decreased transcallosal inhibition. *Dark blue arrow*: increased transcallosal inhibition. (b) indicates potential interventions that could be delivered during a paradigm of upper limb immobilisation in healthy individuals in order to prevent maladaptive or promote adaptive neural plasticity in the motor system. These interventions might include, for instance, covert motor strategies, such as action observation (AO) and (likely) motor imagery (MI) (*red-yellow balloon*), and adjunctive therapies, such as excitatory and inhibitory brain stimulation (+BS and −BS, resp.) and peripheral somatosensory stimulation (PSS) (*red-yellow bolts*). *White tick upward arrow*: increase activity in the motor cortex contralateral to the immobilisation. *White tick downward arrow*: decrease activity in the motor cortex ipsilateral to the immobilisation. The idea here is that this might contribute to the development of alternative motor rehabilitation strategies for treating poststroke upper limb hemiparesis. See text for further details.

the deterioration of overt motor performance, which has also been a reported effect of immobilisation early after its removal (see beginning of Section 4).

5.1. Preventing Maladaptive/Promoting Adaptive Neural Plasticity during Upper Limb Immobilisation. Besides focusing on the neural and behavioural effects of upper limb immobilisation, recent studies have also started to explore how it can be used as a model of maladaptive neural plasticity upon which it is possible to test interventions that aim to prevent this neural plasticity from occurring. Specifically, researchers have employed upper limb immobilisation firstly to induce a depression, that is, a decrease in the size and/or excitability, of the cortical motor representation(s) of the restricted body part(s) and/or an interhemispheric imbalance between homologous representations in favour of the representation(s) ipsilateral to the immobilised body part(s). Then, they would try to prevent these changes from occurring through the concomitant delivery of interventions that are thought to have the potential to activate and adaptively stimulate cortical motor representations in the absence of overt use or sensorimotor experience with the corresponding body part(s). Below, we will review these studies and interventions within the context of motor rehabilitation after stroke.

5.1.1. Background Information: Covert Motor Strategies and Their Infusion into Poststroke Motor Rehabilitation. Covert motor strategies might also be referred to as cognitive motor strategies. They include, for example, motor imagery (MI) and action observation (AO). These strategies are referred to as "covert motor" strategies because of their intrinsic ability to activate the motor system of the brain without the overt execution of movements. As suggested by Sharma et al. (2006), they may achieve that through the "backdoor" of the brain's motor system [91].

Theoretical support for MI and AO as covert motor strategies comes mostly from the "Simulation Theory," which was proposed by Jeannerod almost fifteen years ago. According to this theory, the brain's motor system, including its cortical motor representations in the motor cortex, is part of a simulation network that is activated not only when we move, but also when we imagine ourselves or observe others moving. In this vein, the theory proposes that the neural substrate that is activated for the overt execution of a movement or action is, to a large extent, also activated by the imagination or observation of that same movement or action [92]. Studies from our group and several others performed with healthy participants have provided strong empirical support for the "Simulation Theory," by showing an extensive overlap in neural activation between conditions of overt execution and conditions of imagination or observation

of movements, and this includes activation of the cortical motor representation(s) of the involved body part(s) [93–98]. In addition, we have also shown that this overlap in neural activity does not remain confined to the motor execution domain but also occurs, for example, between movement preparation and MI [99, 100]. This equivalence in neural activation between movement preparation/execution and MI/AO is thought to account for the improvements in overt motor performance that are commonly seen in healthy individuals after MI/AO training [94, 101, 102]. For example, in a classical study, Pascual-Leone and colleagues (1995) showed that MI training alone, in comparison to physical practice, also led to significant improvements in the overt performance of a fine motor skill with the hand. Moreover, the same neural effects that were induced by physical practice were also found in the individuals undergoing only MI training. In both conditions, there was an increase in the size and excitability of the cortical motor representation of the trained hand [102]. Importantly, the findings from this study demonstrate not only that MI on its own can activate the cortical motor representation(s) of the involved body part(s) but, more critically, that MI training can lead to adaptive stimulation of such representation(s). This adaptive stimulation, in turn, translates into improved overt motor performance with the involved body part(s).

Overall, the above findings have spurred the infusion of MI and AO into neurorehabilitation, particularly into the context of poststroke motor rehabilitation [103–105]. Essentially, the underlying assumption here is that MI or AO training can *reactivate* and adaptively stimulate potentially spared cortical motor representations in the stroke-affected hemisphere. This, in turn, would contribute to increasing activity in the ipsilesional motor cortex and thereby *rebalance* the interhemispheric interactions between this cortical area and the homologous region in the contralateral, unaffected hemisphere. Collectively, this would contribute to improvement of the individual's motor function [91, 106–108] (see the "*reactivation*" and "*rebalancing*" theories in Section 2.2). Interestingly, studies by our group and others have shown that the aforementioned similarity reported in healthy individuals between overt movement and MI/AO, in terms of both the neural substrate that is activated and the ability of both overt movement and MI/AO to induce improvements in overt motor performance after training, is largely preserved in individuals after hemiparetic stroke [109–113]. Because MI and AO do not rely on overt movement execution to activate and adaptively stimulate cortical motor representations, they represent rather promising alternative motor rehabilitation strategies for individuals that have poor residual function after stroke and that therefore cannot effectively engage with the overt practice of physically demanding motor tasks. In this case, individuals can make use of such strategies to initiate motor recovery, for instance, during the beginning of their rehabilitation, while they gradually build up their physical capacity with progressive cardiorespiratory and muscle strengthening/endurance exercises [77, 78], or simply up to a point where they are able to fully participate in overt task-specific training. Furthermore, from this point onwards, and for those who already have higher levels of residual function at the beginning of their rehabilitation, MI- and/or AO-based strategies might be used as complementary interventions to be combined with overt task-specific exercises in order to potentiate motor gains [114].

Thus, it follows that covert practice-based alternative motor rehabilitation strategies for stroke, in comparison to overt practice-based strategies, are more compatible with the wider spectrum of functional recovery and therefore are likely to benefit a larger group of stroke survivors. Nevertheless, despite being promising, research in this arena is still in its infancy and more studies are needed before sound recommendations regarding the use of covert motor strategies such as MI and AO as motor rehabilitation strategies for stroke can be made to effectively inform clinical practice.

5.1.2. Covert Motor Strategies during Upper Limb Immobilisation. In light of the aforementioned, researchers have started to investigate how the brain mechanisms of MI and AO interact with the effects of upper limb immobilisation.

In one study, Bassolino and colleagues (2013) immobilised the upper limb of healthy participants for 10 consecutive hours. During this time, individuals were instructed to imagine, with their eyes closed, reach-to-grasp movements being performed with their restrained arm and hand, "MI group," observe the same actions through a computer screen, "AO group," or watch a nature documentary with no human actions, "control group." The size and excitability of the cortical motor representation corresponding to the immobilised hand were assessed with TMS one day before and immediately after removal of the immobilisation. In the control group, both the size and excitability of the cortical motor representation of the restrained hand were reduced after immobilisation. This finding is in line with the findings from the other immobilisation studies already described earlier in this paper (see Section 4). In the MI group, similar changes were reported. However, in the AO group, no substantial changes were noted. Here, the excitability of the cortical motor representation of the immobilised hand was higher than in the other two groups after immobilisation, and its size remained similar to what was observed in all the three groups before immobilisation [115].

Regarding the behavioural effects of immobilisation, it was recently suggested that they might be attenuated by MI practice before removal of the restriction. In one study, individuals had their left hand immobilised for 24 consecutive hours. After removal of the immobilisation, participants were assessed on a hand recognition task, where their goal was to identify, as quickly as possible, whether a hand displayed on a computer screen corresponded to a left or right hand. Those who did not practice MI during immobilisation showed slower response times in the task, particularly for left hand stimuli [116]. It is not known, however, if this modulation of task performance by MI practice was mediated by changes at the level of the cortical motor representation corresponding to the immobilised hand. In addition, whether the gains in performance on the hand recognition/reaction task reported in this study extrapolate to the domain of overt motor performance also remains unknown.

In retrospect, the finding from the study by Bassolino et al., that MI training was inefficient in adaptively stimulating the cortical motor representation of the immobilised hand [115], appears to be not only in relative dissonance with the finding from others, who have otherwise reported adaptive neural plasticity of cortical motor representations with MI training (e.g., see [102] in Section 5.1.1), but also in contradiction to Jeannerod's "Simulation Theory," which predicts adaptive stimulation of cortical motor representations with MI training [92]. A possible explanation for this contradiction, which was indeed acknowledged by Bassolino et al., might be that the effects of MI on the motor system, particularly in terms of stimulating cortical motor representations, are influenced by the "state," that is, the posture, position, and/or history of mobility, of the body parts corresponding to these representations during the imagination process. For instance, studies have shown that if the current state, in this case the posture, of a body part is congruent with the movements/actions being imagined, the size and excitability of the corresponding cortical motor representation increase to a greater extent than when the state is incongruent [117, 118]. This suggests that the afferent, proprioceptive information coming from the body part(s) involved in the imagined movements/actions may play an important role in modulating the effects of MI on the corresponding cortical motor representation(s). Therefore, according to this perspective, the immobilisation of the upper limb in the study by Bassolino et al., by maintaining the hand both in a relatively antagonistic posture and immobile for several hours, that is, in a state which was rather incongruent with the imagined reach-to-grasp movements/actions, would have compromised the effects of MI on the corresponding cortical motor representation [115]. If this is indeed the case, it would have important implications for the use of MI in the context of motor rehabilitation after stroke, especially in cases of low-functioning upper limb hemiparesis. Here, MI training is generally used with the underlying assumption that it can adaptively stimulate cortical motor representations in the damaged cerebral hemisphere and that this might translate into improved motor function (see Section 5.1.1). However, in this context, the state of the patient's paretic upper limb is sometimes largely incongruent with the movements/actions that are usually imagined during MI training, which basically consists of the mental rehearsal of functional movements of the patient's daily living, such as reaching and grasping (see [103] for a review). Not infrequently, the paretic upper limb is found in a state that is characterised by both, a relative immobility or lack of overt voluntary movement and a spastic posture with varying degrees of sustained flexion at the fingers, wrist, and elbow. Such state, in turn, by providing the brain with reduced and/or incompatible proprioceptive information, could decrease or mask the potential of MI as a rehabilitation strategy. In keeping with this hypothesis, Liepert and colleagues (2012) showed that MI of paretic hand movements increased the excitability of the corresponding cortical motor representation in stroke patients with somatosensory deficits to a much lesser degree than in patients with pure motor hemiparesis [119]. Overall, this seemingly important influence of the current state of the body part(s) on the effects of MI on the corresponding cortical motor representation(s) could explain, at least in part, the relative inconsistency in the results from recent clinical trials of MI training after stroke (see [103, 108] for reviews). Thus, given its theoretical and clinical implications, the interaction between the effects of both MI and upper limb immobilisation on the involved cortical motor representations should be investigated in more detail.

We believe the upper limb immobilisation model provides a compelling neurobehavioural framework for exploring covert motor strategies, such as MI and AO, within the context of poststroke motor rehabilitation. This is because upper limb immobilisation not only mimics the maladaptive neural plasticity patterns that are believed to contribute to the motor deficits shown by an individual after a hemiparetic stroke but, critically, also consists of a disease-free model of compromised brain function. Here, covert motor strategies can be investigated in healthy individuals for their potential to adaptively stimulate cortical motor representations, within a context of "stroke-like" maladaptive neural plasticity, without the influence of lesion-related confounding factors that otherwise are inevitably present in disease-based models. This opportunity, in turn, might greatly contribute to sharpening the mechanistic understanding of these strategies and thereby improve their translation to the clinical context of poststroke motor rehabilitation.

5.1.3. The Use of Adjunctive Therapies and the Opportunity to Enhance Adaptive Neural Plasticity during Upper Limb Immobilisation. Recapitulating on the role of the pattern of activity in the efferent and/or afferent neural signalling pathways targeting and/or coming from a particular body part in shaping the corresponding cortical motor representation (see Section 2.1), a recent study tested in healthy individuals the interaction between peripheral somatosensory stimulation (PSS) and upper limb immobilisation. Complementing their previous findings on the effects of immobilisation on both the excitability of homologous cortical motor representations and the interhemispheric interactions between them, Avanzino et al. (2014) showed that a form of proprioceptive stimulation can largely attenuate the maladaptive neural plasticity that is induced by upper limb immobilisation. Specifically, they found that intermittent vibration of a muscle from the immobilised hand delivered throughout the period of immobilisation was able to prevent large decreases in the excitability of the corresponding cortical motor representation and to abolish both, increases in the excitability of the homologous representation in the opposite hemisphere and changes in the interhemispheric balance between the two homologous cortical motor representations [120].

The findings from this latter study, when taken together with those from previously described studies investigating covert motor strategies during immobilisation, invoke the idea that different interventions might be delivered in combination during upper limb immobilisation in order to maximize prevention of maladaptive/promotion of adaptive neural plasticity in the brain's motor system, much like with the use of adjunctive therapies in association with task-specific exercises during poststroke motor rehabilitation

(see Section 3). Here, a potential manipulation could be, for instance, to combine covert motor strategies with brain stimulation (BS) and/or PSS techniques during upper limb immobilisation (Figure 2(b)). It is likely that the effects of such strategies, in terms of adaptively stimulating cortical motor representations, would be strengthened by concomitant BS, delivered to either one or both motor cortices, and/or PSS of the immobilised body part(s). A recent study provides empirical support for this prediction. It was shown that observation of right hand movements combined with sensorimotor electrical stimulation of the median nerve at the level of the right wrist increased the excitability of the cortical motor representation of the involved hand, an effect that was not present when the two interventions were delivered separately. In addition, this modulation outlasted the period of observation-stimulation [121]. It remains to be tested, however, whether a similar manipulation would result in a potentiation of the effect of AO during upper limb immobilisation.

6. Conclusion and Perspectives

Advances in our understanding of the neural plasticity that occurs after hemiparetic stroke, both adaptive and maladaptive, have contributed to the formulation of theories of motor recovery after stroke. Such theories identify the processes that are likely to promote motor recovery, for instance, of poststroke upper limb hemiparesis, and that therefore might be targeted by neurorehabilitation efforts. Contemporary motor rehabilitation strategies target these processes, but because they are essentially centered in the overt practice of physically demanding task-specific exercises, they do not easily translate into benefit for stroke survivors sustaining low-functioning upper limb hemiparesis. For these individuals, motor rehabilitation options are currently limited. MI and AO are two examples of covert or cognitive motor strategies that have a great potential to translate into alternative motor rehabilitation strategies for stroke. Because they can adaptively stimulate cortical motor representations in the absence of overt movement, MI- and AO-based training strategies have a greater potential for benefiting the wider spectrum of functional recovery after stroke, including those individuals with poor residual function. In this paper, we provided theoretical and empirical evidence that an upper limb immobilisation-based neural plasticity model, by capitalising on current theories of motor recovery after stroke, the shortage of overt movements, and a disease-free condition of compromised brain function, provides a very attractive neurobehavioural template for exploring these strategies within this context.

The findings from the immobilisation studies reviewed here, particularly those concerning the effects of immobilisation on the interhemispheric interactions between homologous cortical motor representations, have important implications for a particular contemporary motor rehabilitation strategy addressing poststroke upper limb hemiparesis. This strategy is known as constraint-induced movement therapy (CIMT). CIMT falls within one of those two categories of interventions that were presented in this paper (see Section 3). Essentially, this rehabilitation strategy consists of three elements [122]. These are (1) repetitive and progressive task-specific training with the paretic upper limb for several hours a day, usually for a period of 2 weeks; (2) a "transfer package" made of behavioural techniques used to promote transfer of the gains obtained during the treatment period in a research and/or clinical setting to the individual's real-world environment; and (3) constraining use of the paretic upper limb through immobilisation of the contralateral, less-affected limb. This particular therapy has proven to be an effective intervention for improving paretic upper limb function after stroke and is currently recommended as the treatment of choice for those individuals with relatively high levels of residual function [123]. Despite the fact that CIMT has been extensively investigated during the past few years, the mechanisms mediating treatment success with this intervention are still relatively poorly understood (see [124] for a discussion). One influential proposal has been that functional improvements after CIMT are consequential to the massed overt motor practice with the paretic upper limb, which, in turn, contributes to both reversal of the learned nonuse phenomenon and adaptive neural plasticity, that is, increases in the size and/or excitability, of the corresponding cortical motor representations [125]. It follows from this proposal that the relevance of immobilising the less-affected upper limb for promoting motor gains with the more-affected, paretic limb is often underestimated. More commonly, an indirect, relatively trivial role is attributed to the immobilisation element of CIMT, for example, that it serves only as a "constraining" instrument employed simply to encourage use of the paretic upper limb. As Taub and colleagues (1999) commented on the relevance of the immobilisation element of CIMT, "There is thus nothing talismanic about use of a sling or other constraining device on the less-affected limb. The common factor appears to be repeatedly practicing use of the paretic arm. Any technique that induces a patient to use an affected limb many hours a day for a period of consecutive days should be therapeutically efficacious. This factor is likely to produce the use-dependent cortical reorganization found to result from CI Therapy (23, 58, 59) and is presumed to be the basis for the long-term increase in the amount of use of the more-affected limb" [126]. As already pointed out by others (e.g., see [83]), recent findings from upper limb immobilisation studies suggest, however, that a more sensible appreciation of the contribution of the immobilisation element of CIMT would be that such manipulation might otherwise have a more direct, meaningful role in mediating treatment success, at least in theory. For example, it is possible that, at least in some individuals, the effects of immobilisation of the less-affected upper limb during CIMT would be superimposed to those effects induced by the intensive motor training with the paretic upper limb. More specifically, as long as a condition of true immobilisation, that is, of substantially reduced usage, of the less-affected upper limb is present, it would decrease activity of the contralesional motor cortex, which, in turn, could contribute to reducing transcallosal inhibition from this region towards the homologous area in the affected hemisphere. As a consequence, this could attenuate interhemispheric imbalance and facilitate ipsilesional activation

and hence boost massed practice-induced adaptive neural plasticity (see "*rebalancing*" theory in Section 2.2). Since its original conceptualisation, CIMT has taken many different forms, each of which containing different combinations and/or durations of the three elements of the intervention, which are task-specific training, "transfer package," and immobilisation of the contralateral, less-affected upper limb [127–129] (see [124] for a review). When considering whether or not to include the immobilisation element of CIMT in the rehabilitation program, the above-mentioned consideration should be taken into account, but also the pros and cons of restraining movements of the patient's less-affected upper limb should be carefully weighted.

On a different note, with the advent of noninvasive brain stimulation (BS) techniques during the past years, it has become possible to develop neural plasticity "protocols" that are able to induce relatively predictable changes in the excitability of selected brain regions and that therefore might be used to improve the individual's behavioural capacity under certain conditions. The motor cortex, in particular, has been a major target of such protocols. Here, BS has been used to either directly induce adaptive neural plasticity of cortical motor representations in healthy individuals with excitatory stimulation and thereby improve their motor learning or adaptively modulate neural plasticity patterns after hemiparetic stroke with excitatory and/or inhibitory stimulation and thereby improve the individual's motor recovery (see Section 3 and also [66, 130] for reviews). More recently, neural plasticity research has shown that it is possible to modulate the response of the motor cortex to neural plasticity protocols, to both those exogenously induced through BS and endogenously induced protocols, such as motor learning, by manipulating its activity before delivery of such protocols [131]. In other words, the strength of an excitatory or inhibitory neural plasticity protocol that targets the motor cortex might be either increased or decreased depending on the history of activity of this area. This priming effect has been termed "metaplasticity" [132]. Basically, if activity in a brain region or neuronal network is high, then the strength of a subsequent excitatory protocol is decreased, while the opposite is true for a subsequent inhibitory protocol. Conversely, if activity in that brain region or neuronal network is low, then a subsequent excitatory protocol is enhanced, while the opposite is true for a subsequent inhibitory protocol. An example of this phenomenon was provided by Jung and Ziemann (2009). Briefly, the authors showed that, in healthy participants, motor learning—an endogenously induced excitatory neural plasticity protocol that targets the motor cortex—can be potentiated by decreasing activity/excitability of the targeted motor cortex with a long-term depression- (LTD-) inducing paired associative stimulation (PAS) protocol delivered before the learning paradigm [133]. Motor learning is thought to improve the individual's motor capacity by, among other processes, inducing long-term potentiation (LTP) and thereby adaptive neural plasticity in their motor cortex (see Section 2.1). In the study by Jung and Ziemann, it is likely that the LTD-inducing PAS protocol delivered before motor practice increased, via metaplasticity mechanisms, the likelihood for subsequent LTP in the involved motor cortex and cortical motor representation(s), hence potentiating motor learning [133]. Recently, this finding has prompted others to extrapolate the concept of metaplasticity to the context of motor rehabilitation after stroke. Interestingly, in a proof-of-principle study, challenging the standard approach in BS-based poststroke motor rehabilitation (e.g., see Section 3 and Figure 1(b)), Di Lazzaro and colleagues (2013) found that, in general, inhibitory, activity-decreasing BS of the ipsilesional motor cortex followed by physiotherapy exercises improved the motor outcomes of patients more than sham BS [134]. The results from these two latter studies, when taken together with the findings reported in this paper concerning the effects of upper limb immobilisation on the motor cortex, might spark rather provocative speculations. As demonstrated by Rosenkranz et al. (2014) (see end of Section 4), apart from decreasing the excitability of the corresponding cortical motor representations in the contralateral motor cortex, upper limb immobilisation also seems to alter neural plasticity mechanisms within these representations, such that the larger the decrease in their excitability induced by the restriction, the greater their sensitivity to subsequent LTP-like processes [86]. This suggests that, like BS, but with the advantages of being much cheaper and technically simpler, upper limb immobilisation could also be used as a noninvasive neural plasticity protocol to decrease motor cortex activity/excitability and, within a context of metaplasticity, improve subsequent motor training. For instance, it can be speculated that, in healthy individuals, immobilisation of the upper limb for a certain period of time which is sufficient to substantially decrease the excitability of the corresponding cortical motor representations in the contralateral motor cortex could perhaps facilitate/enhance subsequent motor learning with that limb by increasing the likelihood for LTP in the involved representations. In the same vein, now within the context of poststroke motor rehabilitation, it can also be speculated that a period of immobilisation of the patient's paretic upper limb before a physiotherapy session could boost subsequent practice-induced adaptive neural plasticity of the corresponding cortical motor representations. This, in turn, could eventually enhance rehabilitation outcomes. Despite their rather provocative and speculative nature, the findings discussed previously suggest that such predictions are, at least theoretically, valid. Future studies could test these hypotheses.

Before upper limb immobilisation can be consolidated as a neural plasticity model/protocol in humans, some issues remain to be addressed by future research. First, most of the studies, if not all, on upper limb immobilisation have been conducted with young participants. It would be important to also perform these investigations with aged populations, especially within the context of translational neurorehabilitation research, as the vast majority of stroke survivors are elderly. Second, there is no consensus yet on a possibly ideal immobilisation time to induce the reported changes in the motor system, both those that are measured at the level of the motor cortex and those expressed behaviourally. For instance, studies have used restriction periods ranging from hours, for example, 6, 8, 10, 12, and 24 hours, to days in humans and to months in animals. Determining the optimal length of

immobilisation is critically important to minimise not only costs, but also potential ethical issues that might be present, particularly in long-term immobilisation studies. In this case, the question of whether the effects of immobilisation on the brain's motor system can be potentiated, and perhaps accelerated with exogenous manipulations, such as noninvasive BS, should also be given consideration.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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