Clinical Neurophysiology 118 (2007) 2050–2062

www.elsevier.com/locate/clinph

Side of lesion influences bilateral activation in chronic, post-stroke hemiparesis

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Accepted 12 June 2007

Abstract

Objective: To determine how stroke lesion side and ipsilateral motor pathways influence motor performance in bimanual tasks.
Methods: Stroke subjects and age-matched controls participated in two data collection sessions: (1) motor behavior was examined during a movement task performed in unimanual, bimanual symmetric, and bimanual asymmetric conditions and (2) transcranial magnetic stimulation was used to examine the excitability of ipsilateral and contralateral motor pathways during isometric unilateral and bilateral muscle activation.
Results: Subjects with left hemiparesis and controls demonstrated a performance differential between symmetric and asymmetric motor tasks compared to subjects with right hemiparesis. Contralateral motor pathway excitability decreased and ipsilateral pathway excitability increased during bilateral compared to unilateral activation in control subjects and in the non-affected arm of stroke subjects. Responses in the affected arm were similar to controls in subjects with left hemiparesis but not right.
Conclusions: Changes in motor pathway excitability during bilateral activation may promote more stable performance of symmetric movements. In individuals with hemiparesis, the side of lesion influences neural and behavioral aspects of bimanual tasks. Those with injuries to the right hemisphere exhibit coupling that is more similar to age-matched controls.
Significance: The efficacy of bilateral training interventions may be different between people with lesions in the left and right hemispheres.

Keywords: Stroke; Interlimb coupling; Transcranial magnetic stimulation; Upper limb; Rehabilitation

1. Introduction

Over the last 10 years a number of new therapeutic techniques have been developed to enhance movement characteristics of the affected upper limb in populations with unilateral motor deficit. Constraint-induced therapy (Taub and Wolf, 1997), which involves restraint of the non-affected upper limb to promote enhanced use of the affected limb, has realized beneficial effects for those in the upper quartile of functional ability. However, constraint-induced therapies have proven less successful in people with more moderate to severe motor deficits. Recent studies have suggested that bilateral activation strategies, in which motor tasks are performed with both upper limbs simultaneously, may be a more effective intervention for individuals with higher levels of upper-limb impairment (Mudie and Matyas, 2000; Whitall et al., 2000; Lewis and Byblow, 2004b). While a recent meta-review by Stewart et al. (2006) suggests that bilateral interventions are effective in improving arm function, positive outcomes have not been consistently reported in the literature. To more fully realize

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1388-2457/$32.00
doi:10.1016/j.clinph.2007.06.010

the potential of bimanual training as a therapeutic intervention it would be beneficial to determine how the neural control of bimanual tasks differs from that in unimanual tasks, and to investigate whether lesion location differentially affects the response to these two tasks.

Alterations in motor performance during bimanual tasks are thought to arise through interlimb coupling, an inherent feature of the human motor control system that manifests as mutual interactions between currently moving limbs. During actions that require disparate movements of the upper limbs, coupling mechanisms promote an assimilation of spatial and temporal movement characteristics of the two limbs and performance instability (Kelso et al., 1979, 1983; Franz et al., 1991; Swinnen et al., 1998). In contrast, bilateral synchronous and symmetric movements, where temporally and spatially identical actions are performed with both upper limbs, are an intrinsically stable form of coordination (Kelso, 1984; Semjen et al., 1995). In these instances, it is proposed that interlimb coupling affords a simplification of the motor control strategy, such that two limbs can be controlled as a single functional unit. One consequence of the assimilation effects of interlimb coupling is that spatial trajectories and temporal aspects of a non-dominant limb may be positively influenced when tasks are constrained to be produced in a bimanual, symmetric nature (Carson et al., 1997). The ability to enhance motor output of an individual limb would provide obvious benefits to people with unilateral motor impairments.

The precise neural mechanisms associated with interlimb coupling are uncertain. One possible mechanism is coincident activation of contralateral and ipsilateral descending motor pathways from the primary motor cortices (Cattaert et al., 1999; Kagerer et al., 2003). In support of this, Kagerer et al. (2003) provided evidence of a link between the excitability of ipsilateral motor pathways and the stability of bimanual movement patterns. Other research has suggested a specific role of neural structures in the dominant hemisphere in the coordination of bimanual tasks (Jancke et al., 1998; Urbano et al., 1998). This follows the suggestion that the left hemisphere (in right-handed individuals) is more predominantly involved in motor planning than the right (Leiguarda and Marsden, 2000; Verstynen et al., 2005). Further studies have proposed the involvement of transcallosally-mediated interactions between the two primary motor cortices (Eliassen et al., 1999; Diedrichsen et al., 2003). Although different neural structures may mediate the short-term effects of bilateral activation compared to the longer-term outcomes following a sustained intervention period, examining the neural control of bilateral tasks may provide important information on the potential effects of long-term training.

The aim of the current study was to investigate interlimb coupling in healthy individuals and in a population with post-stroke hemiparesis, with a particular emphasis on determining how side of lesion influences these outcomes. The novel aspect of the current study was to combine neurophysiological analyses with behavioral data to provide a thorough examination of the underlying neural pathways associated with bilateral movement. In one session, subjects performed a simple upper-limb movement task in unimanual or bimanual conditions while motion analysis techniques were used to record the performance of the limbs. In a second session, transcranial magnetic stimulation (TMS) was used to examine the excitability of contralateral and ipsilateral motor pathways from the two cortical hemispheres during unilateral and bilateral muscle activation. We examined two distinct hypotheses: (1) interlimb coupling is mediated by a structure in the left hemisphere, therefore subjects with right hemisphere lesions will display characteristics of stronger interlimb coupling compared to those with lesions in the left hemisphere and (2) interlimb coupling is mediated by the activation of ipsilateral motor pathways, therefore asymmetric bimanual movements will exhibit greater instability in subjects with stronger ipsilateral cortical excitability.

2. Methods

2.1. Subjects

The subjects were 15 individuals with hemiparesis following stroke (see Table 1 for details) and nine healthy control subjects. Control subjects were selected so that the mean age did not differ from the stroke group (control mean 55 ± 12 years; $P = 0.6$). Subjects with stroke were required to be at least 12 months post-stroke, demonstrate residual impairment of upper-limb function without shoulder instability, have the ability to follow simple instructions, and to have no other neurological impairments or orthopedic limitations of either upper limb. All stroke subjects were previously right-hand dominant (Oldfield, 1971). Throughout the manuscript, we refer to the arm ipsilateral to the lesioned hemisphere as the "non-affected" arm, even though there is evidence that motor impairments are present in this side (Colebatch and Gandevia, 1989; Andrews and Bohannon, 2000).

Control subjects (one left-handed) were required to be neurologically intact and to have no orthopedic limitations of either upper limb. Two of the subjects with stroke and one control did not participate in the TMS session due to contraindications to magnetic stimulation. Ethical approval for the study was obtained from the Northwestern University Institutional Review Board and informed written consent was obtained from all individuals prior to participation.

2.2. Session 1: behavioral task performance

The behavioral task was a continuous supination–pronation movement of the forearm. This task was used to provide intra- and interlimb measures of upper-limb function. Subjects were seated on a padded chair with each elbow placed in an arm support so that the forearm was positioned horizontally and the shoulder in a relaxed

Table 1
Details of the stroke group

ID	Age	Sex	Stroke duration	Affected side	FMA	Freq	Lesion location
P1	39	M	6	L	46	0.6	Parietal, occipital lobes
P2	58	M	5	L	43	0.8	Frontal, parietal lobes
P3	69	M	7	L	43	0.9	Frontal, parietal lobes
P4	83	F	4	R	42	1.0	Middle internal capsule
P5	59	F	5	L	43	0.8	Frontal, parietal lobes
P6	34	F	15	R	27	0.6	Frontal, temporal lobes
P7	67	M	10	R	49	1.6	Frontal lobe, internal capsule, corona radiata
P8	66	M	5	L	55	1.2	Posterior internal capsule
P9	53	F	9	L	47	1.0	Frontal, parietal lobes
P10	41	M	29	R	59	1.2	Internal capsule
P11*	59	M	10	L	39	0.8	Frontal, parietal lobes
P12*	60	M	4	R	54	1.0	Frontal, parietal, temporal lobes
P13	83	M	5	R	15	1.0	N/A
P14	46	M	5	R	24	0.6	Internal capsule
P15	57	M	2	L	38	0.6	N/A
Avg	58 ± 14 years	11 M	8 ± 7 years	8 L	42 ± 12	0.9 ± 0.3 Hz	

FMA, Fugl-Meyer assessment (maximum 66); Freq, movement frequency during behavioral task; M, male; F, female; L, left; R, right;* participated in session 1 only.

posture. A wrist support splint was fitted over each arm to maintain the wrist joint in a neutral posture. A small rigid body with four light-emitting diode (LED) markers was securely attached to each of the wrist support splints. During the task, the LED markers were tracked using an Optotrak 3020 system (Northern Digital Incorporated, Waterloo, ON) placed directly in front of the subject. Data were sampled at 200 Hz.

Subjects were instructed to perform the movement task by continuously pronating and supinating the forearm to the maximum range of motion in each direction. The task was conducted in four conditions: unimanual left hand, unimanual right hand, bimanual in-phase (IP; mirror symmetric about sagittal plane; Fig. 1a), and bimanual anti-phase (AP; parallel movements about sagittal plane). The movement task was paced by a metronome. The frequency of the metronome was determined at the start of the session by having the subjects perform three frequency-scaled bimanual movement trials starting in the AP pattern. The starting frequency for these three trials was 0.4 Hz and was increased by 0.2 Hz every 7 s. The frequency at which the movements became unstable (unable to maintain frequency, loss of AP pattern, or severely reduced movement amplitude) was deemed the "critical frequency". For the remainder of the metronome-paced trials, the metronome frequency was constant and was set 0.2 Hz below the critical frequency. Three trials of 35 s duration were performed in each of the four movement tasks in a randomized order.

2.3. Session 2: transcranial magnetic stimulation

TMS was applied using a Magstim 200 (Magstim Company, Wales) with a 70 mm figure-of-eight coil. The stimulating coil was placed over the scalp at the optimal location for eliciting a motor evoked potential (MEP) in the contralateral biceps brachii (BB) muscle (hot spot). The BB were chosen as the target muscle as they are involved in the supination–pronation task and are easily accessible using surface electromyography (EMG). With the coil positioned at the hot spot, the resting motor threshold (RTh) of the contralateral motor pathway was determined. RTh was defined as the minimum stimulus intensity at which a response of greater than 50 μV could be elicited in at least 4 of a train of 8 stimuli while the target BB muscle was relaxed. If responses could not be elicited at intensities below 70% of maximum stimulator output (MSO), for the purposes of setting stimulus intensities, RTh was defined as 70% MSO.

Cortical stimuli were applied at a range of stimulus intensities and in four muscle activation conditions. The stimulus intensities applied were 80%, 100%, 120%, and 140% RTh. In individuals with a high motor threshold, the maximum stimulus intensity was often limited to 120% RTh to avoid subject discomfort. The four muscle activation conditions were: both arms at rest, arm contralateral to stimulation activated, arm ipsilateral to stimulation activated, and both arms activated. During arm activation, the subjects were required to isometrically activate the BB muscle/s to $20 \pm 2\%$ of maximum voluntary contraction (MVC). A visual display of muscle activity from both arms was provided to assist subjects and stimuli were not delivered until muscle activation was at the required level. Ten responses to TMS were collected at each combination of stimulus intensity and muscle activation condition. The order of stimulus intensities and activation conditions was randomized between subjects. In all subjects, the protocol was conducted twice; once with the left hemisphere as the test hemisphere and once with the right hemisphere as the test hemisphere.

Responses to TMS were recorded from the BB muscles using surface EMG. Self-adhesive disposable dual electrodes (Noraxon USA Inc., AZ) were applied over the belly of each muscle following standard skin preparation techniques. EMG signals were amplified and conditioned using

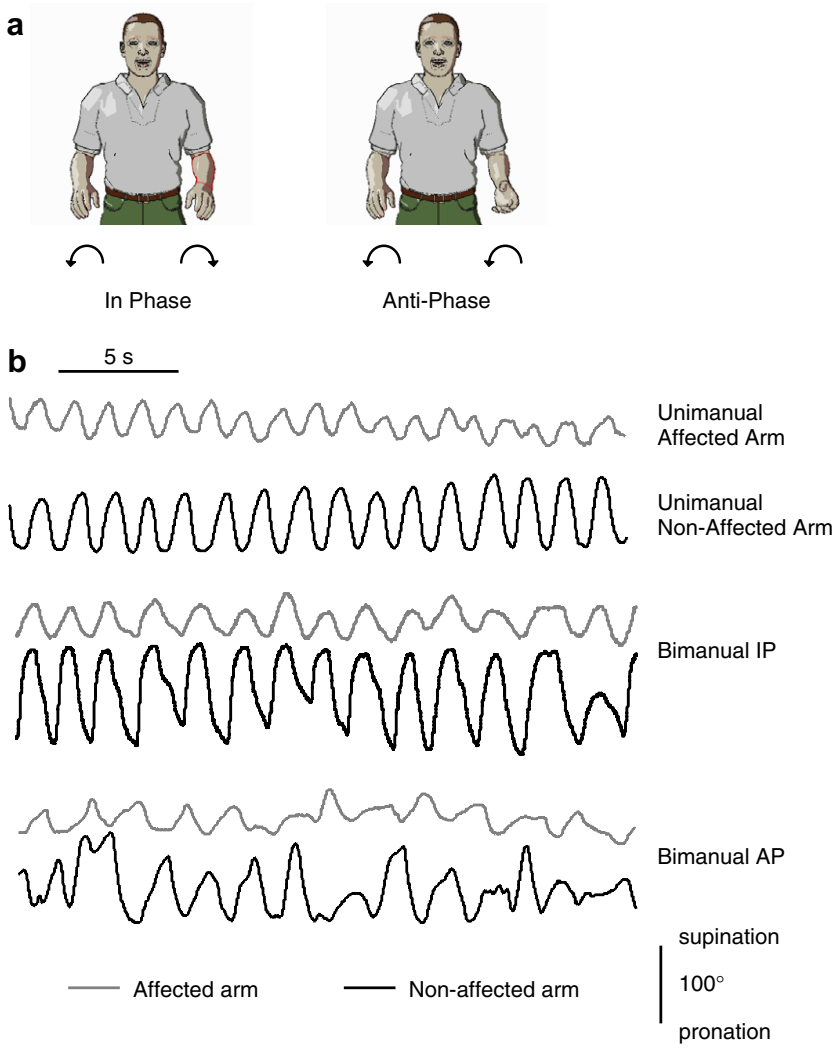

Fig. 1. (a) Illustration showing the two bimanual movement tasks. The subject's elbows were supported and the forearms were free to rotate about the Z axis. (b) Example data from the behavioral task performed by an individual subject with stroke. The data show the supination–pronation angle of the affected (light) and non-affected (dark) arms in the final 30 s of each trial. Supination is shown as positive. IP, in-phase; AP, anti-phase.

a Bortec AMT-8 (Bortec Biomedical Ltd., Canada) with high- and low-pass cut-off frequencies of 10 and 1000 Hz, respectively. The resulting signals sampled at 5000 Hz for subsequent analysis.

2.4. Data processing and analysis

2.4.1. Optotrak motion analysis data

From the rigid bodies attached to the wrist support splints, a measure of rotation around the Z (transverse) axis was obtained, representing forearm supination–pronation angle. A peak-picking algorithm was used to define movement amplitude peaks for the two hands. A measure of spatial performance was acquired by determining the peak-to-peak movement amplitude. Spatial variability was quantified using the coefficient of variation (CV) of movement amplitude (CV = 100 × standard deviation/mean).

Measures of interlimb coordination were obtained in bimanual trials by analyzing the continuous relative phase between the two arms. A measure of the central tendency of the relative phase for each trial was derived and transformed into a measure of uniformity (Mardia, 1972; Burgess-Limerick et al., 1991). This provided an indication of movement stability in the two bimanual tasks in the range 0 (maximum dispersion) to 1 (no dispersion).

All intra- and interlimb dependent variables were obtained from the final 30 s of each 35 s trial. Any portions of a trial in which the subject was performing an incorrect movement pattern, such as AP instead of IP, were discarded (approximately 3% of total trials). The values were averaged across the three trials in each movement task. A repeated measures (RM) analysis of variance (ANOVA) was used to analyze the effect of movement task (unimanual, IP, AP) on the performance variables. In the stroke group, separate ANOVAs were applied for the affected and non-affected arms. Significant effects were investigated using paired t-tests adjusted using a Bonferroni correction factor.

2.4.2. Motor evoked potentials

The analysis of responses to TMS in the arm contralateral to the stimulating coil was restricted to stimulus intensities that were applied to all subjects, *i.e.* 80%, 100%, and 120% RTh. MEPs obtained for each combination of stimulation intensity and muscle activation were averaged. From these averaged responses, MEP latency and maximum peak-to-peak amplitude values were obtained. MEP latency was defined as the first point following the stimulus artifact to exceed 3 standard deviations (SD) of background EMG. MEP amplitude was determined as the maximum peak-to-peak difference in response size in a 30 ms window following the onset of the response.

MEP amplitude was compared between tasks where the activation level of the target muscle was equivalent. That is, comparisons were made between the two conditions in which the target muscle was at rest (both arms at rest, arm ipsilateral to stimulation activated) and between the two conditions in which the target arm was activated (arm contralateral to stimulation activated, both arms activated). For each individual, MEP amplitude was normalized to the maximum MEP amplitude within these tasks. This enabled us to examine the influence of activation of the opposite arm on the excitability of the contralateral motor pathway. A two-way task (rest, ipsilateral arm activation) × stimulus intensity (80%, 100%, and 120% RTh) RM ANOVA was used to compare contralateral MEP amplitude between the two tasks where the target muscle was quiescent. A further two-way task (contralateral activation, bilateral activation) × stimulus intensity (80%, 100%, and 120% RTh) RM ANOVA was used to compare contralateral MEP amplitude between the two tasks where the target muscle was activated. Similar analyses were used to compare the level of background EMG (30 ms prior to stimulus onset) between the two sets of tasks with matched muscle activation.

Responses in the muscle ipsilateral to cortical stimulation were analyzed in the two tasks in which the ipsilateral muscle was activated during stimulation (ipsilateral activation, bilateral activation). The number of stimuli that gave rise to a discernable ipsilateral MEP (iMEP; 10–30 ms onset, >100 μV) was recorded for all stimulus intensities and converted to a percentage of total stimuli given. Paired *t*-tests were used to compare these percentages between the ipsilateral and bilateral muscle activation tasks. Separate tests were conducted for the control subjects and for the affected and non-affected arms of the stroke group. All results are reported as means ± SD.

3. Results

3.1. Behavioral task

Spatial performance was markedly influenced by movement task, but only for the stroke group. Fig. 1b illustrates example data from an individual stroke subject showing the supination–pronation angle during the four movement tasks. Note the reduced amplitude and increased variability of movement in the affected arm in the unimanual task. Also, the performance of both arms is diminished during the bimanual AP task compared to unimanual. Group results from the behavioral task session are displayed in Fig. 2. There were no significant differences between the dominant and non-dominant arms of the control subjects

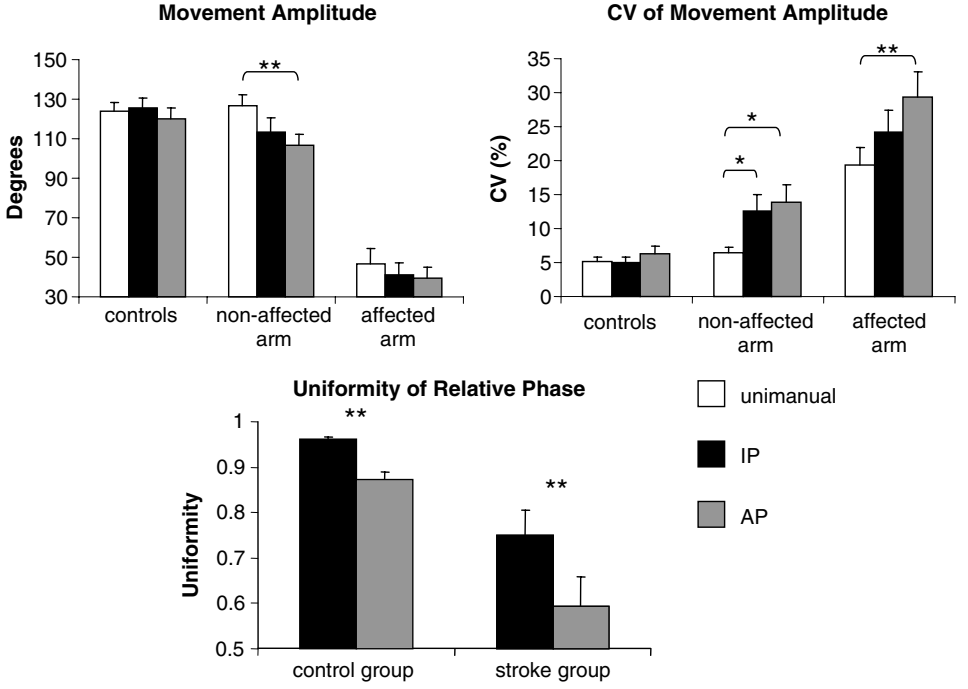

Fig. 2. Group results showing the dependent variables from the behavioral task. Data from the control subjects have been pooled across the dominant and non-dominant arms. Bars are 1 standard error of the mean. CV, coefficient of variation; IP, in-phase; AP, anti-phase. $^{*}P < 0.05$. $^{**}P < 0.01$.

so results from the two arms were pooled (movement amplitude, $P = 0.8$; CV of movement amplitude, $P = 0.06$).

In the initial frequency-scaled trials, the maximum stable movement frequency was higher in the control subjects compared to the stroke group. Therefore, the subsequent metronome-specified movement frequencies for the control group (range: 1.6–2.0 Hz; mean: 1.8 ± 0.2 Hz) were significantly faster than those for the stroke group (range: 0.5–1.6 Hz; mean: 0.9 ± 0.3 Hz; $P < 0.001$). Across all movement conditions, movement amplitude of the affected arm ($42 \pm 25°$) was significantly less than the non-affected arm ($116 \pm 25°$; $P < 0.001$) and the control group ($123 \pm 20°$; $P < 0.001$). In the control subjects, the effect of movement task on movement amplitude ($F_{2,34} = 2.8$; $P = 0.08$) and the CV of movement amplitude ($F_{2,34} = 2.4$; $P = 0.1$) did not reach significance. That is, there were no differences in the performance variables between the movement tasks in the control group.

In the subjects with stroke, reductions in intralimb performance in the affected and the non-affected arms were noted during the AP and, to a lesser extent, IP tasks. For the affected arm, a significant effect of task was evident both for movement amplitude ($F_{2,28} = 5.0$; $P = 0.02$) and the CV of movement amplitude ($F_{2,28} = 7.5$; $P = 0.002$). Post hoc analysis did not reveal any significant differences between the three movement tasks for movement amplitude (all corrected $P > 0.05$); however, it was found that the CV of movement amplitude was larger in AP compared to unimanual ($P = 0.004$). In the non-affected arm there were also significant effects of task for movement amplitude ($F_{2,28} = 11.1$; $P < 0.001$) and the CV of movement amplitude ($F_{2,28} = 7.6$; $P = 0.002$). Further analysis indicated that movement amplitude was smaller in the AP task compared to unimanual ($P = 0.001$). Both the AP ($P = 0.01$) and IP ($P = 0.03$) tasks resulted in a significantly larger CV of movement amplitude compared to unimanual. There were no other significant differences between movement tasks (all $P > 0.05$).

Uniformity of relative phase was taken as a measure of movement stability for the two bimanual tasks. As expected, both the control ($P < 0.001$) and stroke ($P = 0.001$) subjects displayed significantly higher uniformity values in IP compared to AP (Fig. 2).

3.1.1. Effect of lesion location

Our first hypothesis was that lesion side would influence interlimb coupling in the subjects with stroke. The group consisted of eight individuals with left hemiparesis and seven with right hemiparesis, and all were previously right-hand dominant. We found that individuals with left and right hemiparesis displayed differences in their performance of the IP and AP tasks. The group analyses indicated effects of task in both arms of the stroke subjects. To capture these changes in performance in both arms, we combined data from the affected and non-affected sides prior to analysis. Separate paired t-tests were used to compare the dependent variables between the IP and AP movement tasks for those with left and right hemiparesis (Fig. 3). In the group with left hemiparesis, the AP task displayed significantly lower performance measures for

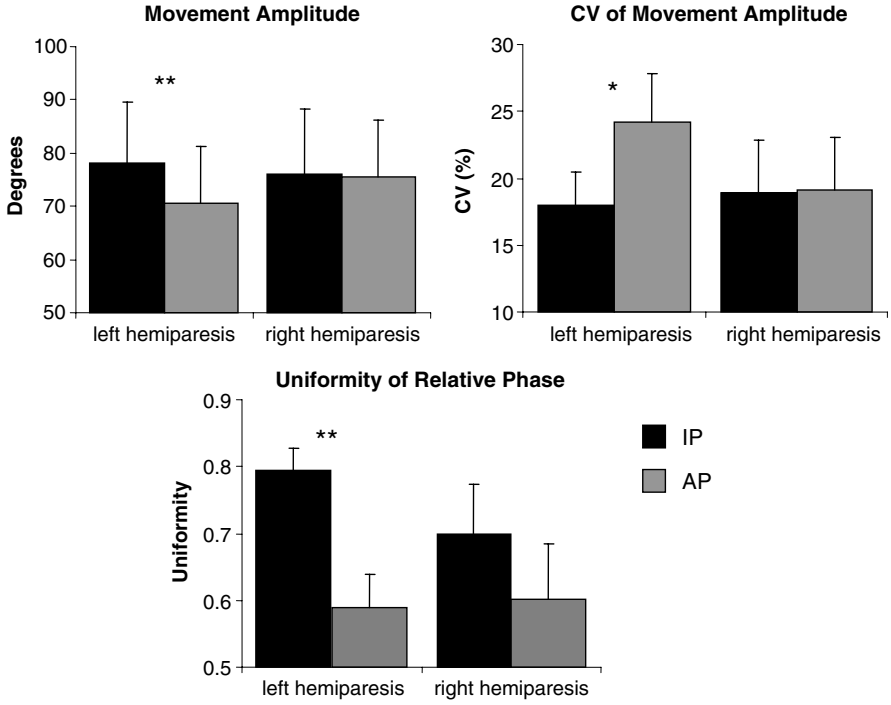

Fig. 3. Group results of the two bimanual movement tasks for the stroke group separated into those with left and right hemiparesis. For the intralimb variables, data from the affected and non-affected arms were combined. IP, in-phase; AP, anti-phase; CV, coefficient of variation. Bars are 1 standard error of the mean. $^{*}P < 0.05$. $^{**}P < 0.01$.

uniformity of relative phase ($P = 0.007$), movement amplitude ($P = 0.003$), and the CV of movement amplitude ($P = 0.03$). For those with right hemiparesis, there were no differences between the IP and AP tasks for any of the dependent variables (all $P > 0.08$). Therefore, subjects with left hemiparesis performed significantly better in the IP task compared to AP, whereas those with right hemiparesis performed the two bimanual tasks at a similar level.

The difference in outcome measures between the IP and AP patterns for the group with left hemiparesis could be due to enhanced IP performance or reduced AP performance. To investigate this, we compared the performance variables for the AP and IP tasks between the two groups. These analyses did not reveal any significant differences between groups for a given task (*t*-tests, all $P > 0.3$).

3.2. Transcranial magnetic stimulation

Contralateral and ipsilateral MEPs were influenced by the state of activation of the two arms. Fig. 4 shows example responses from individual stroke and control subjects illustrating these effects of non-target arm activation. The top traces (Fig. 4a) are from the non-affected arm of a stroke subject. They show a clear increase in resting MEP amplitude when the contralateral limb is activated. Fig. 4b shows responses from a control subject with the target BB muscle activated. There are reciprocal effects on contralateral and ipsilateral pathway excitability during bilateral activation. Group results are presented in Fig. 5 and Table 2. Paired *t*-tests indicated no significant differences in any of the dependent variables between the dominant and non-dominant arms of the control subjects (all $P > 0.2$). Therefore, results from the two arms of the control subjects were pooled. In the control subjects, RTh was greater than 70% MSO in two of the 16 hemispheres tested. In the non-affected and affected hemispheres of the stroke subjects, RTh was greater than 70% MSO in 3 and 12 of the 13 subjects tested, respectively. For both groups and all dependent variables, the main effect of stimulus intensity was significant (all $P < 0.05$). This is a predictable finding and is not reported further in the results section.

3.2.1. Contralateral MEP amplitude

In the control subjects, contralateral MEP amplitude was markedly affected by the state of activation of the opposite arm. When the target arm was quiescent, a main effect of task indicated that contralateral MEP amplitude was significantly larger when the ipsilateral biceps muscle was activated compared to both arms at rest ($F_{1,15} = 53$, $P < 0.001$; Fig. 5a). When the target contralateral arm was pre-activated, a significant effect of task was also present ($F_{1,15} = 8$, $P = 0.01$; Fig. 5b). In this case, activation of the ipsilateral muscle (bilateral activation) resulted in a significant decrease in contralateral MEP amplitude compared to activation of the target arm alone (unilateral activation).

In the non-affected arm of the stroke group similar results to the control subjects were found. When the non-affected arm was quiescent, MEPs were larger when the affected arm was activated compared to both arms at rest ($F_{1,12} = 37$, $P < 0.001$; Fig. 5d). It should be noted that background EMG in the non-affected arm was significantly greater when the affected arm was activated compared to when both arms were at rest ($F_{1,12} = 11$, $P = 0.006$), which may have contributed to the larger MEP amplitude in this condition. This was the only condition in either group where background muscle activation was not matched between tasks (all remaining $P > 0.1$). When the non-affected arm was pre-activated, simultaneous activation of the affected arm resulted in a significantly smaller MEP amplitude compared to the non-affected arm activated alone ($F_{1,12} = 6$, $P = 0.03$; Fig. 5e).

In the affected arm of the subjects with stroke, the main effect of task was significant for responses obtained when the arm was at rest ($F_{1,12} = 5$, $P = 0.05$; Fig. 5g) but not when the arm was pre-activated ($F_{1,12} = 2$, $P = 0.2$; Fig. 5h). This indicates that activation of the non-affected

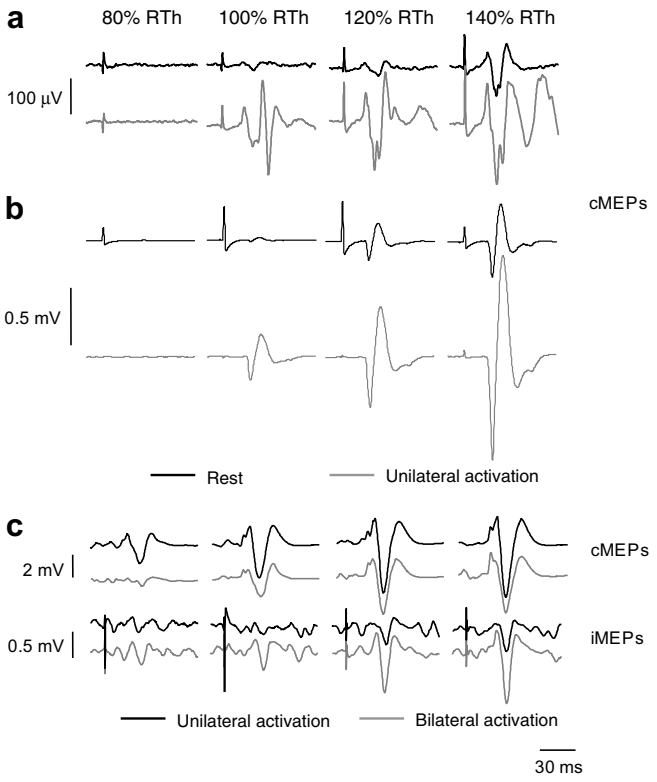

Fig. 4. Example contralateral (cMEPs) and ipsilateral (iMEPs) motor evoked potentials at the four levels of stimulus intensity. (a) Responses in the non-affected arm of a subject with stroke while the arm was at rest. (b) Responses in the dominant arm of a control subject while the arm was at rest. The black traces show MEPs elicited while both arms were at rest. The light traces show MEPs elicited during unilateral activation of the opposite arm (ipsilateral to stimulation). (c) Responses in a healthy control subject while the target arm was activated. The black traces show MEPs elicited during activation of the target arm alone. The light traces show MEPs elicited during bilateral activation of both biceps muscles. Note the difference in scale between the cMEPs and iMEPs. Responses are an average of 10 individual MEPs. RTh, rest threshold.

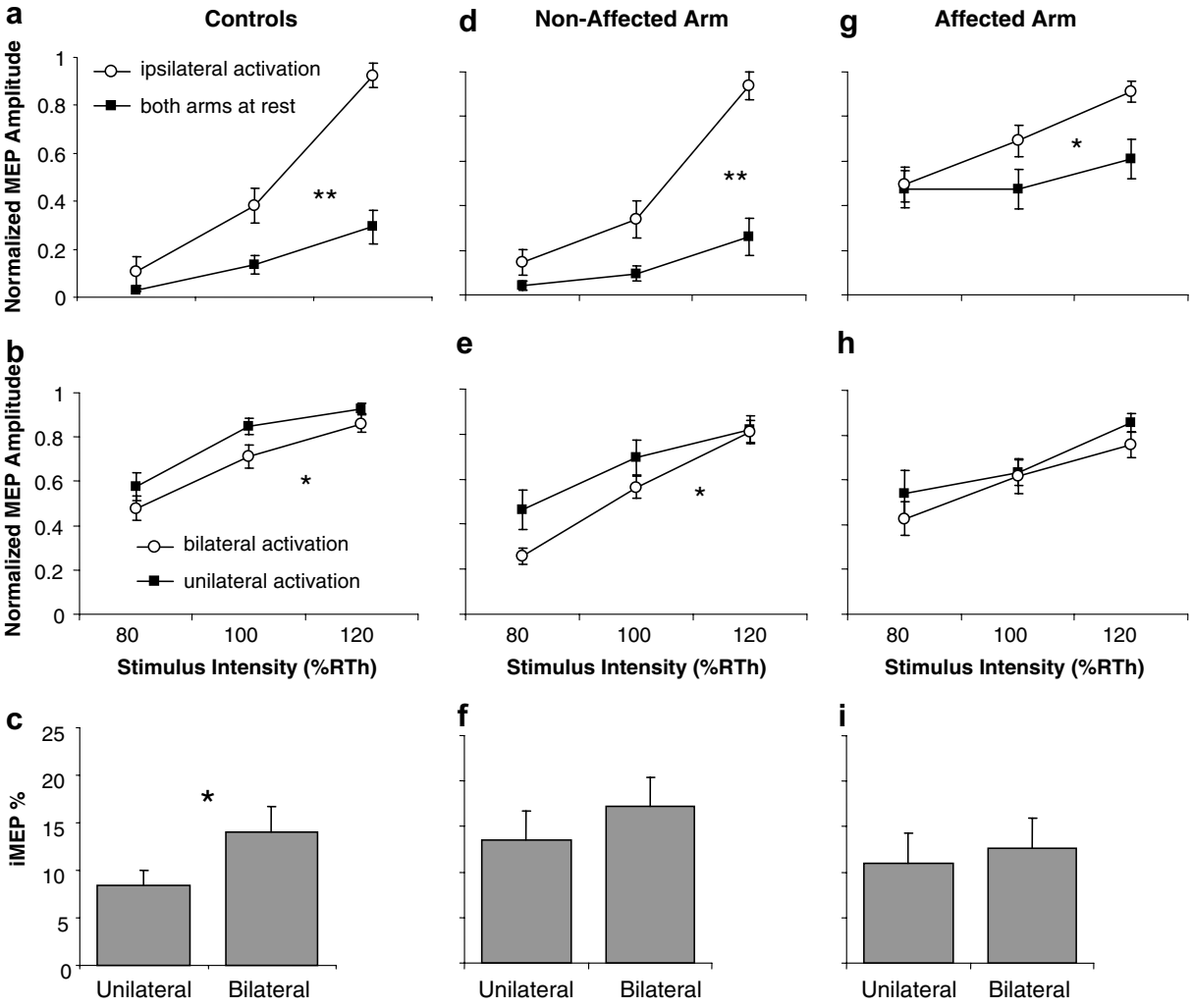

Fig. 5. Group results showing responses to transcranial magnetic stimulation in the contralateral and ipsilateral arms. Data for the control subjects have been pooled across the dominant and non-dominant arms. (a, d, and g) Contralateral motor evoked potential (MEP) amplitude while the target arm is at rest. Ipsilateral activation refers to activation of the non-target arm (ipsilateral to the stimulating coil). Data are shown for the three stimulus intensities that were applied in every subject. MEP amplitude is normalized to the largest amplitude in the two tasks. (b, e, and h) Contralateral MEP amplitude while the target arm is activated. Unilateral activation refers to activation of the target arm alone (contralateral to the stimulating coil). (c, f, and i) Percentage of stimuli from all stimulus intensities that elicited ipsilateral motor evoked potentials (iMEPs). Unilateral trials involved activation of the target arm only (ipsilateral to the stimulating coil). Bars are 1 standard error of the mean. RTh, rest threshold. *Effect of task $P < 0.05$. **Effect of task $P < 0.01$.

arm had no effect on contralateral MEP amplitude when the affected arm was pre-activated.

3.2.2. Ipsilateral MEPs

The percentage of stimuli that elicited iMEPs was analyzed in the two tasks in which the target ipsilateral muscle was activated (Figs. 4 and 5). In the control subjects, across all stimulus intensities tested, a significantly higher percentage of iMEPs were elicited during bilateral activation of the two arms compared to unilateral activation of the target arm alone ($P = 0.02$; Fig. 5c). In the non-affected arm of the stroke subjects, the small difference in the number of iMEPs elicited between unilateral and bilateral activation approached significance ($P = 0.06$; Fig. 5f). In the affected

Table 2
Contralateral and ipsilateral responses to transcranial magnetic stimulation at 120% RTh

	Target arm at rest		Target arm active			
	MEP size (mV)	MEP latency (ms)	MEP size (mV)	MEP latency (ms)	iMEP size (mV)	iMEP latency (ms)
Controls	0.1 ± 0.09	16.1 ± 1.4	6.6 ± 3.7	13.3 ± 2.1	0.8 ± 0.5	25.2 ± 3.5
Non-affected arm	0.2 ± 0.4	15.6 ± 2.5	3.2 ± 3.8	13.3 ± 1.4	0.4 ± 0.2	25.7 ± 7.3
Affected arm	0.02 ± 0.01	19.4 ± 2.4	1.1 ± 2.1	19.5 ± 7.4	0.1 ± 0.07	24.0 ± 6.1

Data are shown for the conditions where the non-target arm was at rest. MEP, motor evoked potential; iMEP, ipsilateral motor evoked potential.

arm, the number of iMEPs elicited was not different between unilateral and bilateral activation ($P = 0.2$; Fig. 5i).

3.2.3. Effect of lesion location

Similar to the analysis of the behavioral data, we analyzed the results from the TMS session separately for those with left and right hemiparesis. Responses to TMS in the affected arm were compared using the same analyses as described earlier. In the subjects with left hemiparesis, contralateral MEP amplitude in the affected arm was significantly larger when the non-affected arm was activated compared to both arms at rest ($F_{1,6} = 11$, $P = 0.006$; Fig. 6a). When the affected arm was activated, there was a small but insignificant effect of task in the group with left hemiparesis reflecting a slight reduction in contralateral MEP amplitude during bilateral activation ($F_{1,6} = 6$, $P = 0.054$; Fig. 6b). For those with right hemiparesis, the effect of task was not significant when the affected arm was at rest ($F_{1,5} < 0.001$, $P = 1$; Fig. 6d) or when it was activated ($F_{1,5} < 0.001$, $P = 1$; Fig. 6e). Consequently, individuals with left hemiparesis displayed changes in contralateral pathway excitability that were similar to the control subjects and the non-affected arm, while those with right hemiparesis did not. *t*-Tests revealed that the difference in the percentage of iMEPs elicited between unilateral and bilateral activation conditions was not significant for those with left or right hemiparesis (both $P > 0.1$; Fig. 6c and f).

3.3. Relationships between task performance and corticospinal excitability

Our second hypothesis was that the individual strength of interlimb coupling would be influenced by the excitability of ipsilateral motor pathways (Kagerer et al., 2003).

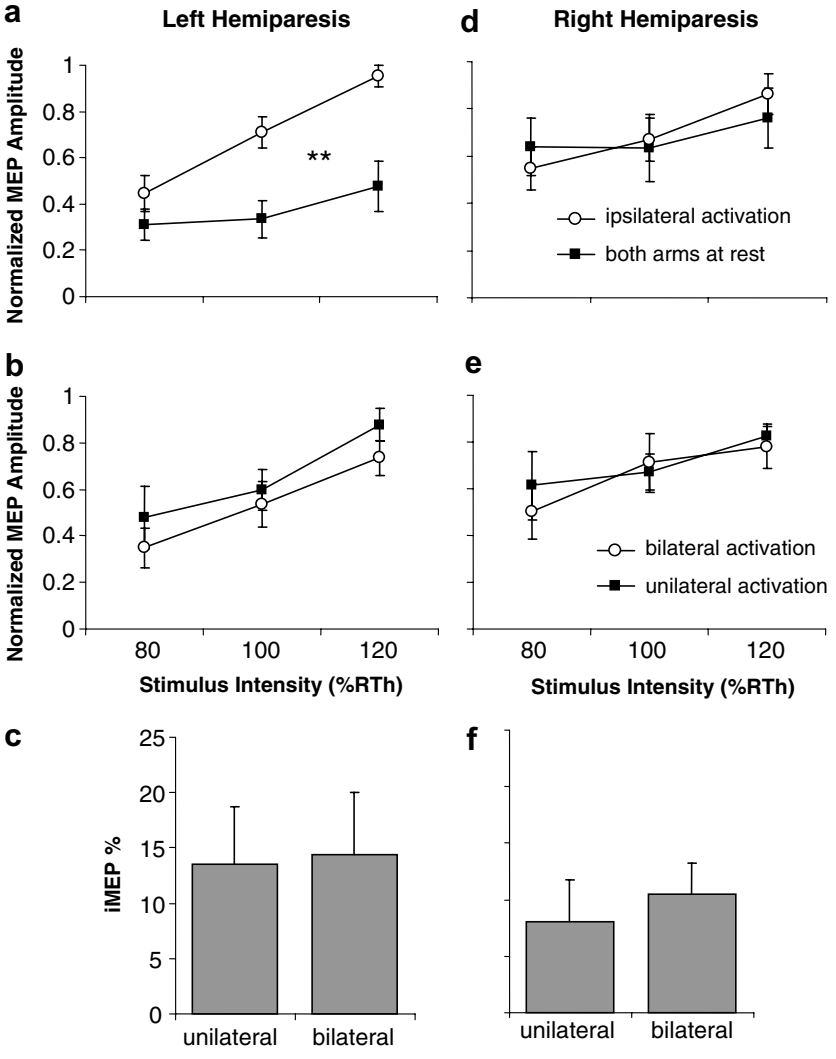

Fig. 6. Group results showing responses to transcranial magnetic stimulation in the affected arm of the stroke subjects separated into those with left and right hemiparesis. (a and d) Contralateral motor evoked potential (MEP) amplitude while the target (affected) arm was at rest. Ipsilateral activation refers to activation of the non-affected arm, ipsilateral to the stimulating coil. (b and e) Contralateral MEP amplitude while the target arm was activated. Unilateral activation refers to activation of the target (affected) arm alone. Bilateral activation refers to activation of both arms. (c and f) Percent of stimuli that elicited ipsilateral MEPs in the affected arm. Unilateral activation refers to activation of the affected arm only (ipsilateral to the coil). Bars are 1 standard error of the mean. **Effect of activation condition $P < 0.01$.

A measure of coupling strength was determined using the ratio of relative phase uniformity (AP:IP), where smaller values indicate lower stability in the AP task compared to IP. Correlations were made between this uniformity ratio and the percentage of iMEPs elicited. These were not significant for the control group (Pearson $R = 0.03$, $P > 0.9$) or for the affected ($R = 0.008$; $P > 0.9$) and non-affected ($R = -0.13$; $P = 0.7$) arms of the stroke group. We also correlated the uniformity ratio with the size of contralateral MEPs at 120% RTh during unilateral activation of the test arm. These correlations also were not significant for the control group ($R = 0.2$, $P = 0.7$) or for the affected ($R = 0.3$; $P = 0.4$) and non-affected ($R = -0.5$; $P = 0.06$) arms of the stroke group. The relationship between the level of impairment (FMA) of the stroke subjects and the ratio of relative phase uniformity ($R = 0.15$, $P = 0.6$), percentage of ipsilateral MEPs ($R = -0.08$, $P = 0.8$), and contralateral MEP amplitude ($R = 0.2$, $P = 0.5$) also were not significant.

4. Discussion

This study examined the excitability and activation of neural pathways that may be associated with interlimb coupling in healthy individuals and in people with post-stroke hemiparesis. We present two novel findings: (1) people with left and right hemiparesis display differences in interlimb coupling and neural pathway excitability during bilateral activation and (2) in healthy subjects, alterations in the balance of excitability of contra- and ipsilateral descending pathways occur during bilateral activation. These results are discussed in further detail below.

4.1. Effect of lesion location

We found differences in behavioral and neurophysiological variables between the stroke subjects with left and right hemiparesis. Those with left hemiparesis showed a stronger performance advantage for the symmetric bimanual task (IP) compared to the asymmetric (AP). In contrast, those with right hemiparesis displayed little difference between the two tasks. Therefore, it appears that interlimb coupling was stronger in those with left hemiparesis, as they demonstrated a performance advantage when homologous muscles were simultaneously co-activated relative to conditions in which they were activated out of phase. Since the individuals with left hemiparesis have an intact left hemisphere, we conclude that the left (or previously dominant) hemisphere may contribute to the strength of coupling between the two limbs (Jancke et al., 1998; Urbano et al., 1998). The results from the TMS session lend further support to the contention that the left hemisphere is involved in interlimb interactions. The subjects with left hemiparesis displayed changes in contralateral motor pathway excitability when the opposite arm was contracted that were similar to the control subjects. That is, activation of the non-affected limb influenced the excitability of the corticomotor pathway to the affected arm. Those individuals with lesions in their left hemisphere did not display these effects.

Other studies have reported similar asymmetries showing the dominant hemisphere to be more influential in the control of the non-dominant arm than vice-versa (Chen et al., 1997; Ziemann and Hallett, 2001; MacKinnon et al., 2004; Newton et al., 2005). In a review paper, Cauraugh and Summers (2005) postulated that bilateral interventions were more effective in stroke rehabilitation when the dominant hemisphere is intact. A recent study that investigated asymmetries in cortical activation in left- and right-handers indicated a prominent role of the left hemisphere regardless of handedness (Verstynen et al., 2005), suggesting that this may be a specialization of the left rather than dominant hemisphere. The results of our study indicated that stroke subjects with left hemiparesis, *i.e.* those with an intact left hemisphere, demonstrated better performance measures in the symmetric compared to asymmetric movement task and showed modulations in neural pathways that were more similar to control subjects. We cannot differentiate whether this was a left- or dominant-hemisphere specific effect. Regardless, it may be possible to exploit these asymmetries to enhance the efficacy of rehabilitation training interventions involving bilateral movements. Interestingly, McCombe Waller and Whitall (2005) reported that subjects with chronic *right* hemiparesis made larger functional improvements following a six-week bilateral arm training intervention compared to those with left hemiparesis. The functional outcome of bilateral activation may therefore depend on the short- versus long-term nature of the intervention, use of asymmetric or symmetric movements, and how well the training tasks transfer from bilateral to unilateral control.

Overall, there were small and largely insignificant differences in the performance variables between unimanual and bimanual symmetric (IP) movement tasks in the stroke and control groups. The behavioral task was chosen so as to provide measures of interlimb coupling and performance stability. In order to generate performance instability, the subjects were paced at a frequency close to their maximum. In the stroke subject group, this was sufficient to reveal differences between IP and AP task conditions. Therefore, it is not surprising that the IP task did not elicit any performance improvements in the stroke group. Indeed, the results follow other studies that have reported no improvements in the affected arm during bimanual performance of repetitive tasks (Rice and Newell, 2001; Lewis and Byblow, 2004a). Adopting a discrete motor task (Harris-Love et al., 2005) or instructing the subjects to focus on their spatial performance may have influenced the outcome measures in the unimanual and bimanual conditions. Although the task gave rise to performance instability in the stroke subjects, it is possible that it was not challenging to the control subjects. This may account for the lack of difference in intralimb performance variables between task conditions for the control group. Many other studies have reported

increased coordination stability in in-phase compared to anti-phase movements during supination–pronation tasks performed by healthy subjects (e.g. Byblow et al., 2000, 2002; Temprado et al., 2003). However, similar to our results, one previous study that also investigated *intralimb* performance stability found no significant differences between the two coordination patterns (Byblow et al., 1994).

4.2. Influence of ipsilateral motor pathways

We were unable to find any direct relationship between ipsilateral motor pathway excitability and the stability of the bimanual tasks in either group. This result contrasts with the finding of Kagerer et al. (2003), who reported that individuals from whom iMEPs could be elicited more readily were less stable in the performance of an asymmetric motor task. The latencies of iMEPs in our study were 5–15 ms longer than the contralateral MEPs. In the study by Kagerer and colleagues, iMEPs had a 3–5 ms longer latency than contralateral MEPs. This suggests that iMEPs in the two studies arose through an alternative neural pathway; perhaps due to the different target muscles adopted. Differences in the motor tasks performed may also have contributed to the different outcomes of the two studies.

Although there were no correlations between motor behavior and ipsilateral excitability, reciprocal changes in the excitability of ipsi- and contra-lateral motor pathways were noted during bilateral activation in the control subjects. Potentially, these changes in the *balance* of motor pathway excitability may be a more important determinant of interlimb coupling than the direct excitability of ipsilateral motor pathways. During bilateral activation of homologous muscles it would be appropriate to release inhibition of ipsi- or bi-laterally descending motor pathways since the same motor output can be directed to both sides of the body. In support of this, Bawa and colleagues (2004) reported that bilateral activation gave rise to an increase in the number of ipsilateral responses that could be elicited in proximal muscles acting on the upper limb. As we controlled the extent of muscle activation in our study, the reduced excitability of the contralateral pathway may represent compensation for heightened input to the motoneuron pool from ipsilateral motor projections.

Many previous studies have shown that contracting the homologous muscle on the opposite side of the body increases contralateral corticospinal excitability to a target arm while at rest (Hess et al., 1986; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Stinear et al., 2001; Woldag et al., 2004; Renner et al., 2005). Fewer studies have examined similar effects while the target muscle also is activated. One such study targeting an intrinsic hand muscle reported no differences in MEP amplitude between unilateral and bilateral activation in healthy subjects (Renner et al., 2005). The same study indicated a slight facilitation of MEP amplitude in stroke subjects during bilateral compared to unilateral activation when both hand muscles were at 50% MVC. The effect was not present at 10% MVC. This is the opposite finding to our results in the control subjects and in the non-affected arm of the subjects with stroke. The conflicting outcomes between these two studies may be due to different neural control mechanisms between distal and proximal muscles of the upper limb. It is known that proximal muscles receive greater input from uncrossed motor pathways compared to muscles located more distally (Kuypers and Brinkman, 1970; Brinkman and Kuypers, 1973) and the relative size of proximal representation in the cortex is smaller (Penfield and Boldrey, 1937). Therefore, the behavioral and neurophysiological outcomes in our study may be specific to tasks involving the proximal upper limb. Alternative results may have been achieved if target muscles located more distally in the upper limb, such as the hand, had been investigated.

The potential role in interlimb coupling of interactions at the level of the spinal cord and transfer through transcallosal pathways should be acknowledged. Earlier findings that contralateral muscle activation facilitates MEPs in individuals with callosal agenesis strongly suggest that the motoneuron pool is influenced at the spinal level (Meyer et al., 1995). Afferent information arising from motor activation in the opposite limb may therefore contribute to the changes in corticospinal excitability through segmental level networks (e.g. Carson, 2005). Previous studies also have reported changes in interhemispheric inhibition during activation of the contralateral limb (Ferbert et al., 1992). It has been suggested that interhemispheric inhibitory activity functions to maintain a focal activation of the opposite hemisphere, so that homologous muscles are not activated simultaneously (Kobayashi et al., 2003). Additionally, it has been reported recently that there are differences in the extent of interhemispheric inhibition between muscles of the upper limb (Harris-Love et al., 2007). This may influence the strength of interlimb coupling between different muscle representations and the efficacy of bimanual tasks involving different muscle representations. Therefore, contributions to interlimb coupling through these mechanisms should not be discounted.

5. Conclusions

Subjects with left and right hemiparesis displayed differential stability in symmetric and asymmetric movement tasks and differential changes in contralateral motor pathway excitability during activation of the opposite arm. This indicates that side of lesion may influence the efficacy of bilateral training interventions for people with stroke. In healthy subjects, changes in the balance of excitability between ipsi- and contra-laterally descending motor pathways were present during bilateral activation. However, no direct correlations were detected between the excitability of ipsilateral motor pathways to the BB muscles and behavioral aspects of bimanual coordination in the motor task performed in this study. Therefore, modulations in

the excitability of ipsi- and contra-lateral motor pathways during bilateral tasks may be a more important contributor to coordination stability.

Acknowledgements

The authors thank Tiffany Viant for technical assistance and Nondas Leloudas and Mary-Ellen Stoykov for their help with data collection. Funding for the study was provided by the Brinson Foundation, the Falk Family Trust, and NIH Grants K25 HD044720 and R21 HD049883-01.

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