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Bilateral and unilateral movement training on upper limb function in chronic stroke patients: A TMS study

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Abstract

The use of activity-dependent interventions has shown some success in promoting recovery of upper limb function in chronic stroke patients. This study compared the neurophysiological and behavioural changes associated with two such rehabilitation protocols: unilateral and bilateral movement training. Twelve chronic stroke patients were randomly assigned to the two training protocols involving six daily practice sessions. Each session consisted of 50 trials of a dowel placement task performed either with both impaired and unimpaired arm moving synchronously (bilateral training group) or with only the impaired arm moving (unilateral training). Kinematic measurements of upper limb movements were made in four unilateral test trials performed prior to and following each practice session. Functional assessments of the impaired upper limb and neurophysiological assessments, using transcranial magnetic stimulation (TMS), of the affected and non-affected cortical hemispheres were made prior to and following the intervention sessions. Individuals receiving bilateral training showed a reduction in movement time of the impaired limb and increased upper limb functional ability compared to individuals receiving unilateral training. In some patients changes to upper limb function were associated with changes to the cortical representation of a target muscle in the non-affected hemisphere. Overall, these findings suggest that a short-term bilateral training intervention may be effective in facilitating upper limb motor function in chronic stroke patients.

Keywords: Chronic stroke; Bilateral movement training; Unilateral movement training; Transcranial magnetic stimulation; Upper limb; Rehabilitation

1. Introduction

Currently there is great interest in rehabilitation-induced recovery of motor function in chronic stroke patients [1,2]. Research into this topic has been stimulated by the dramatic increase in understanding brain plasticity derived from brain mapping techniques such as TMS, PET, and fMRI. Of particular importance is the increasing evidence that in addition to injury-related reorganisation motor cortex function in patients with chronic impairments can be altered by the motor experiences of the individual [3,4]. Such plasticity has major implications for the type of rehabilitative training administered after stroke. Recent reviews of motor rehabilitation and neural reorganisation have indicated that intervention strategies based on sound motor control and learning principles offer considerable promise in promoting recovery in chronic stroke patients [1,5]. In particular, encouraging use of the hemiplegic limb through activity-dependent interventions has evidenced some success in expediting progress toward recovery of upper limb function [6–8]. For example, constraint-induced movement therapy has shown consistent functional gains from intensive practice with the paretic limb while the intact limb is constrained

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[9–11]. An alternative approach, known as bilateral movement training (BMT), uses the intact limb to promote functional recovery of the impaired limb through the facilitative coupling effects between the upper limbs identified in studies of interlimb coordination in healthy adults [1]. The practice of bilateral symmetrical movements may allow the activation of the intact hemisphere to facilitate the activation of the damaged hemisphere leading to improved movement control of the impaired limb promoting neural plasticity. The results of the few studies investigating BMT, however, have produced mixed results.

While Mudie and Matyas [12,13] using single-case multiple baseline designs demonstrated strong after-effects of 30–40 sessions of BMT on unilateral performance of the impaired limb in 12 chronic stroke patients, an attempt to replicate these findings had limited success with 6 acute and chronic patients [14]. Other studies have reported positive results using variations of the bilateral training protocol, including active–passive movements [15], synchronous and alternating movements with rhythmic auditory cuing [16–18], and bilateral movements with neuromuscular stimulation of the impaired arm [19–21]. However, when more than one treatment protocol is used simultaneously it is not possible to ascertain the extent to which the results obtained are due to practicing bilateral symmetrical movements, the additional protocol (e.g., rhythmic auditory cueing), or a combination of protocols. Furthermore, none of the previous studies employing a single bilateral training protocol used a comparison with a unilateral training regime with random assignment of patients to the two interventions [12–14].

The present study had three aims. The first was to directly compare unilateral and bilateral training protocols with random assignment of patients to protocols. Secondly, the effect of bilateral training following a relatively short training duration (6 sessions) was examined. While positive bilateral training effects have been reported with the number of practice sessions ranging from 6 [19–21] to 40 [12], the shortest single protocol study involved the training of three tasks over 20 sessions [14]. The present study used a functional task that involved grasping and lifting a small object (wooden dowel) and placing it on a shelf (target) at shoulder height. The final aim was to investigate the behavioural and neurophysiological effects of practicing placing a single dowel using the impaired hand alone (unilateral group[1]) or placing two dowels using the impaired and unimpaired hands simultaneously (bilateral group). In addition to assessing functional ability prior to and following the intervention, kinematic measurements of movements of the impaired upper arm were obtained during each training session. Neurophysiological assessments were made using single-pulse transcranial magnetic stimulation (TMS). Previous research using TMS has shown consistent increases in motor map size following constraint-induced therapy [22,23]. However, there has been only one previous attempt to measure neurophysiological changes following bilateral training [14] and in that study, complete cortical maps were obtained from only 2 (1 acute, 1 chronic) of 6 stroke patients. It has been hypothesised that practicing bilateral symmetrical movements may decrease transcallosal inhibition from the unaffected hemisphere and, thereby, increase motor output from the affected hemisphere [1,15].

2. Method

2.1. Participants

Twelve individuals with hemiplegia due to stroke participated in the study (Table 1) and were randomly assigned to either a unilateral training (3 males, 3 females, age 60 ± 14 years [mean ± SD]) intervention or a bilateral training intervention (4 males, 2 females, 63 ± 16 years of age). Criteria for inclusion in the study included: having suffered a first stroke at least 3 months prior to the intervention; no multiple infarctions; most components of movement present in the affected extremity but impairment of function relative to the non-affected side; intact cognitive functions; no other neurological disorders. All patients meeting these criteria were included in the study regardless of age, lesion location or lesion type. All participants were living in the community and had previously undergone upper extremity rehabilitation; none were currently receiving treatment and their functional impairment was stable. Ethical approval for the study was obtained from the University of Tasmania Human Ethics Committee.

Table 1
Clinical details of stroke patients

Patient	Age	Sex	Years since stroke	Stroke type	Affected side
Unilateral					
U1	77	F	2.9	L Lacunar infarct	Right
U2	63	F	3.3	R Cerebellar intracerebral	Right
U3	55	M	4.8	R Ischemic stroke	Left
U4	74	F	10.4	R Frontal/Temporal	Left
U5	47	M	1.8	Bilateral MCA	Left
U6	43	M	0.9	R MCA	Left
Mean	59.8		4.0		
Bilateral					
B1	53	M	1.6	R MCA	Left
B2	82	F	1.0	L Cortical Lesion (M1)	Right
B3	73	M	3.4	R Internal Capsule	Left
B4	58	M	8.9	R MCA	Left
B5	40	F	16.2	L Ischemic stroke	Right
B6	75	M	7.0	R Ischemic stroke	Left
Mean	63.5		6.3		

R indicates right, L = left; U indicates Unilateral training, B = Bilateral training, M = male, F = female, MCA indicates Middle Cerebral Artery.

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[1] It should be noted that the aim of the study was to compare the effects of executing the dowel placement task with one or two hands for a set number of trials. The unilateral training, therefore, was not intended to constitute a constraint-induced movement intervention.

2.2. Outcome measures

The functional ability of the affected upper limb was assessed by the Modified Motor Assessment Scale (MAS) [24] prior to and following the intervention. The scale has three sections: (1) upper arm function, (2) hand movements and (3) advanced hand activities with a maximum score of 6 being possible on each section. Kinematic measurement of the movements of the upper limbs were made by an OPTOTRAK three-dimensional motion analysis system tracking infrared emitting diodes (IREDS) attached to the shoulder, elbow, wrist and 1st metacarpophalangeal joint of the index finger. Neurophysiological assessments were made using single-pulse transcranial magnetic stimulation (TMS) delivered to the motor cortex (M1) of both the affected and non-affected hemispheres prior to and following the intervention. During TMS a brief magnetic pulse was applied at a point on the scalp overlying a specific cortical area, resulting in a motor evoked potential (MEP) in the target muscle. Surface electromyography (EMG) was recorded from the extensor digitorum communis (EDC) muscle bilaterally.

2.3. Intervention protocols

Two baseline TMS mapping sessions were completed one week (pre-test 1) and one day (pre-test 2) prior to initiation of the training protocols. Motor impairment assessment using the MAS was also undertaken on the day prior to intervention commencement. Over the next 6 days, the participants completed a series of training sessions involving a dowel placement task. Participants were seated in front of a table on which was a small shelf (height 11 cm). The distance of the shelf was adjusted individually so that each participant could comfortably extend the impaired arm in order to reach the target area in the center of the shelf. For the unilateral training group, the task required participants to lift a wooden dowel (triangle base: 11 × 7.5 cm, handle length: 10 cm, weight: 27 g) from the table and place it on a target located on the shelf. For the bilateral training group, the task required participants to simultaneously lift two dowels, one in each hand, and place them on targets located on the shelf. Correct alignment with the target(s) required a wrist extension(s) of approximately 35°. Participants with residual wrist and finger movement present were required to hold the dowel by closing their hand around its vertical handle. Three patients (2 bilateral, 1 unilateral training) who were not able to grasp objects placed the impaired hand on the starting position and moved it to the target area on the shelf.

Each session began with two ‘warm up’ reaching trials for both the unimpaired and impaired hand before four unilateral test trials were recorded, first with the unimpaired hand and then with the impaired hand (pre-test trials). Participants then performed 50 training trials of the dowel placement task, either with both impaired and unimpaired hand moving synchronously (bilateral training group), or with only the impaired hand moving (unilateral training group) while the unimpaired hand rested on the table. Following the training trials, four unilateral test trials with each hand were recorded (post-test trials).

Kinematic measurements of impaired and unimpaired upper arm movements were made for the unilateral test trials prior to and following the training trials in each session. Neurophysiological (TMS) and motor impairment (MAS) assessments (post-test) were repeated on the day following completion of the six day training period. The investigator who performed the TMS mapping and administered the MAS was blinded as to the assignment of participants to training condition.

2.4. Neurophysiological assessments

Participants were seated in a comfortable chair, with AgCl/Cl surface EMG electrodes (2–3 cm spacing) applied over the belly of the EDC muscle on both hands. The EMG signals were amplified (GRASS Model12 amplifier, filter settings 10 Hz/1 kHz), sampled at 2 kHz and stored on a PC for off-line analysis.

TMS (Magstim 200, Magstim Co., Whitland, Dyfed, UK) was used to map the motor cortex representation of the EDC muscle in both the affected and non-affected hemisphere. The figure-of-eight coil (70 mm diameter each wing) was held tangential to the scalp, with the handle pointing posteriorly and rotated by approximately 30° to the midsagittal line to maintain a perpendicular orientation with respect to the presumed direction of the central sulcus. During TMS mapping, stimulus sites were located using a flexible, snugly fitting cap worn by subjects with a grid of 1 cm markings based on a latitude/longitude system originating at the vertex (Cz). The optimal site for producing MEPs in the contralateral target muscle (‘hot spot’) was located. At the ‘hot spot’, resting thresholds, defined as the minimum stimulus intensity required to produce discernible MEPs of at least 50 μV peak-to-peak in six of ten trials were then determined for each hemisphere.

2.4.1. Mapping protocol and parameters

Following threshold identification, maps of cortical representation of the EDC muscle were created using suprathreshold stimulation (10% above threshold intensity). On each hemisphere, stimulation started with the optimal site (‘hot spot’), and was then expanded to the surrounding points on the grid until sites were reached which did not yield any activation of the EDC; these sites constituted the map borders. Five stimuli were delivered at each location. The waveforms obtained were averaged off-line, and onset latency and peak-to-peak amplitude were determined.

The primary measure of cortical excitability was the volume of a bordered map. In line with the procedure adopted by Stinear and Byblow (2004), MEP data were calculated from a fixed bordered map of 17 sites on the 1-cm grid pattern centered on a position 4 cm lateral to the vertex.

A bordered map was chosen because it eliminated the need to choose a minimum MEP amplitude for inclusion in map calculations, a particularly difficult decision when mapping the affected hemisphere in stroke patients. Furthermore, to elicit MEPs from the affected hemisphere often requires high intensity stimulation causing discomfort in some patients. By using a restricted map area discomfort to patients was minimized [15]. As the area of a bordered map is uninformative, map volume was used as an indication of cortical excitability [25]. *Map volume* was defined as the sum of all MEP amplitudes across the 17 sites for each hemisphere at each testing time (pre-1, pre-2, post-test). In addition, *map center of gravity* (CoG) was calculated as a measure of cortical plasticity [26]. The CoG was determined by weighting the lateral and posterio–anterior coordinates of each point and calculating the average of all the weighted coordinates [27].

2.5. Kinematic measures

Reaching trials in which missing data occurred because of transient occlusion of one or more of the IREDs were first subjected to a cubic spline interpolation. The data were then filtered using a dual pass second order Butterworth filter with a cut-off frequency of 12 Hz. The filtered x, y, and z coordinates were used to compute the transport tangential speed (i.e., the square root of the sum of the squares of the numerical derivatives of the x, y, and z coordinates of the index finger IRED). From this time series, movement onset and offset were determined and movement time (MT) was calculated. Other kinematic measures calculated to assess task performance included the velocity profile, curvature of arm trajectories and elbow angle.

2.6. Statistical analyses

MAS data on the functional ability of the impaired arm for the pre- and post-test were analyzed with a two-way mixed analysis of variance (ANOVA). The factors in the 2×2 ANOVA were *group* (unilateral training or bilateral training) as a between-subject variable and *time* (pre-test vs. post-test) as a within-subject variable.

For the kinematic measures, changes that occurred from Day 1 pre-test to Day 6 post-test were separately analyzed for the two training groups by paired t tests. Similarly, paired t tests were used to examine changes in motor cortex excitability between TMS sessions (pre-1, pre-2, post) for the affected and non-affected hemisphere.

3. Results

3.1. Functional movement ratings

The motor impairment of the affected limb of all participants was assessed prior to and following the intervention period. The scores on the three sections of the MAS obtained for each participant are shown in Table 2. As can be seen, bilateral trained participants showed a pre-test–post-test improvement on each section of the test, whereas no improvement was evident for the unilateral trained group. Importantly, five of the six patients receiving bilateral training showed an improvement on the combined MAS score, with the remaining patient achieving the maximum score on the pre-test and, thereby, was unable to demonstrate improved functional ability at post-test (Participant B2, Table 2). In contrast, only one unilaterally trained patient evidenced a pre- to post-test increase in MAS score. An ANOVA conducted on the combined MAS scores confirmed the difference between the groups giving a significant main effect of Time (pre-test vs. post-test), $F(1,10)=7.14$, $p=.0234$, and importantly a significant Group × Time interaction, $F(1,10)=10.29$, $p=.0094$.

3.2. Task performance: movement kinematics

Data for 2 participants in the unilateral training group were not included in the analysis of movement kinematics due to technical difficulties. The impaired limb median MT exhibited little change after unilateral training (Day 1 pre-test = 2.50 s, Day 6 post-test = 2.74 s, $p=0.7$). Bilateral training, however, led to reduction in MT for the impaired limb over the training period (Day 1 pre-test = 3.31 s, Day 6 post-test = 1.89 s), but the difference did not reach the required level of significance ($p=0.1$). Other kinematic variables measured failed to show consistent training effects. Both groups did show an increase in mean elbow angle over training sessions (Bilateral Day 1 pre-test = 115.36°, Day 6

Table 2
Modified Motor Assessment Scale (MAS) ratings: individual subjects and group means

Group	Upper arm function		Hand movements		Advanced hand activities		Combined mean	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Unilateral								
U1	6	6	5	6	6	6	5.7	6.0
U2	6	6	5	5	5	4	5.3	5.0
U3	6	6	6	4	1	2	4.3	4.0
U4	6	6	5	5	4	4	5.0	5.0
U5	2	2	3	3	0	0	1.7	1.7
U6	4	4	0	0	0	0	1.3	1.3
Mean	5.0	5.0	4.0	3.8	2.7	2.7	3.99	3.83
(SD)	(1.67)	(1.67)	(2.19)	(2.14)	(2.66)	(2.42)	(2.30)	(2.20)
Bilateral								
B1	5	6	0	1	0	1	1.7	2.7
B2	6	6	6	6	6	6	6.0	6.0
B3	4	6	5	6	6	6	5.0	6.0
B4	6	6	2	3	2	2	3.3	3.7
B5	6	6	2	2	1	2	3.0	3.3
B6	6	6	3	4	2	3	3.7	4.3
Mean	5.5	6.0	3.0	3.7	2.8	3.3	3.78	4.33
(SD)	(0.84)	(0.0)	(2.19)	(2.07)	(2.56)	(2.16)	(2.26)	(2.03)

Pre = pre-test Day 1; Post = post-test Day 6.

post-test = 123.82°; Unilateral Day 1 pre-test = 129.29°, Day 6 post-test = 140.38°) indicating an improvement in their ability to fully extend the impaired arm.

3.3. Neurophysiological assessments

Of the 12 participants in the study, technical difficulties prevented us from collecting complete TMS data for two participants and in three other participants (U5, B5, B6, Table 1) TMS was contraindicated due to presence of aneurysm clips. Of the seven patients on whom we were able to collect TMS data, one patient's data were not useable due to an inability to elicit MEPs in the affected hemisphere.

Consistent with conventional TMS analysis, the effects of the interventions on two map parameters, map volume and CoG, were assessed in six participants (3 unilateral training, 3 bilateral training). As map volume reflects the overall level of excitation of the motor cortex, an increase in volume following training indicates an increase in excitability while a decrease in map volume indicates a decrease of excitability. Fig. 1 shows the changes between pre-1, pre-2, and post-tests in mean map volume of EDC muscle representation in the non-affected and affected hemispheres averaged over the six participants. The difference in map volumes between the two baseline sessions was not statistically different for either the non-affected (5.93 vs. 5.60) or affected (1.39 vs. 1.46) hemispheres ($p > 0.7$). Therefore, pre-2 values were taken as the reference for evaluating treatment effects.

For the affected hemisphere map volume did not change significantly between pre-2 (1.46) and post-tests (1.35) ($p = 0.6$). There was, however, a decrease in mean map volume in the non-affected hemisphere (pre-2 = 5.60; post = 4.22) that approached significance ($t(5) = 2.1$, $p = 0.09$). Furthermore, a Spearman's rho correlation analysis of the change in map volume and change in MAS score between pre-2 and post-tests revealed a significant negative correlation (−.883, $p = 0.02$) for the non-affected hemisphere, but not for the affected hemisphere (.206, $p = 0.7$). Thus, the reduction in the map volume of the non-affected hemisphere was associated with improvement in the functional ability of the impaired arm.

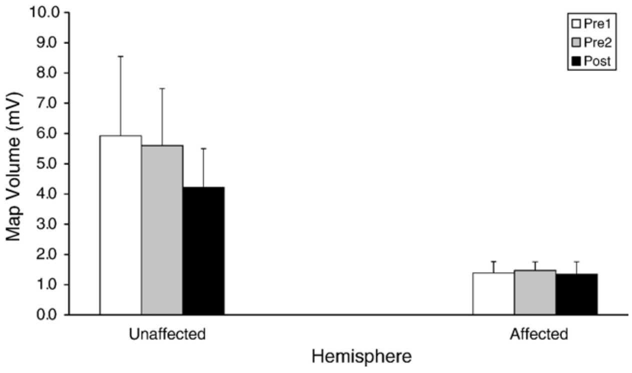

Fig. 1. Mean map volumes of the extensor digitorum communis muscle in the non-affected and affected hemispheres at pre-1, pre-2, and post-test.

Table 3
Change (pre–post) in MAS and bordered map volume for non-affected and affected hemispheres

Patient	MAS	TMS map volume non-affected hemisphere			TMS map volume affected hemisphere		
	% Change	Vol pre-2	Vol post	% Change	Vol pre-2	Vol post	% Change
Unilateral							
U1	+6%	13.30	9.70	−27%	0.65	0.86	+33%
U2	−5%	1.68	2.12	+26%	1.63	0.63	−61%
U3	−5%	1.07	0.90	−17%	0.91	0.70	−23%
Bilateral							
B1	+16%	8.64	5.70	−34%	1.08	0.99	−8%
B2	0%	4.47	3.79	−15%	2.37	3.24	+37%
B3	+17%	4.41	3.12	−29%	2.16	1.65	−24%

Table 3 shows the relationship between changes in the functional ability of the impaired upper limb (MAS scores) and changes to map volume for individual patients. For the affected hemisphere there was not a clear relationship between changes in functional ability and changes in cortical excitability. In contrast, for the non-affected hemisphere positive changes in MAS scores were associated with decreases in map volume. This was particularly evident in the bilateral training group where participants B1 and B3 increased their MAS scores by more than 10% and exhibited decreases in non-affected hemisphere map volume of greater than 20%. Participant B2 also showed a decrease in map volume but was unable to demonstrate improvement on the MAS due to ceiling effects (see above). This patient, however, did show improved impaired limb kinematics in terms of reduced movement time (Day 1 pre-test = 2.26 s, Day 6 post-test = 1.58 s; $t(3) = 3.169$, $p = .051$), and increased elbow angle (Day 1 pre-test = 143.63°, Day 6 post-test = 151.05°; $t(3) = -6.93$, $p = .006$). These improvements in movement kinematics are consistent with previous research showing that clinically recovered stroke patients still exhibit residual motor deficits that can be improved by training [28]. For the three unilateral trained participants the relationship between MAS scores and non-affected hemisphere map volume was less clear.

There were no changes in the CoG of the EDC muscle representation in either the non-affected or affected hemisphere as a result of movement training. The CoG of the EDC map, however, was significantly more medial (4.51 cm) in the affected than the non-affected (4.17 cm) hemisphere ($t(5) = 3.73$, $p = 0.0014$).

4. Discussion

The results of this study suggest that training involving the practice of actions bilaterally and simultaneously may be effective in promoting recovery of upper limb motor function in chronic stroke patients. Of particular importance was the significant increase by members of the bilateral training group in tests of functional ability of the upper limb, demonstrating a generalization from the training of a specific movement to general upper limb function. Moreover, individuals receiving bilateral training showed improvements in the time to complete the test movement with the impaired limb while little change was observed in impaired limb movement time in individuals engaging in unilateral training [cf. 13].

Interlimb coordination studies in healthy adults have identified the coupling of homologous muscles as the preferred control mode of the motor system. The present results indicate that this tendency can be exploited to promote functional recovery of a paretic limb in chronic stroke patients. Furthermore, there is strong neurophysiological evidence to suggest that when the impaired and non-impaired arms are moved symmetrically, crossed facilitatory drive from the intact hemisphere will produce increased excitability in homologous motor pathways in the impaired limb [1,29].

Additionally, cortical damage from stroke produces hyperexcitability of the contralesional M1 [26,30] leading to abnormally high levels of transcallosal inhibition (TCI) on the lesioned hemisphere, thereby further impairing motor performance of the paretic hand [31]. There is recent evidence of improved affected hand performance in chronic stroke patients from reducing the abnormal inhibitory drive to the ipsilesional hemisphere [32,33]. Furthermore, balanced interhemispheric interactions appear necessary for normal voluntary movements [34], and the restitution of the normal balance between the two hemispheres has been linked to better recovery following stroke [35]. It has been hypothesized that practicing bilateral symmetrical movements may facilitate motor output from the ipsilesional hemisphere by normalizing (TCI) influences [1]. Interestingly, in the subset of patients assessed with TMS in the present study, the two bilaterally trained patients exhibiting the largest increase in functional ability showed a large decrease in map volume of the target muscle in the non-affected hemisphere post-intervention. A similar decrease in motor cortex excitability in the non-affected hemisphere has been reported following active–passive bilateral movement therapy [15]. There was also a statistically significant negative correlation between unaffected hemisphere excitability and increased functional ability of the impaired arm. A corresponding increase in excitability in the affected hemisphere, however, was not observed. As MEPs elicited from the affected hemisphere in stroke patients can be highly variable and unreliable due to disturbance of the induced electric current produced by physiological changes to the lesion area, comparisons between the two hemispheres may not be appropriate [36]. In addition, bilateral training may promote increased involvement of pathways not investigated in the present study, such as spared corticopropriospinal pathways [1].

The effectiveness of bilateral movement training in promoting stroke recovery is also likely to depend on the extent of damage sustained to direct corticospinal pathways [37]. While bilateral movements may also help recruit secondary motor areas in both hemispheres, recovery promoted by these areas will be less than that obtained through direct corticospinal projections [37,38]. The lack of a consistent relationship between changes in the functional ability of the impaired upper limb as evidenced by MAS scores and changes to brain excitability may relate to the heterogeneity of the patient group used in the present study. Recent research has shown that lesion location greatly influences the pattern of motor cortex excitability observed [39,40].

There is clearly a need to examine cortical plasticity associated with bilateral therapy in a larger group of chronic stroke patients and to determine the type of patient, in terms of side and site of lesion, who might benefit most from bilateral training. Finally, it is important in future research to determine the components of the therapy critical to the bilateral effect. For example, it needs to determine whether beneficial outcomes are only evident when the training involves mirror-symmetrical movements of the upper limbs or whether enhancement will occur with other types of synchronous movements?

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