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Bilateral versus ipsilesional cortico-subcortical activity patterns in stroke show hemispheric dependence

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Abstract

Background: Understanding of interhemispheric interactions in stroke patients during motor control is an important clinical neuroscience quest that may provide important clues for neurorehabilitation. In stroke patients bilateral overactivation in both hemispheres has been interpreted as a poor prognostic indicator of functional recovery. In contrast, ipsilesional patterns have been linked with better motor outcomes.

Aim: We investigated the pathophysiology of hemispheric interactions during limb movement without and with contralateral restraint, to mimic the effects of constraint-induced movement therapy. We used neuroimaging to probe brain activity with such a movement-dependent interhemispheric modulation paradigm.

Methods: We used a functional magnetic resonance imaging block design during which the plegic/paretic upper limb was recruited/mobilized to perform unilateral arm elevation, as a function of presence versus absence of contralateral limb restriction ($n = 20$, with balanced left/right lesion sites).

Results: Analysis of 10 right hemispheric stroke participants yielded bilateral sensorimotor cortex activation in all movement phases in contrast with the unilateral dominance seen in the 10 left hemispheric stroke participants. Superimposition of contralateral restriction led to a prominent shift from activation to deactivation response patterns, in particular in cortical and basal ganglia motor areas in right hemispheric stroke. Left hemispheric stroke was, in general, characterized by reduced activation patterns, even in the absence of restriction, which induced additional cortical silencing.

Conclusion: The observed hemispheric-dependent activation/deactivation shifts is novel and these pathophysiological observations suggest short-term neuroplasticity that may be useful for hemisphere-tailored neurorehabilitation.

Keywords

Stroke, interhemispheric interactions, physiotherapy, motor control, handedness, functional magnetic resonance imaging

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Introduction

Neurorehabilitation of motor deficits of the upper limb after a stroke episode often shows poor results.[1,2] Although stroke is an important cause of mortality[3] its survival rate is increasing leading to important challenges in the field of rehabilitation.[4–8]

The problem needs to be analyzed from its onset, in the acute phase of the stroke, in particular in which concerns neurophysiological adaptations and the window for plasticity. It is indeed important to understand the rules that determine changes in modulation properties of neural circuits and in neuroplasticity.[9,10]

In stroke patients the cortical activation of the ipsilesional hemisphere has been suggested to be associated with better outcomes in recovery of motor functions.[11]

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In contrast, overactivation or increase of the contralesional hemisphere has been associated with sustained neurologic and motor deficits.[12,13]

Motor compensations maybe expressed by hyperactivation of the contralesional hemicorpus, as motor recruitment of the trunk has been linked to less available recruitment of the more affected upper limb, limiting recovery.[14] In contrast, motor selective/specific patterns of compensation[15] were reported to be associated with better outcomes for rehabilitation.[16] Specific approaches, such as constraint-induced movement therapy (CIMT), use motor restriction of the contralateral upper limb (currently applied only to the hand) to help the paretic arm to redevelop lost motor functions. In longitudinal studies, the CIMT was reported to be able to change neural circuitry patterns from bilateral cortex motor activation to ipsilesional cortical activation.[17,18] In any case, the use of the dichotomy of motor restriction versus facilitation has traditionally been used in physiotherapy, although its neuroscientific basis needs additional support.[19,20]

It is important to understand the physiological effect that results from the isolated restriction of the superior limb, as implemented by CIMT. If such restriction is maintained in time it becomes a "constraint technique." Here, by studying the physiological effects of such restriction, we aimed to provide a biological basis for such technique and its effective promotion of recovery of the "bad limb" in a hemispheric-dependent manner.

We posit that it is very important to study movement-dependent brain activation/deactivation patterns to better understand mechanisms underlying motor control.[21–25] Different action goals and movement modulation (inhibition or facilitation) provide potentially relevant aspects to consider in rehabilitation.[26] Here, we investigated the role of interhemispheric interactions in motor control and brain activity regulation as a function of inhibition/restriction of upper limb motion, as applied to stroke patients. By testing procedures usually applied in the physiotherapy in stroke patients, one might gain insights into the effects with potential influence on optimization of motor recovery. Here, neural modifications were studied on a short-term basis after the restriction manipulation as a prior step for studies of long-term effects of procedures often applied in physiotherapy sessions.

Methods

Participants

Twenty stroke patients (12 female/eight male; age: 68.3 mean $\pm$ 10.04 years), all right handed according to the Edinburg Handedness scale,[27] participated in this single arm, within-subject study design. Data concerning patterns observed in normal control participants are described in a previous report.[26] All patients had only one first clinical episodic of stroke prior to the study (see Table 1, which summarizes clinical and demographic data). This project was approved by the ethics committee of Faculty of Medicine, University of Coimbra, Portugal. All participants or family gave written informed consent, prior to their participation, according to the Declaration of Helsinki.

Patients were selected by team members of the Stroke Unit, Department of Neurology, Coimbra University Hospital. Inclusion criteria included the ability to understand and execute the motor task evaluated in this study. Stroke patients with clinical unstable (due to causes such as respiratory infection and fractures) or education level below full literacy were excluded.

The acute stroke group was evaluated after the first clinic episodic on average after 10.2 ± 4.3 days, with stroke location in territory cerebral middle artery. Left and right stroke patients were matched (all comparisons for the following variables not significant): in the right hemisphere stroke group, the following data were obtained: age 67 ± 10.1 years, volume area of territory cerebral middle artery: 45.8 ± 54.6 cm^3, National Institutes of Health Stroke Scale (NIHSS): 14.5 ± 5.9, and score of the Chedoke McMaster Stroke Assessment of the arm: 3.4 ± 2.7. In the left hemisphere stroke group data were as follows: age 69.4 ± 8.8 years, volume area of territory cerebral middle artery 46.8 ± 53.3 cm^3, NIHSS: 11.3 ± 5.9, and score of the Chedoke McMaster Stroke Assessment of the arm was 4.3 ± 2.9.

In both right and left hemisphere groups we had similar distributions in terms of stroke severity as quantified by NIHSS and motor shoulder incapacity as assessed by the Portuguese version of Chedoke McMaster stroke assessment scale. Concerning stroke affecting the right hemisphere, and according to the NIHSS we had the following distribution in terms of stroke severity: one minor, six moderate, and three moderate to severe. In terms of the evaluation of motor ability and impairment, and according to the Chedoke McMaster Stroke scale for the arm we had four hemiplegic cases and six hemiparetic conditions. Concerning stroke affecting the left hemisphere, and according to NIHSS we had the following distribution in terms of stroke severity: five moderate, three moderate to severe, and two severe. According to the Chedoke McMaster Stroke scale for the arm we had four hemiplegic cases and six hemiparetic conditions.

Magnetic resonance imaging (MRI) scanning

The stroke lesion was quantified by the ABC/2 formula[28] using the flair sequence of MRI (SyngoFast

Table 1. Clinical/demographic characteristics of stroke patients

Patient	Stroke side	Days of stroke	Lesion Volume (cm^3)	Hemiplegic/ hemiparetic side	Age	Sex	NIHSS initial	Chedoke McMaster scale	
								Shoulder pain	Arm
No. 1	Right	8	76	Left hemiplegic	49	F	19	6	1
No. 2	Right	23	25	Left hemiparetic	82	F	6	1	7
No. 3	Right	7	21	Left hemiparetic	70	M	1	7	5
No. 4	Right	9	91	Left hemiparetic	47	M	19	7	7
No. 5	Right	9	75	Left hemiplegic	69	M	12	7	7
No. 6	Right	19	1	Left hemiparetic	73	M	7	7	1
No. 7	Right	7	1	Left hemiparetic	70	F	8	7	7
No. 8	Right	7	3.3	Left hemiplegic	70	M	16	6	6
No. 9	Right	12	2.3	Left hemiplegic	69	M	14	4	1
No. 10	Right	9	172	Left hemiparetic	75	M	11	6	1
No. 11	Left	7	1.7	Right hemiplegic	72	F	10	6	2
No. 12	Left	9	156	Right hemiplegic	80	F	23	7	2
No. 13	Left	9	15.2	Right hemiplegic	78	F	19	6	6
No. 14	Left	9	21	Right hemiparetic	63	F	11	6	1
No. 15	Left	12	7.6	Right hemiparetic	76	F	7	6	1
No. 16	Left	9	69	Right hemiplegic	54	F	22	7	7
No. 17	Left	7	22	Right hemiparetic	74	F	18	7	6
No. 18	Left	7	3.7	Right hemiparetic	57	F	7	6	1
No. 19	Left	10	34	Right hemiplegic	77	F	16	5	1
No. 20	Left	15	128	Right hemiparetic	61	F	12	7	7

F: female; M: male

National Institutes of Health Stroke Scale (NIHSS): score 0: no stroke symptoms; 1–4: minor stroke; 5–15: moderate stroke; 16–20: moderate-to-severe stroke; 21–42: severe stroke.

Chedoke McMaster Stroke Scale (impairment inventory: shoulder pain): Stage 1 more pain than Stage 5. Stage 6 no shoulder pain, but at least one negative prognostic indicator is present; Stage 7 shoulder pain and prognostic indicators are absent/(impairment inventory: stage of arm): Stage 7 better than stage 1.

View (Siemens)).[29] The ABC/2 method has the advantage of being objective, highly consistent across centers in large-scale studies. It is widely used in stroke units worldwide as an easily accessible evaluation procedure, with several studies showing similar accuracy as compared to planimetric analysis (for instance, Sims et al.[28]: "ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes").

Functional magnetic resonance imaging (fMRI)—Motor paradigm

All participants underwent one structural magnetic resonance scan and two fMRI scanning sessions: (1) the dominant upper limb was restrained while the nondominant upper limb performed an arm elevation (AE); (2) the opposite stimulation pattern was applied (nondominant restrained upper limb and dominant facilitation of AE).

Sequence of motor paradigm

The sequence of the motor paradigm was composed of five 30 s blocks. The first condition consisted of a simple facilitation of AE. The second condition was a combination of the facilitation of the AE plus the contralateral upper limb restraining (AE + LR) inhibiting its motor action. All blocks were subdivided in three periods of 10 s. In total, there were 15 periods, repeated 10 times (cycle repetitions) in a random order. A scheme of the fMRI experimental design is described in Figure 1.

Detailed task description

The task is described in detail elsewhere.[26] The facilitation of AE refers to the arm flexion, at the glenohumeral joint, with the elbow in full extension. A customized Cellacast® splint was placed on the anterior part of arm and forearm in order to ensure elbow extension (Figure 1C and F).

Near bore manual assistance by the researcher/physiotherapist was applied to all subjects to help initialize/orient arm motion.

The facilitation of AE was defined as a motor action composed by three periods with 10 s each: upward, hold, and downward. To facilitate the movement, a mobilization was performed in assisting-active mode, in which the researcher/physiotherapist induced the movement. For each period, subjects heard verbal instructions indicating the motor activities.

AE is integrated in activities of daily living and the flexion of arm reflects a component of motion in the shoulder complex. Previous to a stroke the elevation of arm is integrated in automatic movements groups, given the repeated experience in executing them. For this reason, we used a strategy based on intermittent facilitation, with short speed boosts in the same way that automatic walk is promoted. This enabled an overall similar pattern of stimulation/facilitation across subjects.

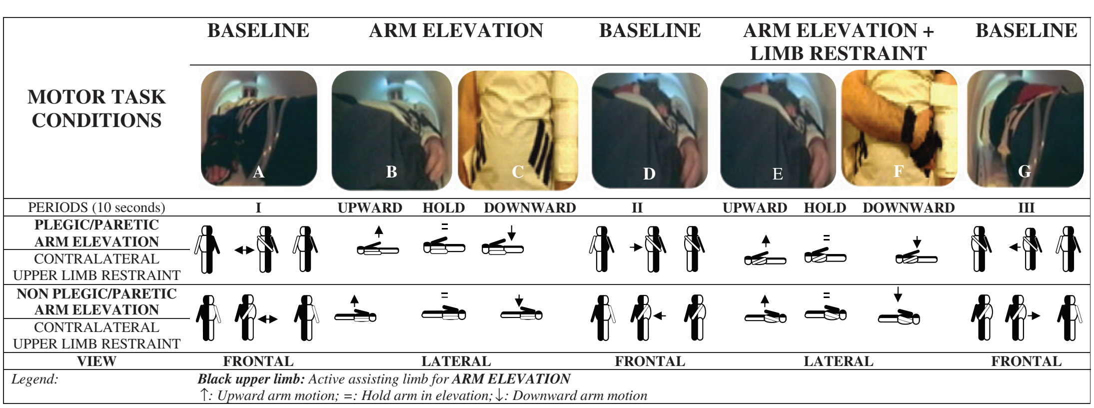
The rest periods had two types of position: (1) the upper limbs were in neutral position, resting along the body; (2) one upper limb was in neutral position and the contralateral limb was restrained, with shoulder adduction, crossing over the middle line of trunk (Figure 1).

The contralateral limb restraint (LR) was achieved by keeping shoulder adduction, crossing the arm in such a way that the hand was over the contralateral pelvis. Customized abdominal and hand slings with Velcro® strips were used to ensure an efficient limb restriction and quick release. Thus, this promoted inhibition of muscle activity in the upper limb.

We used three periods involving restraint manipulations: (1) the limb is placed in the restraint position (adduction of shoulder with crossing the middle line of trunk), but it returns the neutral position; (2) the limb is placed in restraint position and stays (in a position of shoulder adduction); (3) the limb is released from the restraint position (starts in the adduction shoulder and returns to the neutral position).

Data acquisition. Magnetic resonance data were collected on a 3 Tesla Siemens Tim Trio. High-resolution anatomical images were acquired for each participant using a T1-weightd MPRAGE sequence $1\,mm \times 1\,mm \times 1\,mm$ voxel size, repetition time (TR): 2300 ms, echo time (TE): 2.98 ms, flip angle (FA): 9°, field of view (FOV): 256 mm. The fMRI for each shoulder elevation

Figure 1. Schematic of the experimental design in fMRI experiments. Limb manipulation during the experimental blocks (and control contralateral motion or restraint positioning during mid-period in baseline) is depicted by arrow symbols.



(dominant and nondominant) was obtained using a T2-weighted BOLD contrast echo planar imaging sequence 2.5 mm × 2.5 mm × 3 mm voxel size, TR: 3000 ms, TE: 38 ms, FOV: 256 mm. During each experiment, T1-weighted anatomical images were collected first followed by the functional runs. Each set included 10 continuous scans for first run and second run.

Image processing and data analysis

The location of the stroke was previously defined to a region that received blood perfusion by middle cerebral artery vascular territory infarction. The volume of the ischemic area was measured using a brain structural magnetic resonance scan, in flair sequence, visualized by software SyngoFast View (Siemens), and quantified using the formula of ABC/2 (where A is the greatest hemorrhage diameter by CT, B is the diameter 90° to A, and C is the approximate number of CT slices with hemorrhage multiplied by the slice thickness).

The imaging data analysis was performed using the Brain Voyager Software (QX version 2.4; Brain Innovation B.V., The Netherlands). Head motion was corrected and three-dimensional temporal filtering and slice scan time correction were performed. Maps were automatically registered into the standard Talairach space. Head motions > 2 mm implied subject exclusion. Movement of upper limbs was video monitored.

In the first-level analysis, data were analyzed for each subject separately using general linear models (GLMs) to identify significantly activated voxels. After model estimation, contrast images derived from each participant were calculated and analyzed individually. Then, a second-level analysis, using one-way repeated measures ANOVAs (within-group design), was conducted. In the first stage, whole-volume GLMs were computed and corrected for temporal serial correlations, for subsequent group inferences. Each fMRI session with tasks for dominant and nondominant shoulder elevation was then processed separately, using a random effects analysis. This allowed inferring whether the observed results might be generalized to the population. Statistical maps were corrected for multiple comparisons using the false discovery rate procedure for individual analysis in for BrainVoyager QX,[30] with $p < 0.05$ and group analysis with $p > 0.05$, with the Monte Carlo 1000 interactions. Cluster-size thresholding allowed for the definition of volumes of interest in relation to defined Brodmann regions.

Statistical models for region of interest (ROI) analysis. In order to compare the recruitment of brain regions induced by the contrast presence versus absence of contralateral LR during AE ((AE + LR) versus (AE)) we first used the number of significant voxels in ROIs corresponding to sensorimotor cortex, basal ganglia, and cerebellum. For comparison we used, as stated above, the contrast analysis of (AE + LR) versus (AE), with $p < 0.05$ (see above).

Results

Functional activation patterns

We found different brain activity patterns between right and left hemisphere stroke during plegic/paretic AE. For nonplegic/paretic AEs we also found different patterns for the dominant and nondominant upper limbs. The addition of a contralateral upper limb restriction led to a deactivation in all conditions that was also hemisphere dependent.

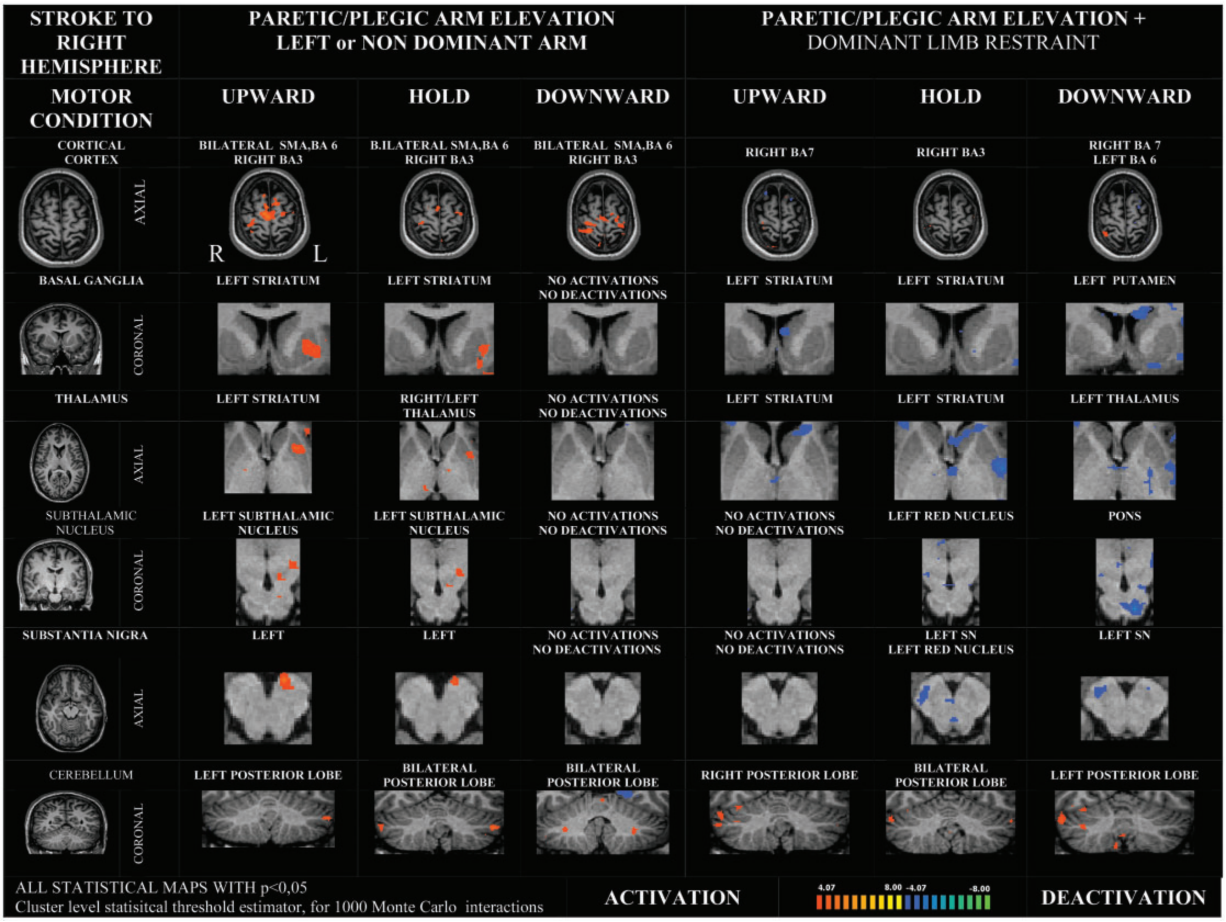
Cortical bilateral activation only in right hemisphere stroke during plegic/paretic AE. In patients with *right hemisphere stroke*, cortical activation in bilateral sensorimotor cortex was found, during plegic/paretic AE (nondominant or left arm), especially in the supplementary motor area (Brodmann area 6) (Figure 2). Subcortically, we observed a contralesional activation pattern localized in left striatum, subthalamic, and red nucleus. The cerebellar activity was ipsilateral in the upward condition, during AE, and bilateral during the hold and downward periods (for more detailed information see Supplementary tables, Appendix 1, Supplementary Tables 1, 2, and 3).

Ipsilesional cortical activation only in left hemispheric stroke during upward plegic/paretic AE. In patients with *left hemispheric stroke* (Figure 3), we found a small ipsilesional cortical activation of sensorimotor cortex and ipsilateral cerebellum activation only during upward plegic/paretic AE (dominant or right) (for more details see Supplementary Tables 4 and 5 in Supplementary tables, Appendix 1). During hold periods, we observed bilateral deactivations and during downward phases a bilateral activation.

Subcortically, we also found a deactivation of ipsilesional striatum, bilateral thalamus, and right red nucleus during upward and hold periods. During the downward period we observed dominance of bilateral activation in subcortical regions and cerebellum (Supplementary tables, Appendix 1 see Supplementary Tables 4 and 5).

Whole brain deactivation during AE with contralateral limb restriction. In patients with right hemispheric stroke, the presence of dominant upper LR during plegic/paretic AE results in the silence of contralesional cortical areas while maintaining ipsilesional activation of

Figure 2. Statistical maps of group analysis of the *right* hemispheric stroke patients during plegic/paretic AE in presence/absence restriction of contralateral upper limb.



the sensorimotor cortex. The basal ganglia deactivated but cerebellar activity was similar in both conditions (with and without LR).

In patients with left hemispheric stroke, the nondominant upper LR during plegic/paretic AE resulted in bilateral reduction of cortical activation. During the hold phase, we found a deactivation of contralesional supplementary motor area and ipsilateral primary motor cortex. The subcortical pattern of activity was similar in both conditions of plegic/paretic AE. Concerning cerebellar activity changes activations predominated over deactivations.

In sum, concerning both nonplegic/paretic AEs (Figures 4 and 5) of dominant or nondominant upper limbs, when restraint of contralateral upper limb was added, we observed cortical, subcortical, and cerebellar deactivation. Only dominant AE was associated to contralateral cerebellar activation.

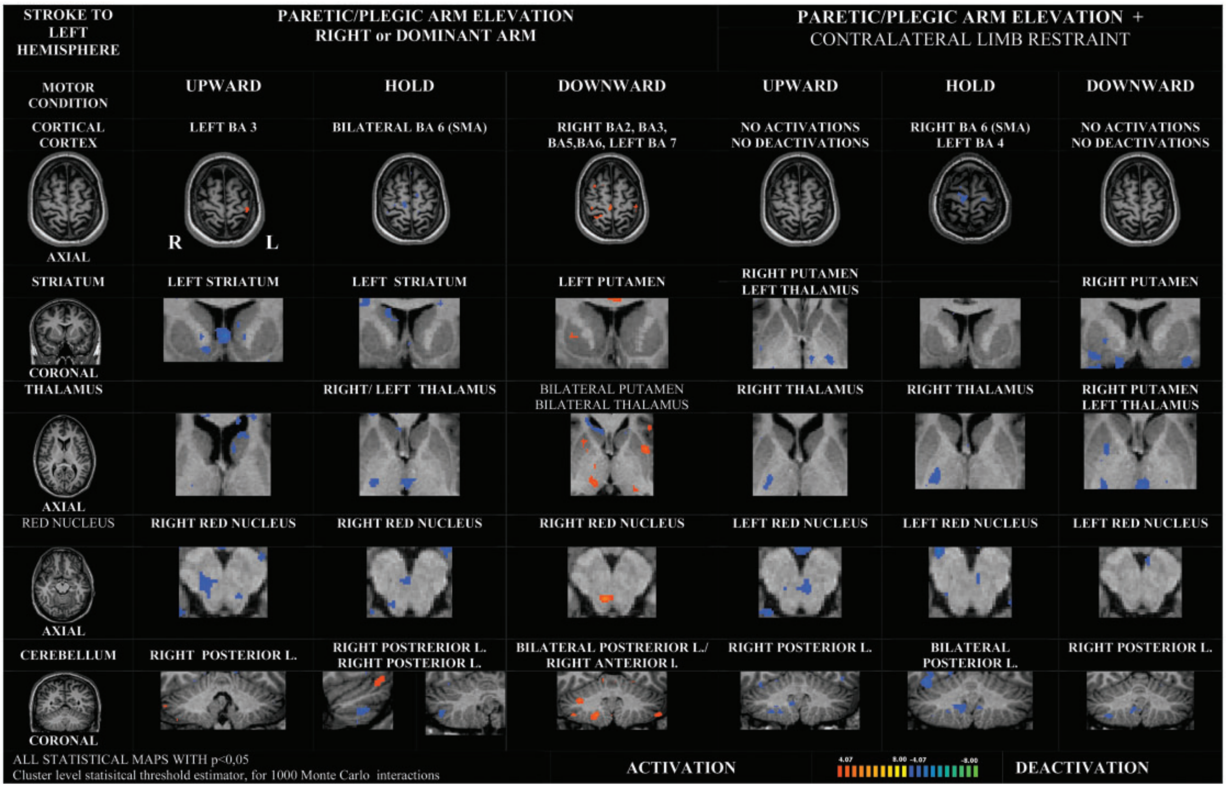
Summary of results as a function of movement phase

Cortical deactivation is only present in dominant nonplegic/paretic AE

Statistically significant deactivation of ipsilesional hemispheric or ipsilateral relative to nonplegic/paretic dominant AE was only observed during upward periods. During hold phases, this deactivation was stronger, extending to bilateral sensorimotor cortex.

Disparities between subcortical activity during nonplegic/paretic AE. During upward and hold periods, dominant AE was associated with deactivation of bilateral striatum and ipsilateral substantia nigra and red nucleus. The nondominant AE was associated with activation of contralateral striatum and bilateral substantia nigra.

Figure 3. Statistical maps of group analysis of the *left* hemispheric stroke patients during plegic/paretic AE in presence/absence restriction of contralateral upper limb.



Ipsilateral cerebellar activity during nonplegic/paretic AE

Irrespective the side of the AE (either dominant or non-dominant upper limb) ipsilateral activation of cerebellum was observed.

Supplementary Tables 6–8 and 10 elucidate either activation or deactivation patterns (in either LH and RH stroke patients) when taking into account restraint of the paretic/plegic arm while the healthy arm is mobilized, to show the restriction-induced effects. In Supplementary tables, Appendix 1, Supplementary Table 9 lists the statistically deactivated regions in stroke patients with right cerebral hemispheric damage when only the dominant arm is elevated, without restriction.

Supplementary Table 11 provides a summary of the main results.

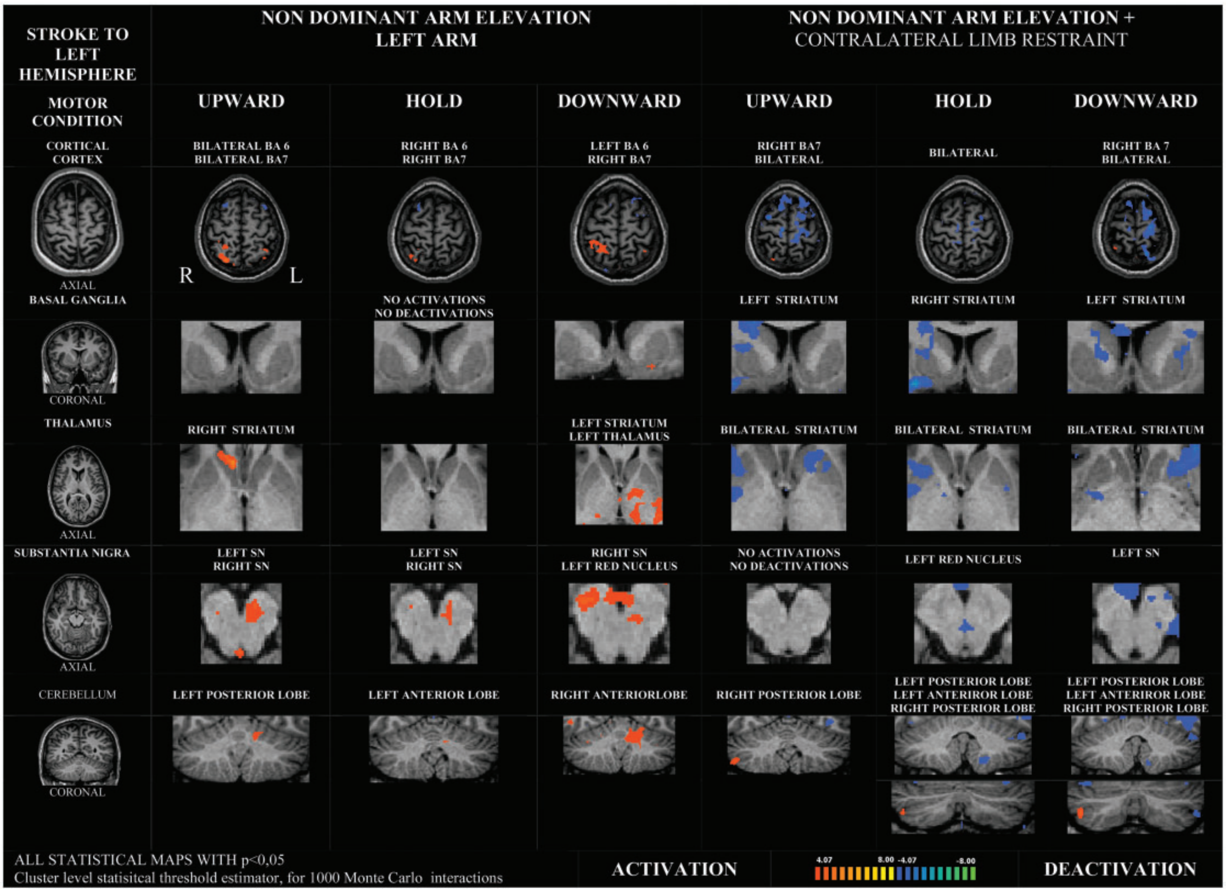
Discussion

The present study aimed to investigate whether motor facilitation/restraint procedures, believed to be useful in neurorehabilitation, promote neuromodulation of interhemispheric neural circuitry after a clinical episode of stroke. We focused on understanding whether the elevation of the arm when the contralateral arm is restrained leads to physiologically relevant impact in motor networks. The present study contributed to understand the underlying cortical physiology and the modulation evoked by arm restriction, as present CIMT rehabilitation approaches.

The hemispheric side of the lesion influences brain activity patterns in stroke, in a dominance-dependent manner

The different right and left hemispheric movement evoked brain activity patterns after an episode of stroke has been suggested to be dependent on the hemispheric dominance and of the side of the lesion.[31] We found that contralateral upper limb restriction reduces cortical, subcortical, and cerebellar activity not only in the plegic/paretic arm during elevation but also in the "good" arm. Cerebral circuitry is accordingly modulated by both motor control-related

Figure 4. Statistical maps of group analysis of the *left* hemispheric stroke patients during nondominant AE in presence/absence restriction of contralateral upper limb.



facilitation and restraining procedures, in a dominance-dependent manner. Importantly, neurophysiological responses depended strikingly on the phase of arm movement and type of motor action. These findings uncover possible brain mechanisms underlying the activation/deactivation balance which seems to be critical to drive motor recovery.

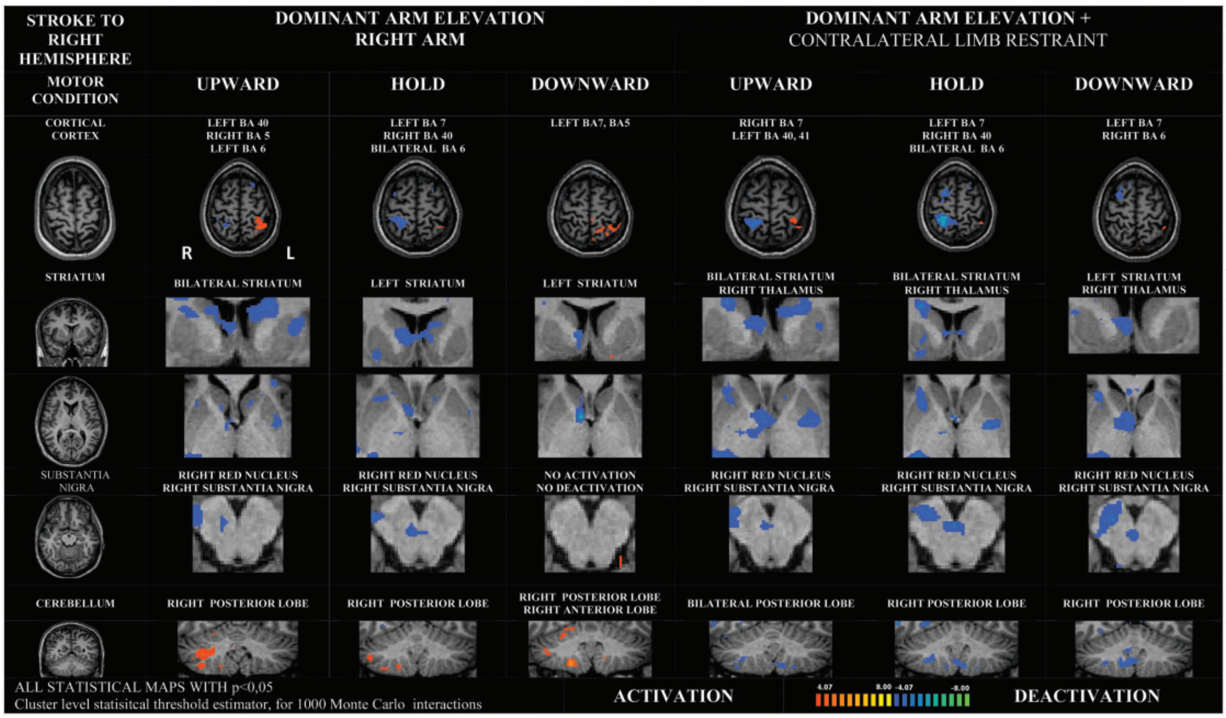
We also found bilateral cortical activation during plegic/paretic AE. However, this pattern was only observed for the right hemispheric stroke. The more localized ipsilesional/contralateral activation observed in the left hemispheric stroke patients suggests a hitherto unrecognized pattern of hemispheric dependence. Its functional significance and relation with outcome needs to be clarified in future studies.

The fact that each phase of movement recruits distinct muscle activity patterns (concentric, isometric, and eccentric) may help explain why different motor programs may have different underlying cortical and subcortical mechanisms and interhemispheric regulation.

Clinical implications: neurophysiological biomarkers

Our findings provide an important addition to understand the relationship between motor control and brain activity patterns in relation to neurorehabilitation, and in particular CIMT. The bilateral cortical activations in right hemispheric stroke lesions are interesting because such a pattern has been suggested to be predictive of more difficult motor recovery.[11] Epidemiologic studies have so far not reported differences between motor recovery for left and right stroke. A previous study in healthy participants with the same motor task[26] found a similar type of physiological neuromodulation in healthy controls as observed here in stroke patients, suggesting that short-term plastic mechanisms are still available in early stages. Although recent metanalyses[11,13] suggest that bilateral cortical activation was associated with jeopardized recovery and ipsilesional cortical recruitment was linked with better outcomes, this is not necessarily inconsistent with the idea that

Figure 5. Statistical maps of group analysis of the *right* hemispheric stroke patients during dominant AE in presence/absence restriction of contralateral upper limb.



bilateral activation may precede more lateralized patterns, in a favorable manner (e.g. Nowak et al.[32]).

Our experimental results concerning the elevation of the nonaffected arm were similar and consistent with the notion of an appropriate balance between active and stop/inhibit commands of muscle activity. This idea is explained by the postulate of an ideal balance of inhibition/excitation ratio.[9,10,33–36]

Based on our findings, it might be useful to use transcranial magnetic stimulation (TMS) protocols[37] to drive motor recovery. These clinical protocols could be based on two principles: first inhibition of overactivation and second the reestablishment of healthy brain activity patterns in accordance with the previously dominant side, before the lesion. We therefore suggest that future studies should implement protocols that value the side of stroke lesion and the hemispheric dominance. For the right hemispheric stroke we suggest that TMS should be designed to inhibit the nonaffected cerebral hemisphere aiming to inhibit bilateral cortical activation or ipsilateral overactivation. For the left hemispheric stroke we also suggest the use of an inhibiting TMS protocol to inhibit the nonaffected hemisphere to "reproduce" the cortical deactivation patterns observed in healthy participants reported in our previous study and in "good" AE (to the right) by left stroke patients. Our work suggests the need to clinically stratify as a function of the site of lesion and future studies should further address the role of hemispheric dominance and other sources of heterogeneity.

Our results also highlight the ability to manipulate a motor condition by using movement restriction techniques that lead to changes in brain activity patterns in stroke patients.

Other important aspect to take into account in future studies is the quantification of hemispheric dominance and handedness with measures that are based on neurophysiological (brain and muscle skeletal) signals. Our results seem to confirm the theories that propose the therapeutic implementation of inhibitory modulation of the nonaffected hemisphere[38,39]/less affected hemibody.[10,40–43]

Physical therapy implications

Our work suggests that inhibitory modulation may be a very important tool in physiotherapy, namely in CIMT, and that future interventional approaches should explore the hemisphere-dependent balance between excitation and inhibition of motor networks.

Conclusions

We found different brain activity patterns in stroke patients who are dependent on the hemispheric side of the lesion. These findings support the asymmetry theory applied to motor control. The main implications of these findings emphasize the physiological impact of restriction, as applied in the classical CIMT therapy, in the engagement of inhibitory interactions. It sheds light on the relative role of inhibition as a counterpart of facilitation, which are important concepts in the field of motor recovery. Finally, the identified hemisphere-dependent functional imaging signatures can potentially be used in future diagnostic and therapeutic strategies taking into account the functional heterogeneity of neurophysiological signals that drive motor recovery after neurologic damage.

Authors' contributions

Wrote the paper: ACV, MC-B, PB, AGP, JS-F. Methods: ACV, PB, MC-B, AGP. Data selection: ACV, AGP, MC-B, GC, JS-F, AG. Data extraction: ACV. Analysis and interpretation of data: ACV, MC-B, GC, JS-F, AG, AGP.

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Declaration of conflicting interests

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