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Cortical overlap of joint representations contributes to the loss of independent joint control following stroke

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Abstract

The loss of independent joint control in the paretic upper limb is a cardinal sign of movement disorders following stroke. However, the underlying neural mechanisms for such a loss following stroke are still largely unknown. In order to investigate the possible contribution of altered sensorimotor cortical activity to the loss of independent joint control, we measured electroencephalographic (EEG) and torque signals during the generation of static shoulder/elbow torques. We found significant increases in the overlap of shoulder and elbow joint representations at the cortical level in stroke subjects as compared to control subjects. Linear regression results demonstrated significant associations between the cortical overlap of joint representations and the degree of the loss of independent joint control. Therefore, we conclude that an increased overlap of cortical representations for shoulder and elbow contributes to the expression of the loss of independent shoulder/elbow control of the paretic upper limb in chronic hemiparetic stroke survivors.

Keywords

Chronic hemiparetic stroke; Electroencephalogram; Muscle synergies; Motor control; Cortical motor maps

Introduction

The loss of independent joint control is a cardinal sign of movement disorder following stroke. An example of this behavior is the obligatory abnormal coupling between shoulder abduction (SABD) and elbow flexion (EF) in the paretic upper limb, described as the ‘flexion synergy’ by Twitchell and Brunnstrom (Brunnstrom, 1970; Twitchell, 1951). Abnormal coupling between SABD and EF can severely impair the active range of motion required for functional reaching when individuals with stroke actively lift the affected limb against gravity (Beer et al., 2004; Beer et al., 2007; Sukal et al., 2007). Although the serious functional impact and nature of these impairments have been well documented through quantitative means (Beer et al., 2007; Sukal et al., 2007), the underlying neurological mechanisms responsible for their manifestation remain largely unknown.

The presence and severity of movement deficits following stroke have been reported to be related to changes in activity and spatial organization of sensorimotor cortices (SMC). A

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number of studies using different imaging modalities have provided evidence for the enhancement of activity in undamaged preexisting networks, manifested as increased sizes and amplitudes of cortical activity following stroke (Cicinelli et al., 1997; Cramer et al., 1997; Platz et al., 2000; Rossini et al., 1998; Weiller et al., 1992). These activations then slowly decrease over time or following rehabilitation, usually expressed as less recruitment and activity in the unaffected hemisphere (Dong et al., 2007; Jang et al., 2004; Liepert et al., 2004; Traversa et al., 1997). However, the direct associations between altered cortical activity in SMCs and specific motor disorders expressed in stroke survivors are still absent from the current literature. More specifically, studies that investigate the neural mechanisms underlying the loss of independent joint control in the paretic upper limb of chronic hemiparetic stroke subjects have not been conducted yet.

Previous quantitative studies have demonstrated the expression of the loss of independent joint control in the form of abnormal increases in the co-activation level between shoulder abductors and elbow flexors during static SABD and EF motor tasks (Bourbonnais et al., 1989; Dewald et al., 1995). Such abnormal muscle co-activation pattern in the paretic limb may be due to an abnormal increase in the overlap of cortical representation for elbow and shoulder joint/muscles. Evidence for cortical overlap of joint/muscles representations has been provided by results in both animals (Clark et al., 1988; Godde et al., 1996; Gribble and Scott, 2002; Hoffer et al., 2005; Rathelot and Strick, 2006) and human subjects (Cramer et al., 2003; Devanne et al., 2006; Godde et al., 1996; Marconi et al., 2007; Melgari et al., 2008; Schabrun and Ridding, 2007; Singh and Scott, 2003; Tyc and Boyadjian, 2006). It has been suggested that such overlaps may be the neural substrate to create a wide variety of functional muscle synergies (Melgari et al., 2008; Rathelot and Strick, 2006). Especially for shoulder and elbow joints, results in monkey experiments have shown that certain neurons in the primary motor cortex responded to both shoulder and elbow loads (Gribble and Scott, 2002). Thus a certain level of overlap for the joint's representation may facilitate movement encoding. However, we hypothesize that significant increases in overlap at cortical level could result in losses of independent joint control as observed following stroke. Our results demonstrate the existence of an abnormally increased level of overlap and its correlation with the loss in the independent shoulder/elbow joint control in the paretic upper limb.

Methods

Subjects

We recruited 13 chronic hemiparetic stroke subjects (age: 59.54 ± 2.8) with moderate to severe impairment and 10 control subjects (age: 46.8 ± 4.6). Motor function of the upper extremity of stroke subjects was evaluated using the Fügl-Meyer motor assessment (Fügl-Meyer et al., 1975). This assessment includes the evaluation of tendon reflexes and the performance of proximal and distal voluntary movements of the impaired arm. Cumulative scores approaching 60/66 for the upper extremity indicate only mild involvement, while scores less than 20/66 indicate severe disability. Clinical information regarding our stroke subjects is listed in Table 1. All of the control subjects were right-hand dominant and did not have a history of neurological injury or impairment. All subjects provided written consent prior to participation in the study that was approved by the Institutional Review Board of Northwestern University and in compliance with the principles of the Declaration of Helsinki.

Motor paradigm for cortical imaging

Participants sat in a Biodex chair (Biodex Medical Systems, Shirley, NY) that completely supported the trunk. The trunk was restrained to the back of chair with straps crossing the chest and abdomen to prevent trunk and pelvis motion during the experiment. Subjects were casted at the wrist and secured to a six degree of freedom (DOF) load cell with the shoulder at 75°

abduction, 40° flexion and the elbow at 90° flexion angle (see Fig. 1). In this position, the tip of the hand was approximately aligned with the median sagittal plane of the subject.

The motor tasks involved in this study were self-initiated torques generated in the SABD or EF direction from rest to 25% of the subject's maximum voluntary torque (MVT). All the subjects were instructed to generate torque only in the required directions. At the beginning of each trial, an auditory signal was given to the subject indicating the start of the task. After that, subjects were required to maintain a resting state for 5–7 s and then to self-initiate the generation of torque in the required direction to 25% ± 10% of their MVTs and to hold the torque at this level for 0.3 s. (Note: we chose to ask subjects to hold for only 0.3 s because most of our severely impaired stroke subjects could not hold any longer.) At the end of each trial, oral feedback was given to inform the subject of success for the trial or the reason for an unsuccessful trial. Subjects were instructed to avoid eye movements and movements in other parts of their body during the performance of each trial.

Prior to the data collection session, subjects went through a training session (about 1 to 3 h) to make sure they were able to easily perform the elbow/shoulder torque generation tasks without visual feedback. Following the training session, an anatomical MRI of the brain was taken in a 3 T magnet scanner (Siemens, Erlangen, Germany) using a T1-weighted gradient echo pulse sequence. Images had a field of view of approximately 231 mm, voxel size of 1.0×1.0 mm and slice thickness of 1.0 mm. Subsequently, the actual data collection session was scheduled.

During the actual data collection session, MVTs and maximum EMGs of each subject were recorded in three randomly ordered blocks consisting of the torque generation of shoulder flexion/extension (SF/E), shoulder abduction/adduction (SABD/ADD), and elbow flexion/extension (EF/E). Subjects then performed totally 100 to 150 trials for each of the required motor tasks as trained without visual feedback. In an effort to avoid fatigue, subjects completed trials in several randomly ordered blocks (20–30 trials for one block) consisting of SABD or EF with rest periods of about 15 s between trials, and about 20 min between blocks. The typical duration of the experiment was around 5 to 6 h, including 2.5 to 3 h for experiment setup, a half hour break for lunch, and 2 to 2.5 h for data collection.

Data collection for cortical imaging

We simultaneously collected force/moment signals, surface EMG signals from both arms and scalp EEG signals during each data collection session. Forces and torques generated at the wrist were measured using a six degree-of-freedom load cell (JR^3 Inc., Woodland, CA) and then converted online to torques at the elbow and shoulder based on a free body analysis of the upper limb (Beer et al., 1995). Surface EMG signals were recorded by active differential electrodes (Delsys, 16 and 8 Channel Bagnoli™ EMG System, Boston, MA) with 1 cm inter-electronic distance. The Delsys EMG system also provided pre-amplification (gain=1000) and single pole high pass filtering (cutoff frequency=6 Hz). Prior to data collection, all EMG signals were then filtered at 500 Hz (8-pole Butterworth, Frequency Devices Model 9016, Havelhill, MA) to prevent aliasing and amplified in a second stage with the gain depending on the amplitude of the signal. Correct electrode placements were verified by examination of EMG activity on an oscilloscope while performing muscle testing procedures, as described by Kendall (Kendall and McCreary, 1983). Nine muscles on the paretic (stroke) or dominant (able-bodied) upper limb, including the biceps brachii (BIC), brachioradialis (BRD), triceps brachii long head and lateral head (TRILO and TRILA) muscles at the elbow; the anterior (ADL), intermediate (IDL) and posterior deltoids (PDL); and pectoralis major vertical and horizontal fibers (PMJV and PMJH). In addition, EMG signals from the BIC, BRD, TRILA and IDL from the other arm were also recorded to test for the presence of mirror muscle activity. Scalp recordings were made with a 163-channel EEG system using active electrodes (Biosemi, Inc., Active II, Amsterdam, The Netherlands). The electrodes were mounted on a stretchable fabric

cap based on a 10/20 system (see Fig. 1). All data were sampled at 1 kHz. Furthermore, the positions of EEG electrodes on the subject's scalp were recorded with respect to a coordinate system defined by the nasion and pre-auricular notches using a three-dimensional magnetic digitizer (Polhemus, Colchester, VT). This allowed for the co-registration of EEG electrodes with each subject's anatomical MRI data. Collection of the EEG data was synchronized with torque and EMG data using a TTL pulse generated when the primary torque exceeded 0.15 Nm to mark the on-line detected torque onset.

Data analysis

Torque and EMG signal analysis—EMG signals in this study were used as monitoring signals for undesired muscle activations, such as muscle contractions in any arm during the resting period, mirror muscle activation from the non-tested arm, and signs of muscle fatigue. Torque and EMG signals were initially semi-automatically inspected for artifacts. Trials with artifacts (e.g., non-stable baseline, or EMG–torque ratio higher than the mean of EMG–torque ratio plus 3 times standard deviation which suggesting a muscle fatigue, or EMGs from the non-tested arm that may suggest fatigue or mirror movements) were eliminated. Remaining shoulder and elbow torques were baseline-corrected and averaged using a 250 ms moving window. The torque responses were then aligned with the off-line adjusted torque onset (i.e., an adjustment between the offline detected torque onset and on-line the TTL signal. This adjustment was used to generate off-line adjusted torque onset for aligning different trials.) and then ensemble-averaged. Torque responses were then normalized by the MVTs in each degree of freedom (DOF).

Torque coupling ratio (TCR) was then used to quantify the level of independent joint control in each of the tested arms. TCR was defined as

$$\mathrm{TCR}=\frac{\sum_{i\in S}|T_i^N|}{\sum_{j\in A}|T_j^N|}, \tag{1}$$

where T_i^N is the value of normalized torque in the *i*th direction; *i* and *j* are the indices of torque directions; and *S* and *A* are sets of torques in the secondary directions (i.e., directions that are not required by the motor task, such as SF/E and EF/E for a SABD task) and in all directions, including SF/E, SABD/ADD and EF/E, respectively. Resulting TCR values range from 0 to 1. Torque generation only in the required primary torque direction (i.e., SABD for a SABD task) while not in secondary directions (e.g. EF or SF for a SABD task) will produce a torque coupling ratio (TCR) equal to 0, while large torque generation in any secondary direction will produce a TCR closer to 1.

EEG signal analysis

The 163-channel EEG signals were visually inspected for the presence of artifacts. In addition to trials that were already eliminated due to torque and EMG artifacts, EEG trials that exhibited artifacts (e.g., eye blinks, sweat potentials, etc.) were eliminated from further analysis. The remaining EEG trials were aligned to the off-line adjusted torque onset, segmented, baseline-corrected (from −2000 to −1800 ms) and ensemble-averaged from −2000 ms to 500 ms (with torque onset at 0 ms).

The ensemble-averaged EEG signals were imported into the CURRY software environment (Compumedics Neuroscan Ltd., El Paso, TX) for a multi-stage processing procedure: 1) re-

referencing to the common average, 2) low pass filtering with a cutoff frequency of 50 Hz, 3) SNR estimation, and 4) co-registration of EEG electrode positions with the reconstructed subject skin (based on the subject's MRI). The cortical current distribution in the time period between 150 ms and 100 ms prior to the torque onset was then computed using the low resolution electromagnetic brain tomography (LORETA) method (Lp=1) (Pascual-Marqui et al., 2002; Pascual-Marqui et al., 1994) based on a subject-specific boundary element method (BEM) model in CURRY V5 with the regulation parameter equal to 1/SNR. Possible sources were located on a cortex layer with 3 mm distance between each node. This inverse method was chosen because it outperformed all other available inverse methods in CURRY when using both simulated EEG data and real cortical sensory evoked potentials (Yao and Dewald, 2005). Although the inverse calculation was performed over the whole cortex, only the activities in the region of interest (ROI), in this study bilateral sensorimotor cortices, were further analyzed using quantitative measurement indices explained in subsequent sections.

We chose to reconstruct the cortical activity during the time window of 150 to 100 ms before the onset of torque for both groups. For control subjects, this time window occurs during the early phase of the motor potential (MP) and prior to the onset of EMGs. It therefore corresponds to activity related to the release of the motor command and possibly some motor planning (Hallett, 1994). Even though the relationship between this time window and the onset of MP or EMGs is slightly more variable within the stroke group, we argue that these differences are negligible. Conduction latency differences between control and stroke subjects from the cortex to the periphery have been shown to be less than 5 ms for elbow muscles and 7 ms for shoulder muscles (Schwerin and Dewald, 2004). In addition, we averaged cortical activity over a 50 ms time window after desampling to 256 Hz, thereby minimizing the effect of slight timing differences for cortical activity related to a torque onset.

Our region of interest (ROI) consisted of the bilateral sensorimotor cortices (SMCs), including the premotor, supplementary motor (SMA), primary motor (M1) and primary somatosensory (S1) cortices on both hemispheres. The ROI on each hemisphere was independently and manually chosen in CURRYaccording to the accepted locations of these areas in neurophysiology literature. A MATLAB (The Mathworks, Inc., Natick, MA) routine was written to automatically extract all sources from the current density reconstructions that resided in the ROI.

To identify changes of the cortical overlap of active area (OAA) for shoulder and elbow representations following stroke, we quantitatively evaluated the OAA between shoulder and elbow activities in SMCs. The OAA is defined as:

$$\mathrm{OAA}_{\mathrm{SLD/ELB}} = \frac{\sum_{i}^{I} Cs_i^{\mathrm{Norm}} \times Ce_i^{\mathrm{Norm}} \times \alpha_i}{\sum_{i}^{I} \alpha_i} \tag{2}$$

where Cs_i^{Norm} and Ce_i^{Norm} are the normalized strengths of the current in the *i*th triangle in SMCs while generating SABD and EF torques, respectively; and α_i is the area of the *i*th triangle. (Note: when developing the BEM model, the surface of cortex was divided into many triangles.) The OAA therefore quantifies the overlapping active area between cortical activity in the SMCs for the SABD and EF tasks.

Statistical significance was chosen for *p*-values less than a significance level of 0.05, and results close to statistical significance ($0.05 \leq p < 0.1$) were also reported.

Results

Motor task performance

Maximum voluntary torques (MVTs) were measured at the shoulder and elbow joints at the very beginning of each experiment. Results of MVTs and MVT coupling patterns were similar to results presented in previous publications, showing decreased MVTs in all directions as well as increased coupling between SABD and EF for stroke survivors when compared to results in control subjects (Dewald and Beer, 2001).

All participants included in this study were able to perform SABD and EF at 25% of their MVT with a success rate higher than 90% (Note: we refer to these two motor tasks as SABD and EF for the remainder of this paper). Box-plots of the normalized torques in different directions during for the holding phase of the two motor tasks are shown in Fig. 2. As shown in this figure, although torque coupling patterns vary especially in stroke subjects, we see evidence of increased “flexion synergy” patterns in the paretic arms of stroke subjects for sub-maximum tasks, reflected by the increased elbow flexion torque when performing SABD (the upper plot of Fig. 2, $p<0.05$) or an increased trend of shoulder abduction torque when performing EF (the lower plot of Fig. 2, $p<0.1$).

Torque coupling ratio (TCR) was computed at each time point for every trial. TCR during the early holding phase (the first 100 ms of the plateau phase) was then used as the dependent variable in a two-way analysis of variance (ANOVA) (subject group and motor task) analysis to test the difference in TCRs between two groups. Results showed that significantly larger spontaneous secondary torques were generated by stroke subjects ($p<0.0001$) than by control subjects. No significant interaction between group and task was found ($p>0.1$). Both results shown in Fig. 2 and results of TCRs indicate the existence of abnormally increased torque coupling between shoulder and elbow joints in stroke subjects even when only performing a single-joint task at the level of 25% of MVT.

EEG signal and reconstructed cortical activity

Fig. 3 shows the ensemble-averaged EEG, EMG and torque data from one control and one stroke subject. The mean signal-to-noise ratios (SNR) of our EEG data were higher than 10 for both groups and tasks. A two-way ANOVA (group and task) analysis showed NO significant difference in SNR either between the two groups or between two tasks. The EEG data clearly show the Bereitschaftspotential (BP) followed by the motor potential (MP), as documented by Deecke for a self-paced voluntary motor task (Deecke, 1987;Deecke and Kornhuber, 1978). Reconstructed cortical activity within the ROI during the window from 150 to 100 ms prior to the onset of torque in one control and one stroke subject is shown in Fig. 4.

Quantitative analyses of overlapping active area (OAA) were then performed over the ROI. A one-way ANOVA for comparing OAA of the two populations (stroke vs. control) showed a significant increase in the OAA in SMCs in the stroke group compared to the control group ($p=0.03$).

Correlation between cortical imaging results and motor task performance

We further investigated whether the quantified overlapping active areas between SABD and EF tasks was associated with the torque coupling ratio as measured at the periphery of the upper limb. Fig. 5 shows the OAA and TCR of each of the control (represented by open triangles) and stroke (represented by open circles) subjects when they performed the two motor tasks. A normal probability plot for OAA and TCR confirms that both variables have normal distributions. Therefore, a simple linear regression between OAA and TCR with a two-tailed test was performed separately for the two motor tasks using the pooled data from both groups.

Results are shown by the dashed line in Fig. 5. For both the SABD and EF tasks, a significant linear relationship between OAA and TCR was found (SABD task: $p<0.01$, $R^2=0.318$, EF task: $p<0.01$, $R^2=0.279$).

Correlation between cortical imaging results and outcome measurement as well as between torque measurement and outcome measurement

We further investigated the agreement between quantitative measurements, at either central or periphery, and clinical assessment. In Fig. 6, results are shown for the two association tests using the two-tailed Spearman Rank Correlation test. There was a significant association between the OAA and FM scores ($\rho=-0.596$, $p<0.05$) and a noteworthy trend for association between the sum of torque coupling ratios of the two tasks and FM score ($\rho=-0.521$, $p<0.1$). The sum of torque coupling ratios of both SABD and EF tasks was chosen because FM score was also a sum of multi-joint function.

Discussion

Overlap of joint representation in healthy subjects versus in stroke subjects

Overlap of cortical joint representations was also found in our healthy subjects, which is in agreement with previous findings showing that multiple representations of individual muscles at cortical level overlap with each other (Devanne et al., 2006; Marconi et al., 2007; Melgari et al., 2008; Tyc and Boyadjian, 2006). In healthy subjects, overlap can be due to branching axons of the monosynaptic connections between cortex and motoneurons in the spinal cord. Overlap caused by using monosynaptic connections is reported to generate limited functional synergies, usually a few muscles that have similar actions about a joint, and they rarely innervate the motoneurons of functional antagonists (Melgari et al., 2008; Rathelot and Strick, 2006). Such overlap is found to be very important for flexible brain reorganization and plasticity in human subjects (Devanne et al., 2006; Singh and Scott, 2003). Therefore, a certain level of cortical overlap of joint/muscle representation, as we found in our control subjects and as reported before (Devanne et al., 2006; Marconi et al., 2007; Melgari et al., 2008; Tyc and Boyadjian, 2006), may suggest the representation of “normal muscle synergies” (Melgari et al., 2008) in the motor cortex. This cortical overlap probably allows the brain to control multiple muscles to generate a simple motor task more effectively.

Cortical overlap of joint representation following stroke has not been reported before in either animal models or human subjects. This study has for the first time shown that following stroke, the cortical overlap of joint representation increases significantly. Furthermore, we also demonstrate that this cortical overlap is associated with the degree of coupling between shoulder and elbow joints and with the impairment level as measured by the Fügl-Meyer Score. Our findings imply that abnormal increases in cortical overlap of joint representation may contribute to the loss of independent joint control that is observed in the form of “abnormal muscle synergies” in stroke survivors.

Possible mechanisms underlying the increased cortical overlap of joint representation following stroke

Quantitatively, the increase in cortical overlap of joint representation can be present because the cortical area for each joint expended and/or because the centers of gravity (CoG) of the two joints shifted closer. Both the extension of area and the shift of CoG following stroke have been reported before (Cicinelli et al., 1997; Cramer et al., 1997; Liepert et al., 2004; Traversa et al., 1997).

Neural mechanisms underlying the increase of cortical overlap can be complex. Several different mechanisms may be involved. The first is an increased usage of secondary motor

cortices, such as supplementary motor area (SMA) and the premotor cortex, and their associated projections. As shown in Table 1, 7 out 13 stroke subjects show an anteriorly-shifted CoG of cortical activities for both SABD and EF tasks, suggesting a greater involvement of premotor cortices. Results obtained in the monkey have shown that unlike in M1, where stimulation typically evokes simple movement of single joint, stimulation of the premotor areas often evokes more complex movements involving multiple joints (Graziano et al., 2002;Stark et al., 2007). Anatomically, corticofugal projections to the spinal cord from secondary motor cortices overlap more than that from M1 (He et al., 1995). Furthermore, corticoreticular projections to brainstem regions from secondary motor cortices, such as the premotor cortex, are relatively larger as compared as those from M1 (Kably and Drew, 1998). Therefore, using the premotor cortex to send motor commands either directly to the spinal cord or via the brainstem can result in an increased overlap of cortical joint representations and thus cause a loss of independent joint control in the stroke subjects. Finally, the greater branching of bulbospinal compared to corticospinal projections at the spinal cord may further amplify this loss (Dewald et al., 1995;Ertelt et al., 2007;Sukal et al., 2007).

Another possible mechanism for the increased cortical overlap of joint representation in stroke survivors is an increased usage of ipsilateral motor cortices and corticobulbospinal pathways for sending motor commands. An increase in ipsilateral cortical activity has been found in stroke subjects for various motor tasks (Cao et al., 1998). Furthermore, transcranial magnetic stimulation connectivity studies have shown increased latencies of motor evoked potentials when stimulating muscles in the paretic arm over the unaffected hemisphere as compared to the activation from the contralateral cortex in control subjects (Schwerin, 2006). This may indicate activation of more indirect corticospinal connections from the nonlesioned hemisphere, possibly via the brainstem. In our study, 7 out of 13 stroke subjects showed ipsilaterally-shifted CoGs for both SABD and EF tasks and another 2 stroke subjects had ipsilaterally-shifted CoGs for one of these two motor tasks. These results suggest an increased use of ipsilateral motor cortices via corticobulbar spinal pathways when performing shoulder/elbow tasks with the paretic limb in our stroke subjects. Since bulbospinal pathways have been reported to branch more at the spinal cord than the corticospinal track (Kuypers, 1964, 1981), an increased reliance on them following stroke may explain the abnormal coupling between SABD and EF, as shown in this study and in previous studies (Dewald et al., 1995, 2001; Ertelt et al., 2007). More specifically, an increased dependence on the descending reticulospinal tract may explain the abnormal coupling since this tract has been demonstrated to primarily project to shoulder abductors and elbow flexors (Davidson and Buford, 2004).

The decrease of cortical inhibition due to the reduction of Gamma-AminoButyric Acid (GABA) interneurons could be another mechanism underlying the increased cortical overlap that is observed in this study. It is known that the motor cortex contains a large population of inhibitory GABAnergic neurons (Jones, 1993). These inhibitory inter-neurons are important to prevent adjacent neurons, not associated with the intended activity, from firing aberrantly (Jones, 1993) and thus are involved in the generation of spatiotemporal patterns of muscle activity (Matsumura et al., 1991). Reduction of GABAnergic inhibition could result in the abnormal muscle co-activation (Matsumura et al., 1992; Schneider et al., 2002). Following stroke, cortical inhibition in the affected hemisphere is reduced as demonstrated by TMS studies (Liepert et al., 2000; Manganotti et al., 2002). Such a reduction could result in changing 50% of cortical neurons from an inactive to an active state (Matsumura et al., 1992), and thus could increase the overlap of cortical representation for adjacent joints and result in the loss of joint/muscle representation as reported in this study.

The last mechanism that we would like to discuss is the long-term change in sensory feedback from muscles involved in the abnormal muscle coactivation patterns following stroke (Dewald et al., 1995). The expression of these abnormal patterns starts from the acute stage following

a stroke, which can be a result of a release of basic movement patterns stored in the brainstem (Cailliet and Kaplan, 2002). These abnormal muscle coactivation patterns could result in more correlated sensory feedback. And the more correlated sensory feedback could increase the overlap of these muscles in the motor cortex (Clark et al., 1988; Godde et al., 1996; Melgari et al., 2008; Schabrun and Ridding, 2007). In contrast to previously reported results that show adaptations after learning or normal usage of muscles, our results in chronic stroke subjects demonstrate an aberrant plasticity following injury. Aberrant cortical plasticity following other type of nervous system injury, such as amputation, has also been reported before (Elbert et al., 1997; Flor et al., 1998; Karl et al., 2001; Weiss et al., 2000). However, none of the previous reports has shown a direct link between features of the reorganized motor cortices and any characteristics of motor output as shown in this study. If the abnormally increased cortical overlap between joints, which we observed in chronic stroke subjects, is indeed related to the long-term changes in sensory feedback, then we speculate that overlap in cortical activity related to uncoupled degrees of freedom, such as SABD and elbow extension, will be less than that for abnormally coupled ones (e.g., SABD and EF). We are currently conducting experiments to explore this possibility.

Possible limitations to the interpretation to our data

An alternative interpretation of the increase overlap in stroke survivors is weakness. Due to muscle weakness following stroke, it is possible that “over-activation” is required for activating muscles with a higher magnitude to implement the required motor task. However, since we normalized the motor task to 25% of the subject’s maximum voluntary torque, weakness is an unlikely contributor to the results presented in this study. Furthermore, previous studies have provided clear evidence that demonstrates that the loss of independent joint control or synergies is not related to weakness present following stroke (Beer et al., 1999).

Another possible confounding factor is the complexity of the motor tasks. It is possible that the same motor task is more complex for stroke individuals than that for control subjects. Increased complexity of motor task may result in an increased level of overlap for the joint representation at cortical level. In this study, however, we chose very simple single joint motor tasks. All subjects were well trained in the mastery of these tasks as evidenced by the high success rate (greater than 90%) for each of the participants. Therefore, we argue that our results are not likely to be biased by the complexity of our two motor tasks.

A related confounding factor is the ‘attention load’ related to the task performed by subjects. It has been shown that motor cortices are attention-load dependent regions. In these regions, there is a monotonic gain across the entire range of attention load (Culham et al., 2001). In effort to equate ‘attention load’ between groups, we used very simple motor tasks that both control and stroke subjects were able to perform easily. Furthermore, online feedback was eliminated: neither visual feedback nor proprioceptive feedback (Note: a static setup was used in our study) was provided. Therefore, subjects did not need to make adjustments during the performance of motor tasks, and thus no significant difference in the attention load was expected between the two groups of subjects.

Finally, one possible critique of our results is that the increased cortical overlap of joint representations in chronic stroke survivors is not a surprise given that stroke subjects activate different muscle combinations than control subjects. We argue that the cortical overlap of joint representations reported in this study was obtained from a time window before the onset of EMGs. Therefore, cortical activities obtained in this study were not biased by changes in muscle activation in the paretic arm of post-stroke survivors; instead, they resulted from trying to implement the same task, i.e., generating joint torque only in the required direction. In short, the results reported in this study provide evidence demonstrating that an increased overlap of

joint representations over motor cortices contributes to the loss of independent joint control during the execution of a simple single-degree-of-freedom shoulder/elbow motor task.

Clinical implications

An important implication of present findings is that an efficient therapy geared towards overcoming the abnormal synergy may be able to reduce cortical overlap. Our laboratory is currently investigating whether reductions in abnormal joint torque coupling in the paretic upper limb, resulting from targeted physical interventions (Ellis et al., 2005), will decrease cortical overlap in chronic stroke participants. Such a finding would further confirm the link between cortical overlap and independent joint control and would suggest that selective neurorehabilitation interventions can result in a more efficient use of remaining neural substrates following stroke.

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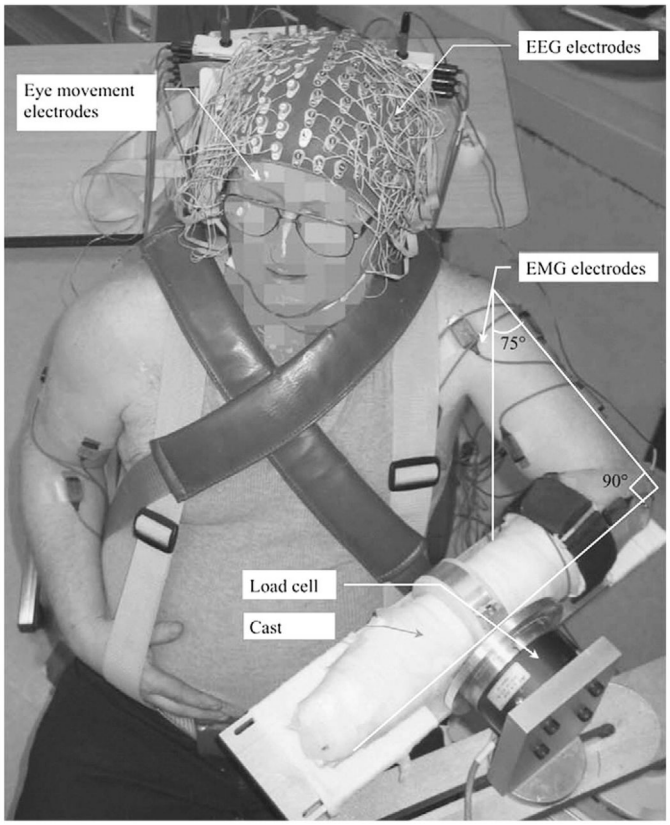


Fig. 1.
The setup of the experiment.

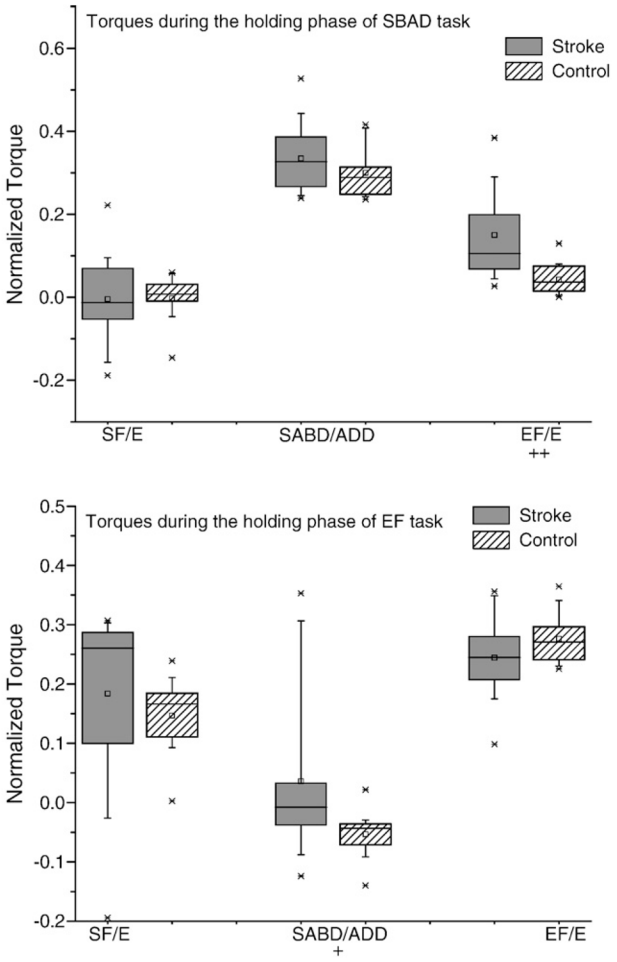
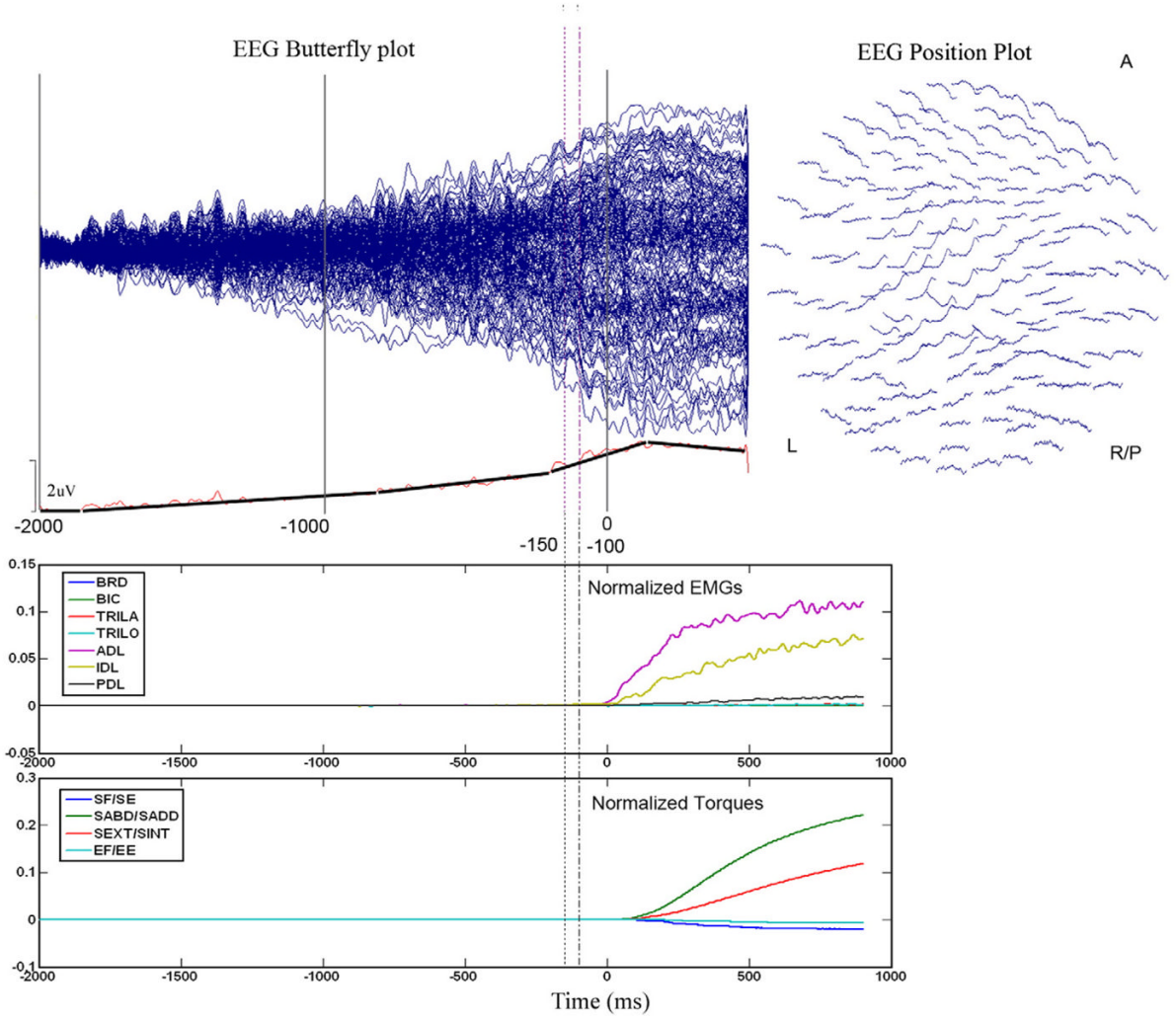


Fig. 2.

Box-plots of normalized torques in SF/E, SABD/ADD and EF/E directions for control and stroke groups. The horizontal lines in the box denote the 25th, 50th, and 75th percentile values. The error bars denote the 5th and 95th percentile values. The symbols below the 5th percentile error bar denote the 0th and 1st percentile values. The symbols above the 95th percentile error bar denote the 99th and 100th percentiles. The square symbol in the box denotes the mean of the column of data. $+p<0.1$, $++p<0.05$.



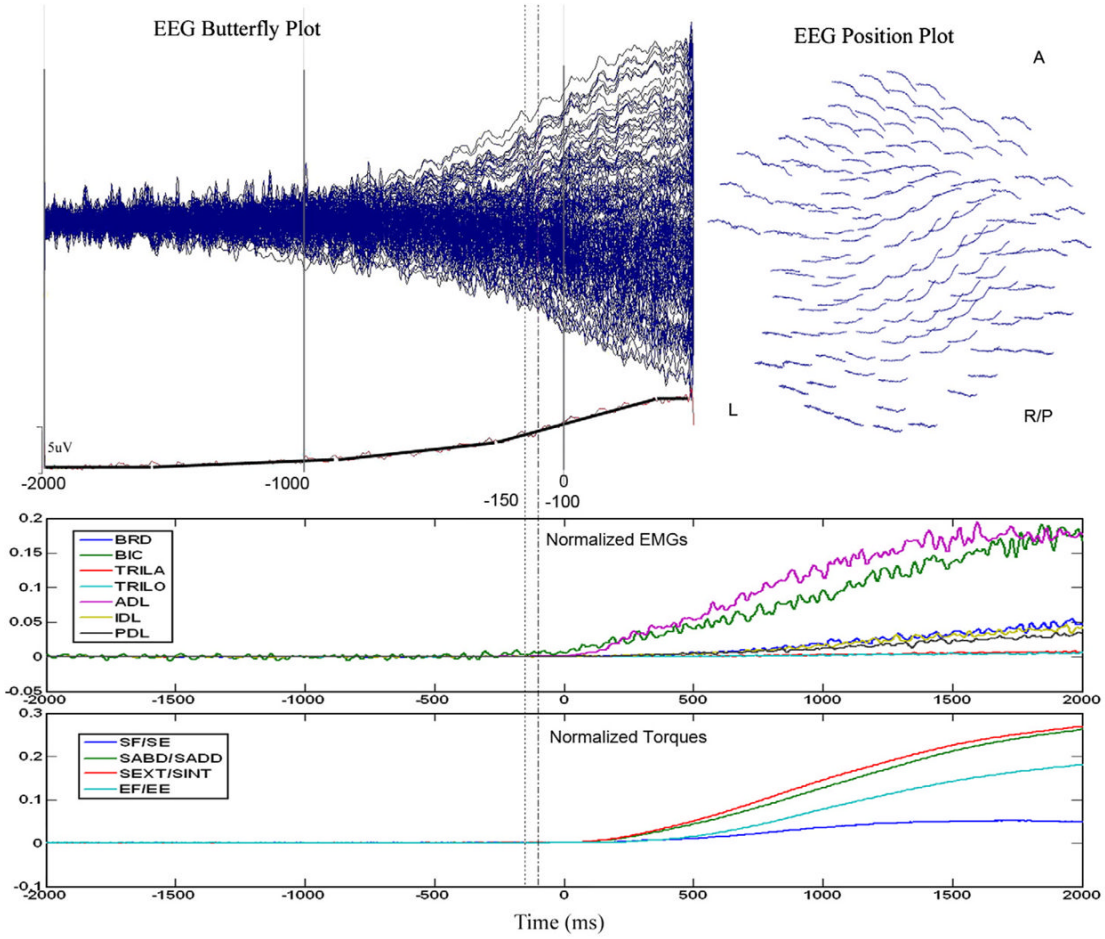


Fig. 3.
Ensemble averaged EEG, EMG and toque data in control subject C5 (upper) and in stroke subject S6 (lower).

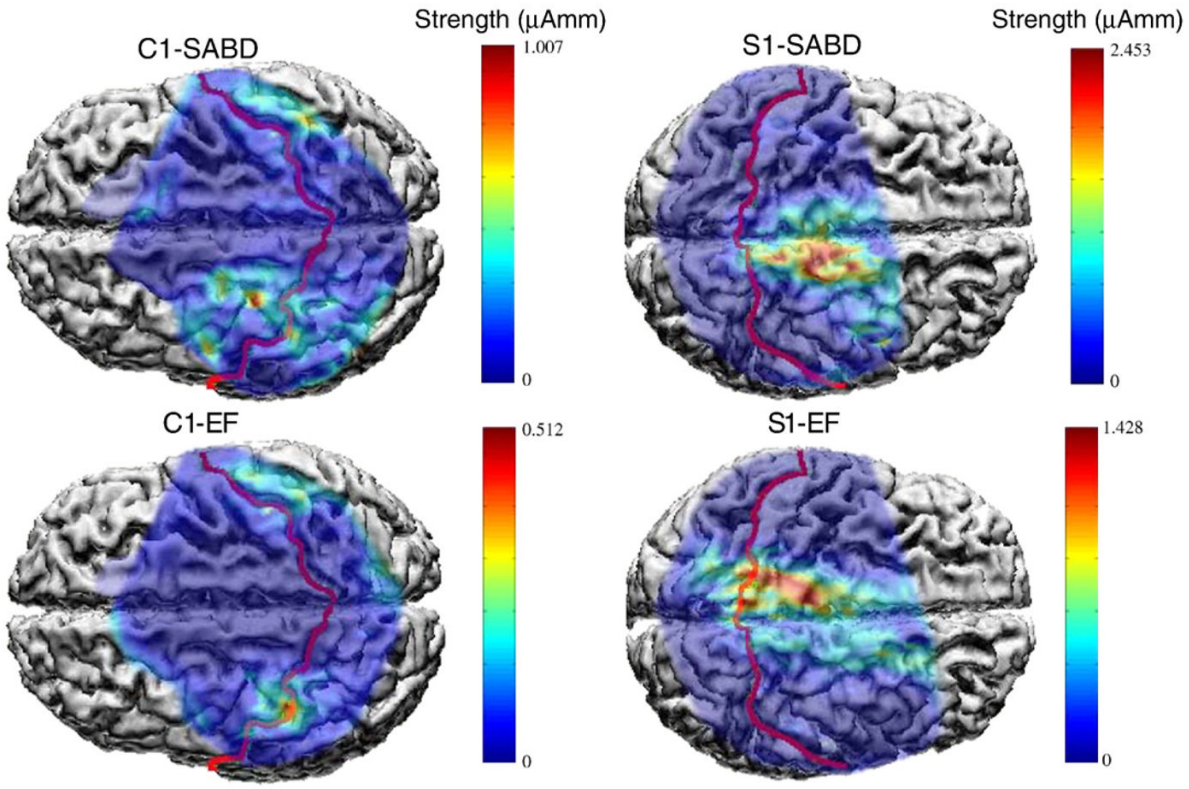


Fig. 4.

Sensorimotor cortical current strength in control subject C1 and stroke subject S1 during the generation of SABD (the first row) and EF (the second row) torques. The red traces in this figure illustrate the location of the central sulcus. The color bars show the current strength (unit: μAmm).

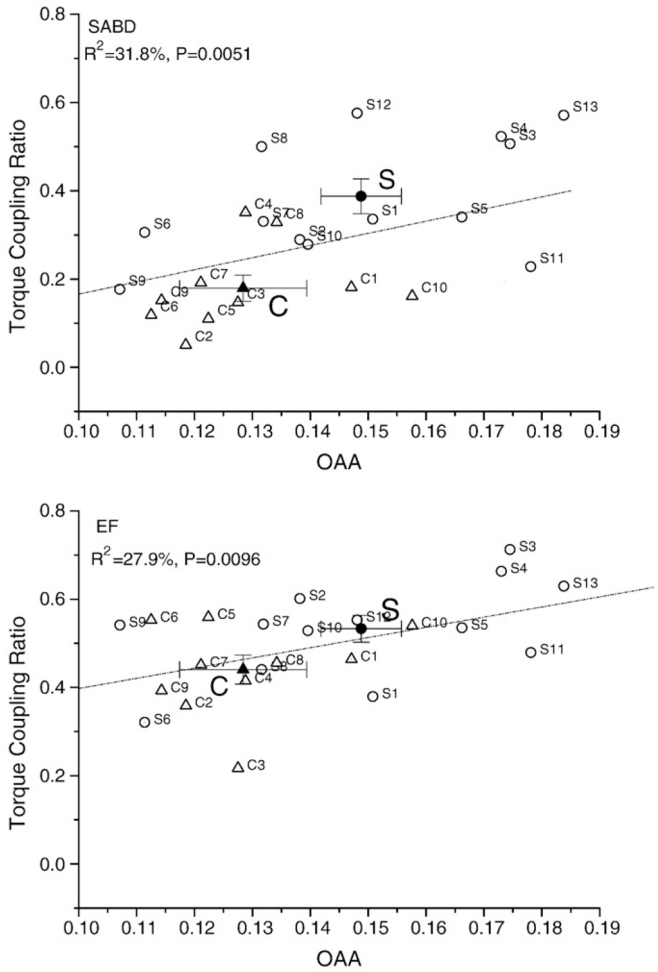


Fig. 5.

OAA and TCR for all subjects when performing SABD (upper) and EF (lower) tasks. The solid circle and triangle show the group means of OAA and TCR for the stroke and control groups, respectively. The horizontal and vertical bars extending from the dots show the standard errors of OAA and TCR. The dash line represents the linear fit results between OAA and TCR. Simple regression analysis and two-tailed test results are shown on the top of each plot.

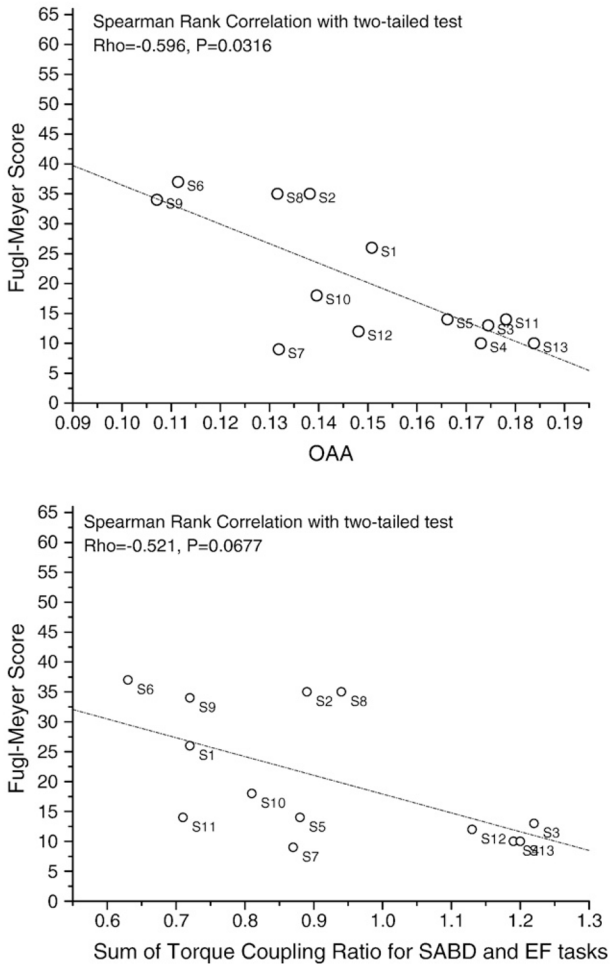


Fig. 6.

Relationship between outcome measurement (i.e., Fügl-Meyer (FM) score) and overlapped active area (upper), as well as relationship between FM score and the sum of torque coupling ratio for SABD and EF tasks (lower) for all stroke subjects.

Table 1

Lesion locations and Fügl-Meyer scores for subjects with hemiparesis

Patient	Age	Sex	Affected hand	Dominant hand	Site of lesion	Years of stroke before the experiment	FM score	Ipsilaterally/contralaterally located CoG (SABD/EF)	Anteriorly/posteriorly shifted CoG (SABD/EF)
S1	60	M	L	L	R. posterior limb of IC	1.5	26/66	C/I	A/A
S2	51	F	R	R	L. dorsal lateral SMA and PM. sub cortical white matter.	5	35/66	I/I	A/A
S3	59	M	L	R	R. IC and R. Th and R. LS and R. sub cortical white matter	21	13/66	I/I	A/A
S4	47	M	L	R	R. IC and R. Put and R. CL	8	10/66	C/C	A/A
S5	59	M	R	R	L. Put, GP, IC, and superior Th. which spares to the CN	10	14/66	C/C	NA/A
S6	66	M	L	R	R. body of CN, IC and some involvement of lateral Th	3.5	37/66	I/I	NA/A
S7	46	M	R	R	L. IC and L. LS and L. SMA	1.5	9/66	I/I	A/A
S8	80	M	L	R	R. IC, Th	6	35/66	C/C	NA/A
S9	71	F	L	R	R. BG: CN, Put.	2.75	34/66	I/C	A/NA
S10	50	F	R	R	L. posterior IC, superior L. Th, L. BG	10	18/66	I/I	NA/NA
S11	60	F	R	R	L Th, IC, BG, Put, GP	3.9	14/66	I/I	NA/A
S12	55	F	R	R	L BG, Put, GP and L Th, IC.	21.2	12/66	I/I	A/A
S13	70	F	L	R	R CR, IC, BG, Th	7	10/66	C/I	A/A

IC: internal capsule, SMA: supplementary motor area, PM: premotor cortex, LS: lateral sulcus of sylvius, Put: putamen, CL: claustrum, GP: globus pallidus, Th: thalamus, CN: caudate nucleus, CR: corona radiata, BG: basal ganglia. In the last two columns, ‘C’ and ‘I’ mean ipsilaterally and contralaterally located CoGs; ‘A’ and ‘P’ mean anteriorly and posteriorly shifted CoGs, respectively; and ‘NA’ means CoGs still locate in M1 area.