International Journal of Physical Medicine & Rehabilitation

Bani-Ahmed et al., Int J Phys Med Rehabil 2017, 5:3
DOI: 10.4172/2329-9096.1000400

Research Article OMICS International

Primary Motor Cortex Ipsilateral to the Paretic Arm - A Potential Neural Substrate for Compensatory Trunk Use in Chronic Stroke

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Received date: March 22, 2017; **Accepted date:** April 10, 2017; **Published date:** April 12, 2017

Abstract

Objective: Arm motor recovery after stroke is primarily attributed to the primary motor cortex (M1) plasticity. While the M1 contralateral to the paretic arm (cM1) is undoubtedly critical for recovery, the role of the ipsilateral M1 (iM1) is still inconclusive. For instance, an abnormally increased activity in the iM1 is reported immediately after stroke and normalizes at the chronic stage in recovered patients. Whether persistent iM1 hyperactivity in chronic stroke reflects a less efficient type of plasticity (so-called maladaptive) is still far from settled. We investigated the functional significance of the iM1 hyperactivity with respect to compensatory behavioral strategies employed by patients suffering from chronic arm paresis.

Methods: Functional MRI and trunk kinematics data were collected during paretic arm movements in 11 patients before and after a four-week training specifically designed to improve the motor control of the paretic arm and diminish the behavioral (trunk) compensation comprising of variable practice of a reach-to-grasp task with feedback given as knowledge-of-performance. Eight age-matched healthy controls underwent similar evaluations and training. Magnitude of iM1 (and cM1) activation and anterior trunk displacement were analysed.

Results: Before training, patients exhibited significantly stronger iM1 activation, increased trunk motion, and significant positive correlations between these two variables compared to controls. After training, patients significantly decreased iM1 activation and displayed a trend toward decreased trunk use. The correlations between iM1 activation and trunk motion persisted and were different from those in controls.

Conclusion: Our preliminary data provide evidence that functional iM1 plasticity is related to behavioral compensation, suggesting a maladaptive role of the iM1 in chronic subcortical stroke. We however recommend caution in interpreting these results until more work is completed.

Keywords: Chronic stroke; Behavioral compensation; Ipsilateral primary motor cortex; Functional MRI; Trunk kinematics kinematics-fMRI

Introduction

Stroke is the leading cause of long-term motor disability in adults [1]. Acutely, approximately 75% of stroke survivors are left with arm motor dysfunction [2]. This dysfunction is only partially improved with traditional rehabilitation techniques - a large proportion (30-60%) of patients in the chronic stage of recovery is unable to incorporate their paretic arm into activities of daily living [3]. Novel training regimes show promise [3,4], but they are resource intensive. Given anticipated growth in stroke incidence and prevalence [5], there is a compelling need for better restorative therapies to increase recovery of the arm motor control.

Development of new (and better) therapies clearly depends on a finer knowledge of the neural substrates underlying such recovery. In modern neuroscience, the notion that the adult cerebral cortex is capable of widespread functional and structural plasticity in response to stroke is axiomatic [6,7]. For stroke survivors exhibiting motor impairment, such plasticity has been demonstrated in the perilesional cortex and in both injured and uninjured hemispheres [8-10]. The common assumption is that this plasticity must be functionally relevant. This issue is, however, far from settled. For the primary motor

cortex, (M1), while the M1 contralateral to the paretic arm (cM1) is undoubtedly critical for recovery [8], the role of the ipsilateral M1 (iM1) is still inconclusive. As this field has advanced, a consistent finding is an abnormally increased activation in iM1 immediately after unilateral stroke [11-13]. This hyperactivity may [14] or may not [15-18] normalize at the chronic stage, likely depending on the injury severity. Some investigations contend that these chronic iM1 changes have maladaptive relevance. This hypothesis has motivated a variety of non-invasive brain stimulation interventions targeting the reversal of these changes to promote recovery [19-23]. However, not all evidence supports this hypothesis [24-28]. An argument can be made that these changes have adaptive relevance, as a result of remodeling of ipsilateral projections, particularly in those with poor function [16,29,30]. Yet, recent meta-analyses do not agree on the available evidence to either support or reject this role [27,28]. Finally, a case can be made that, with respect to recovery of the paretic arm, iM1 plasticity is functionally irrelevant [26,31]. In the face of these contradictory results, it is clear that we are missing key facts about iM1 role in arm motor improvement after stroke. Further, the terminology used to describe motor recovery has not adequately distinguished between the concepts of motor recovery (return to the pre-morbid movement pattern) and compensation (the use of alternative movements and potentially effectors to accomplish the same action) [32]. Indeed, to date, all fMRI studies have used clinical indicators of impairment (i.e., Fugl-Meyer test) or function (i.e., Barthel Score, NIH Stroke Scale) and/or motor outcomes (i.e., movement speed, movement errors) to measure intervention-related recovery without consideration of how these gains are truly attained. Thus, the lack of clear definitions of recovery has led to confusion in interpretation of treatment efficacy, often leading to equivocal results. Another important point, which is perhaps underappreciated, is whether these two behavioral mechanisms - recovery *vs.* compensation - could be distinguished at the neural level. One simple way to look at this is to consider recovery as restoration of function in neural tissue that was initially injured or metabolically depressed (primarily in the injured hemisphere, i.e., cM1) and compensation as functional recruitment of brain areas that did not participated prior to injury in the task (i.e., iM1).

Therefore, in the present study, we aimed to investigate the relationships between iM1 activation and compensation in the chronic stage of stroke and whether these relationships are altered by an intervention specifically designed to improve the motor control of the paretic arm and diminish compensation. We performed task-related fMRI assessment immediately before and after a four-week impairment-oriented training period (1080 repetitions of a reach-to-grasp task executed with the paretic arm) [33-36]. The short- and long-term effects of this type of training has been investigated previously by us [33,34] and others [35,36] and found this training to be associated with a moderate improvement of the arm motor control and a decrease in the alternative (compensatory) movement strategy (i.e., the use of the trunk) used. Trunk compensation has been widely studied by us [32,37,38] during tasks executed with the paretic arm. Precisely, the patients increased the trunk use to compensate for lack of or diminished elbow extension to bring the hand to the object during unilateral reaching with the paretic arm [38]. This compensation is related to the severity of hemiparesis [38]: patients with less active range of elbow (and/or shoulder) motions would increase this behavioral compensation with training; those with higher levels of motor function would increase the ability to exploit the range of the arm joint motion which led to decrease of the trunk use [38,39].

Based on overwhelming evidence of iM1 hyperactivity in humans [40-42] and animal models [43,44], we predicted that patients would show increased activity in iM1 relative to healthy controls during a task executed with the paretic arm. If iM1 hyperactivity was adaptive, then patients would show a negative relationship between this variable and the trunk motion. If maladaptive, then these two variables would be positively related. If functionally irrelevant, then there were no detectable relationships. We also examined the longitudinal changes in both the iM1 activity and trunk motion. Considering brain remodelling during different training paradigms in stroke [45-48], we expected to find a decrease in iM1 activation after training. Based on our prior findings from interventional stroke studies [33,34,49], we also expected a decrease in trunk motion. Similar hypotheses with those proposed prior training were explored after training.

Materials and Methods

The study was performed with the approval of the University of Kansas Medical Center (KUMC) Human Subjects Review Board. All participants gave written informed consent before the study.

Age/Sex	Months after stroke	Infarct location	Infarct volume	FMUE
57/M	6	L/BG, ALIC, CR	25.3	64
48/F	11	L/PLIC, BG	17.9	61
61/F	27	L/CP	1.2	57
45/M	27	R/BG, CR	21.9	36
61/M	15	L/P	0.7	25
63/F	48	L/P	0.5	31
44/F	106	L/BG, AL+PLIC, CR	60.4	25
59/M	144	R/PLIC, BG	1.4	25
57/M	48	L/BG	6.9	25
58/M	27	L/ PLIC, BG	1.4	24
61/M	24	L/BG, AL+PLIC, CR	10.5	10

Table 1: Demographic and clinical characteristics of stroke survivors (M: Male; F: Female; L: Left; R: Right; BG: Basal Ganglia; CR: Corona Radiata; PLIC: Posterior Limb Internal Capsule; ALIC: Anterior Limb Internal Capsule; CP: Cerebral Peduncle; P: Pons; Infarct volume measured in cm^3; FMUE: Fugl-Meyer Upper Extremity, normal=66, recorded prior training).

Participants

All participants were right-handed according to the Edinburgh Handedness Inventory [50] and without MRI contraindications.

Stroke survivors were selected from the KUMC stroke database between 2008 and 2012. Out of a 138-candidate pool, 18 met the following inclusion criteria: i) a single subcortical infarction (verified on T1/T2-weigthed MR images), ii) arm motor impairment, Fugl-Meyer Upper Extremity (FMUE)>10, and iii) able to understand simple instructions (no receptive aphasia, Token test) or had no other neurological/psychiatric/orthopedic disease (medical chart) that would

have interfered with training. Of these, three patients were excluded for severe claustrophobia and four due to lesion characteristics (multiple strokes or cortical stroke affecting motor areas or cerebellum). Thus, 11 survivors participated (64% male, age from 44 years to 63 years old, mean ± SD, 55.8 ± 6.8 years, time after onset from 6 mo to 144 mo, 44.7 ± 42.9 mo, Table 1).

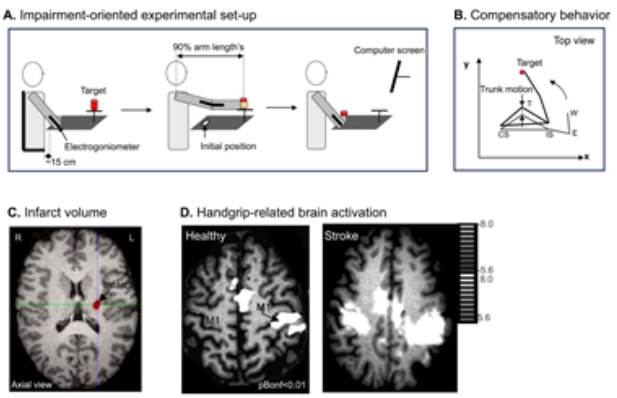

Figure 1: (A) Impairment-oriented training experimental set-up: The seat height was adjusted according to the participant's lower leg length so the feet could rest comfortably on the floor and the table height was set to coincide with the mid-point between the inferior margin of the sternum and the umbilicus. At the initial position, the participant had the arm to be trained rested on the table in front of and across to the body (elbow angle≈90deg). The contralateral arm rested alongside the body. The participant reached and grasped an object, placed on a platform located in front of him/her at shoulder height and on median line (elbow extension≈150-160deg), with the whole hand and transported it to the initial position at a comfortable self-selected speed. The participant had no arm or trunk restrictions during movement. Visual feedback about the elbow extension (reported to a "healthy" elbow extension for survivors) was provided with faded frequency throughout the practice session (for the first 30 trials, after every trial, for the second 30 trials, after every second trial and for the last 30 trials, after every five trials). (B) Diagram for the experimental set-up for reaching-to-grasp movement (top view). Movements were made with vision and without arm or trunk restiction. The lines joining the reflective balls located on the wrist (W), elbow (E) and the ipsilateral (IS) and contralateral (CS) define schematically the impaired arm of the participant while those joining the reflective balls on both shoulders (IS and CS) and trunk (T) define the trunk. The grey diagram represents the initial position of the participant while the black diagram represents the final position. The circle located in front of the participant represents the target. (C) Manual tracing of brain lesion in a patient with infarct in middle cerebral artery (MedINRIA). R, right, L, left. (D) The contrast between Move and Rest during handgrip task yielded activity in bilateral primary motor (M1) cortices, premotor cortices, cingulate motor area, inferior parietal cortex, and contralateral somatosensory cortex (white) in one patient with moderate hemiparesis (57 years old, male, left BG infarct, FMUE=25, see Table 1). This activity was clearly larger and bilateral compared to an age/sex-matched control.

Eight age-matched healthy controls (25% male, age from 34 years to 66 years old, 58.4 ± 10.3 years) with normal T1/T2-weighted MRI, and with no history of neurological/psychiatric/orthopedic disease, head trauma, or substance abuse were also recruited.

Study protocol

Kinematic (and clinical for patients) assessments followed by MRI evaluations within a 24 h interval were performed on two separate occasions: immediately before and after training.

Impairment-oriented training

All participants completed 12 practice sessions (90 repetitions/day, 3 days/week, 4 consecutive weeks, n=1080) consisting of repetition of a reach-to-grasp task. Because 82% suffered a left hemispheric stroke meaning that most had impairment of the dominant arm, we trained the impaired arm in survivors and the dominant arm in controls. Participants were seated in front of a table (Figure 1A). At the initial position, the participant had the arm to be trained rested on the table. An object was placed within a comfortable range for grasping (about 90% arm's length vertically oriented [51]) on a platform located in front of the participant. Because variable practice facilitates learning, retention, and generalization better than constant practice [52,53] we introduced a variable component during training. We used nine cylindrical objects of varying diameters (4, 6, and 8 cm diameter) and weights (50, 100, and 150 gms). We chose the sizes similar to routinely used objects, i.e., can, cup, and jar. Objects were presented in a random order. In response to an auditory signal, the participant reached and grasped the object with the whole hand and transported it to the initial position at a comfortable self-selected speed. The patient had no arm or trunk restrictions during movement. Participants received visual feedback about their elbow extension by using an electro goniometer (Exos, Inc., Woburn, MA, USA) located on their lateral epicondyle. Elbow extension was displayed on a computer screen after the end of the task. Mean elbow extension from the healthy group was presented as a target goal on the same screen. To minimize dependence on feedback, we decreased the feedback frequency throughout the practice session (for the first 30 trials, feedback was provided every trial, for the second 30 trials, every 2nd trial and for the last 30 trials, every 5 trials). We selected this task because it is dependent upon the M1 and its corticofugal projections [54-58], is familiar to participants, and recruits the trunk movement in those with diminished elbow extension. Based on our prior work [33,34,49] we expected that our training (of a specific arm motor impairment-elbow extension which is significantly related to the use of trunk) would result in elbow extension improvement and trunk motion decrease. Such decrease in compensation is considered as marker of true motor recovery [32]. Finally, note that our objective was not to evaluate the efficacy of a specific motor training but to provide an ideal training setting for studying compensation.

Kinematic assessment of compensation (trunk motion during a reach-to-grasp task)

We assessed the anterior trunk displacement using a similar task as the training task. A 4 cm diameter cylinder was fixed on a platform located in front of the participant aligned with the midline of the trunk, at 90% of extended arm's length and at the participant's shoulder height. We instructed participants to reach and grasp the cylinder in response to an auditory tone and hold the hand in the final position until a second tone signalled the end of the trial. There were no

restrictions of trunk or arm movements or feedback provided during data acquisition.

Prior to recording, participants practiced the task five times. Then, 20 movements performed with full vision were recorded by using motion analysis system (VICON, Oxford Metrics). Five reflective balls were positioned on the participant's arm (#1-ulnar process; #2-lateral epicondyle; acromion processes of #3-ipsilateral and #4-contralateral shoulder) and sternum (#5). In the present study, we used the displacement in the sagittal plane of the reflective ball #5 to define anterior trunk displacement (cm, Figure 1B). Each movement was recorded for 3-6 s at a sampling rate of 100 Hz.

Clinical assessment of arm motor impairment

In addition to the trunk metrics, we also assessed the arm motor impairment using a validated, reliable, and highly recommended scale as a clinical and research tool in stroke (FMUE, normal score=66 [57]). As stated above, FMUE is mainly focus on task accomplishment and is not qualitatively sensitive enough to discriminate how the task is achieved [58].

Functional MRI testing

MRI studies were conducted on a 3 Tesla MR system (Siemens Medical Solutions, Erlangen, Germany). The MRI experimental protocol has been detailed previously [59]. Briefly, a T2- weighted MRI was acquired to confirm stroke location, exclude undiagnosed pathologies, and assess the white matter changes (hyperintensities, WMH, Fazekas visual rating scale [60]). Shortly, this is a scale grading WMH according to severity: 0-none or a single punctate lesion, 1-multiple punctate lesions, 2-early confluency of lesions, and 3-large confluent lesions. The scores 0 and 1 are considered normal in the elderly. T1-weighted MRI (MPRAGE, TR=2300 ms, TE=3 ms, FOV=240 mm, matrix=256 × 256, resolution=1 × 1 × 1 mm^3) was also acquired and used to confirm stroke location and extract stroke volume. A stroke mask was created on each patient's MRI by manually tracing each lesion on slice-by-slice basis in the axial view of T2-weigthed images in MedINRIA software (Medical Image Navigation and Research Toll by INRIA, Cedex, France). Lesion was defined as tissue with abnormal high signal intensity on each image (Figure 1C) and as subcortical if they include >50% of subcortical tissue [61]. Infarct volume was calculated using MIPAV.

A gradient echo blood oxygen level-dependent (BOLD) scan (TR=2000 ms; TE=50 ms; FOV=240 mm; matrix=64 × 64; slice thickness=5 mm; 25 slices; 0 skip; resolution=5 × 5 mm^2; 100 time points) was acquired. Two alternating conditions were repeated five times: movement (20 s)- where participants performed a handgrip (with the impaired hand for patients; dominant hand for controls); and rest (20 s) - where participants were resting motionless. Total run time was 3 min 28 s. During scanning, a target pressure was set at 25% of maximal voluntary contraction (MVC) for each participant. Prior to scanning, participants generated MVC on three five-second trials; the highest peak pressure produced was used as the MVC. The pre-training MVC value was also used after training. The target pressure was indicated by a vertical bar on the screen placed in front of the participant (LabVIEW 7.1, National Instruments, Texas). The handgrip rate was indicated visually by a green circle displayed on the screen for 2 s at every 4 s (a red circle was provided with the same rate during the rest condition). The green circle indicated to the participant to perform a single brief handgrip until the column representing applied pressure reached the vertical bar displayed on the screen, at which point the grip could be released.

Prior to scanning, participants were trained until comfortable with the task, to confirm the absence of associated or mirror movements (by observation and palpation), and to ensure that the participant is able to control the force output. We used an air-filled polymer bulb connected to a pressure transducer. After each handgrip, the bulb was actively inflated helping the hand to release. After scanning, we evaluated the perceived effort during task execution by using a Visual Analog Scale (0=no effort, 10=maximum effort). We carefully monitored this task to ensure that task performance and perceived effort were comparable between groups and sessions. The handgrip task was selected because: i) it is a subset of the reach-to-grasp training; ii) the cortical mechanisms controlling the hand are likely integrated with those of the elbow and shoulder, as part of the system underlying reaching, prehension, and object manipulation [62], iii) handgrip strength is correlated with the arm motor performance [63], iv) it returns earlier than fractioned finger movements [64], that is, we were able to study survivors with different degrees of impairment, and v) it allows to minimize the movement-related fMRI signal artifacts.

BOLD data were analyzed using Brain Voyager software (Brain Innovation B.V., Maastricht, Netherlands). Motion correction was performed by rigid-body transformation and the estimated parameters were inspected for head movement. None of our participants moved their head more than 2 mm in any direction. Then, 3D spatial smoothing (4 mm Gaussian filter) was used and the time series in each voxel was high-pass filtered at 0.01 Hz. A general linear model was used to contrast BOLD signal between conditions, modelled by a boxcar function convolved with a two- gamma function designed to estimate spatiotemporal characteristics of the BOLD response. Whole brain imaging data were collected. Although our fMRI task activates a large network (e.g., contralateral somatosensory cortex and bilateral premotor cortices, cingulate motor area, inferior parietal cortex and intraparietal sulcus, insula cortex, cerebellar vermis, and both inferior and superior cerebellar hemispheres), we focused on iM1 based on its role in high-level motor control [65] and its potential to gain control of the paretic UE (through the ipsilateral corticospinal projections for the paretic proximal muscles [66], the corticoreticulospinal projections for the paretic distal muscles [67,68] and the indirect contribution through the bilateral connections with premotor/parietal cortices [69]). Based on its critical role for motor recovery [8], we also quantified the cM1 activation. Specifically, we defined the M1 using anatomical landmarks - the anterior bank of the central sulcus with the caudal border lying in the depth of the central sulcus close to its fundus and anterior border abuts Brodmann area 6.

Then, within each M1, voxels that were significantly activated for movement *vs.* rest ($p<0.01$, Bonferroni-corrected) were selected. A maximum of 100 contiguous voxels were selected and centered on the coordinates for the mean center-of-gravity (which is weighted according to the strength of activity) as calculated from the local extent of active voxels. This procedure ensures comparable-sized M1s across individuals. Percent BOLD signal changes were examined, and the mean percent signal change (MPSC) values for the entire run (movement *vs.* rest, Figure 1D) were calculated for each time point, before and after training. Because similar brain activations are elicited during a handgrip task executed with either the dominant or non-dominant hand in healthy controls [48], and 82% of our patients had left hemisphere injury, we compared the iM1 in patients to the right M1 in controls.

Statistical analysis

We summarized all data by mean and standard deviation and for M1 MPSC and trunk motion we also used percent change of the values before training: % change=(mean before–mean after) × 100/ meanbefore.

Considering the small sample size, we used Wilcoxon signed-rank test for the within-group comparisons and Wilcoxon rank-sum test for between-group comparisons. Spearman rank order correlation was used to examine the relationships between BOLD and trunk measures and intra- and inter-rater reliability for infarct volume and WMH quantification (SAS 9.3 Software).

Results

Participants

Stroke survivors were moderately impaired (FMUE=35.1 ± 17.8, Table 1), had no lesions involving the M1 (on T1/T2-weighted structural MRI) or white matter changes (Fazekas scores varied between 0 and 1), and had an average infarct volume of 13.5 ± 18.0 cm^3. A high agreement between two evaluators was found for both white matter changes and infarct volume drawing ($p<0.01$ in all instances). Patients were not apraxic, cognitively impaired, or clinically depressed. The patients were on anti-hypertensive (91%), cholesterol-lowering (45%), and/or antiplatelet (45%) therapy, but were not receiving inpatient or outpatient treatment.

During scanning, all stroke survivors, including those with more severe hemiparesis (FMUE<30) were able to generate grip forces within the range given by their low MVC strength with their paretic hand. There were no evidence of associated/mirror movements and the perceived effort was similar with that in healthy controls (from 1-no effort to 2-light effort).

Baseline iM1 activation and trunk motion are significantly greater in stroke survivors compared to controls

As expected, stroke survivors showed significantly greater iM1 activation compared to controls (1.11 ± 0.67 *vs.* 0.007 ± 0.005 in controls, p=0.001, Figure 2A and Table 2). As predicted, moderately to severely impaired patients where not able to extend their elbow and moved their trunk (13.0 ± 12.3 cm *vs.* 2.9 ± 1.1 cm in controls, p=0.02, Figure 2B) to bring the hand to the target. Trunk motion was negatively correlated with the paretic UE impairment, as assessed by FMUE (r=-0.75, p=0.008).

	iM1		cM1	
Controls	**Before training**	**After training**	**Before training**	**After training**
1	0	0	0.6	0.75
2	0.01	0	0.6	0.73
3	0	0	0.99	0.97
4	0.01	0.01	0.52	0.75
5	0.01	0.01	0.81	0.84
6	0.01	0.01	0.54	0.68
7	0.01	0.01	0.72	0.8
8	0	0	0.75	0.83
9	0	0	0.88	0.96
10	0.01	0.01	0.7	0.78
11	0.01	0.01	0.42	0.64
12	0.01	0.01	0.63	0.93
Mean ± SD	0.007 ± 0.005	0.006 ± 0.005	0.68 ± 0.16	0.80 ± 0.11°
Stroke				
1	0.01	0.01	0.69	0.58
2	0.01	0.01	0.75	0.95
3	1.12	0.01	0.67	0.81
4	1.21	1.16	1.05	0.85
5	1.16	0.78	1.21	2.21
6	0.97	0.93	0.59	1.14

7	0.93	0.01	0.53	0.65
8	2.1	0.17	1.2	0.91
9	1.42	1.18	2.33	1.39
10	1.22	1.18	1.09	2.57
11	2.05	0.63	1.24	1.35
Mean ± SD	1.11±0.67 **	0.55±0.52°,*	1.03±0.51	1.22±0.64
°<0.01 signifies between-session differences in MPSC within group; *<0.05, **<0.001 signify between-group differences in MPCS.				

Table 2: Mean percent signal change before (baseline) and after training in primary motor cortex ipsilateral (iM1) and contralateral (cM1) to the tested hand in controls and stroke survivors.

Baseline iM1 activation was significantly correlated with trunk motion in stroke survivors compared to controls

Notably, the correlations between the iM1 activation and trunk motion in patients were positive, significant, and higher than in controls (r=0.86, p=0.001 *vs.* r=0.28, p=0.5, Figure 2C). We also found significant and negative relationship between the iM1 activation and the FMUE scores (r=-0.74, p=0.01).

Training-related clinical changes in stroke survivors

All participants (patients and controls) completed the training sessions. While all participants completed the reach component of the task, the severely impaired patients did not have sufficient motor control to perform the whole action - some grasped the objects from the top while some were not able to transport the objects to the initial position. Similar to prior studies using similar motor training and clinical outcome measures [33,70], the patients significantly improved the arm motor impairment over the training (FMUE scores increased by a mean of 3.9 ± 2.9 points, range from 1 to 9 points, from 34.8 ± 17.8 to 38.7 ± 16.7, p<0.001). Patients also reported improvements in activities of daily living (e.g., two regained the ability to use under-arm deodorant; two others were able to reach and grasp objects placed at a higher level than pre-training level - consistent with improved range of elbow extension ability- the trained variable).

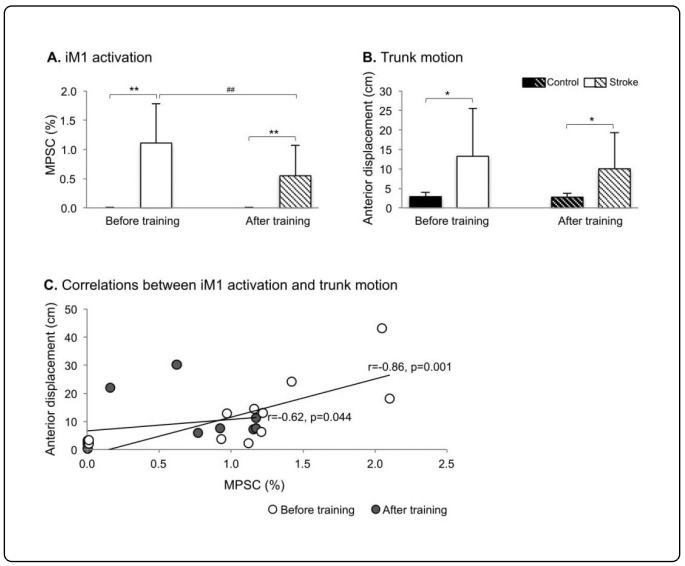

Figure 2: Mean (+SD) of mean percent signal change (MPSC) in the primary motor cortex (M1) ipsilateral to the tested hand (A) and of anterior trunk displacement (B) before and after training in controls (black bars) and stroke survivors (white); *p<0.05, **p<0.001. (C) Scatterplot of Spearman correlations between mean percent signal change (MPSC) in the primary motor cortex (M1) ipsilateral to the tested hand and trunk motion before (white circles) and after (grey) training in stroke survivors.

iM1 activation and trunk motion in controls did not change with training

In controls, there were no significant changes in iM1 activation (from 0.007 ± 0.005 to 0.006 ± 0.005, 12% change, p=0.3, Figure 2A) or trunk use (from 2.9 ± 1.1 cm to 2.8 ± 1.0 cm, 5.6% change, p=0.1, Figure 2B) with training. The correlations iM1 activation-trunk motion were not different from pre-training baseline for controls (r=0.22, p=0.6). iM1 activation and trunk motion in stroke survivors decreased with training but remained significantly different from control. As predicted, iM1 activation in patients decreased significantly with training (from 1.11 ± 0.67 to 0.55 ± 0.52, -50.2% change, p=0.008, Figure 2A and Table 2). Despite a noteworthy decrease in activation, the between-group significant difference in iM1 activation remained (p=0.002). A trend to less use of trunk was found after training in patients (from 13.0 ± 12.3 cm to 10.1 ± 9.2 cm, p=0.05, Figure 2B). Although there was an overall decrease by 22.2% in patients, it was not enough to diminish the between-group difference in trunk use (p=0.03) or to change the relationship with the clinical impairment (r=-0.84, p=0.001).

iM1 activation was positively and significantly correlated with trunk motion in stroke survivors compared to controls after training

Although the magnitude of the relationships between iM1 activation and trunk motion decreased after training, they remained higher and significant (iM1, r=0.62, p=0.044) from those in controls (r=0.22, p=0.6, Figure 2C). cM1 activation and trunk motion before and after training in stroke survivors *vs.* controls

Although not developed here, we also investigated the relationships between cM1 activation and trunk motion before and after training and found no significant relationships (p>0.05 in both instances). The group-differences in cM1 activation did not reach statistical significance neither before nor after training (before training, 0.68 ±

0.16 in controls *vs.* 1.03 ± 0.51 in patients, p=0.05; after training, 0.80 ± 0.11 *vs.* 1.22 ± 0.64, p=0.06, Table 2). Although the cM1 activation increased during training with a similar magnitude in both groups (18.4% and 18.1% respectively), only the change in controls reached statistical significance (p=0.02 in controls, p=0.4 in stroke survivors, Table 2). After training, the cM1 activation was significantly correlated with the paretic arm impairment (r=-0.64, p=0.03).

Discussion

To our knowledge, this is the first demonstration that quantifying the compensatory behaviour might be worthwhile for understanding the functional relevance of the iM1 reorganization in chronic stroke. Specifically, we studied the relationships between the iM1 activation and the trunk use during a reaching task executed with the paretic arm prior to and after intensive four-week training, specifically designed to improve the motor control of the paretic arm and decrease compensatory trunk use. These relationships were positive, significant, and different from healthy controls (which underwent the same training paradigm) in both instances, before and after training. As detailed below, these preliminary findings are supporting the potential role of iM1 in compensating for the brain damage rather than directly gaining control of the paretic arm in our sample.

Ipsilateral M1 activation is positively related to the compensatory behavior in stroke survivors

Consistent with overwhelming evidence from fMRI [40-42] and movement kinematic studies [71-73] including ours [38] in stroke, we found before training higher iM1 activation and greater trunk use during the paretic arm movements in chronic patients relative to controls. Notably, the relationships between these two variables were different in our patients compared to controls: iM1 activation pattern was tightly related to the trunk motion and overall correlation was higher (positive and significant) than in controls. Thus, stronger iM1 activation is associated with greater trunk use. It is theoretically possible that the iM1 increase in activation may reflect a dysfunction of the motor system and represent a maladaptive response. It is likely that this area plays a role in compensating for the brain damage rather than directly gaining control of the paretic arm. This is also supported by our findings of the negative relationships found between iM1 activation and FMUE scores, indicating a low reliance on the ipsilateral motor pathways to control the paretic arm. These preliminary findings corroborate prior studies contend that iM1 plasticity has maladaptive relevance in those suffering from chronic arm paresis [19-23].

Consistent with our predictions, stroke survivors exhibited training-related motor remodeling in the hemisphere ipsilateral to the paretic arm, i.e., significant decrease in iM1 activation. This result is in line with past stroke reports [47,48] and could be interpreted as a suppression of iM1 due to the restitution of the circuits within the M1 in the ipsilesional hemisphere. Indeed, patients exhibited an increase in contralateral (ipsilesional) M1 activation with training, albeit not statistically significant different from the pre-training baseline. Importantly, the increase in cM1 (by 18%) was similar to that in controls. This is interesting because a part of the M1 output was damaged by infarction in most survivors (Table 1). One explanation is that neurons that escaped infarction but were functionally impaired [59] may recover with training. Alternatively, enhanced activity in spared fibers could lead to new growth, branching of intact fibers [74] possibly altering the anatomical connections with premotor areas and potentially enlarging the motor output zone [45,74]. This apparent increase in the hemisphere contralateral to the paretic arm is consistent with prior results in non-human primates [75] and in humans [45,46] showing that after restorative therapies, the motor performance of the paretic hand may relay predominantly on the activity in the contralateral motor areas. However, our findings demonstrated a negative (and significant) relationship between the cM1 activation and the paretic arm impairment after training, suggesting that other mechanism may explain the iM1 decrease in activation. For example, another explanation could be the reduction in the task difficulty with learning [76]. Because the task difficulty was quantified and there were no changes in the patients' perception over the training, the possibility that task difficulty differences contributed to smaller BOLD activations in iM1 can be ruled out. Finally, patients showed significant decrease in trunk use and if we consider the positive relationship between these two variables, decrease in compensation would be related to decrease in iM1 activation. Therefore, we may speculate that these findings provide support for the potential role of the iM1 behavioral compensation. Notably, this is only for chronic stroke, not for the acute/sub-acute stroke, which is a completely different population.

Following the information presented thus far, it is obvious that there is a long-standing and contentious debate whether iM1 reorganizational changes are maladaptive, adaptive, or functionally irrelevant for motor recovery of the paretic arm. This understanding is crucial because iM1 is a target of great interest for rehabilitation efforts [77,78]. Thus, our preliminary results may have important implications for neurorehabilitation. Given that motor function could be altered through non-invasive brain stimulation, preventive or permissive strategies for compensatory behavior could be developed. Although the permissive approach might be appropriate in patients with severe impairment and poor prognosis, for less impaired patients, several arguments support emphasizing the preventing approach. However, our training approach, in line with prior reports [34,49,79], demonstrated a major reduction in compensation in our sample. Considering also the potential development of longer-term medical problems such as pain, discomfort and joint contractures [80] and/or learned non-use of the paretic arm [34,81,82] associated with the use of such compensatory behavior, we may speculate that a preventing approach could be appropriate in this subpopulation. Yet, the present study has not been designed to respond to these issues but to simply identify the link between iM1 activation and behavioral compensation in a sample evincing severe to mild arm motor impairment. Notably, the findings in this pilot study are preliminary and larger samples are needed to explore such link.

Limitations

This study has several limitations: i) small sample size; yet, one strength of this study was the use of restrictive inclusion criteria and a controlled motor training paradigm to reduce heterogeneity, so the current findings are relevant to this particular stroke type and location, as well as for this type of training; ii) we controlled for mirror movements *via* observation and palpation; obviously, these methods are only qualitative; iii) the muscle recruitment during handgrip might depend on body position [83], i.e., supine position with the arm extended and pronated during MRI *vs.* upright position with the arm in neutral position during training/clinical evaluation - we investigated the relationship body position-handgrip MVC in a group of healthy controls and found smaller MVC in upright than in supine position. Because we did not evaluate this relationship in survivors, we could

not exclude that our participants although they use same muscles, they might change their efficacy; iv) if a background activation exist prior to the handgrip task, we would expect that these patients exhibit lower magnitude of MPSC compared to controls, which we did not find; v) although BOLD reliability in our M1 is likely to be moderate to good after stroke [84], we interpret our data with caution; vi) all patients have subcortical infarcts - this limits generalization to a wider stroke population; vii) stroke chronicity [10] have been reported to impact motor recovery and should be taken into account in future studies; and viii) we did not evaluate the meaningful clinical decrease of trunk use; and ix) certainly, clinical changes were important, but the subjectively described changes are also worth emphasizing as they indicate the potential of this training paradigm to generalize to other behaviors that are of high ecological relevance. However, this study was not designed to evaluate the overall behavioral effects of this training.

Conclusion

Although no power analyses were performed, our data provide however important information for formulating hypotheses in future confirmatory studies. Specifically, our preliminary findings suggest the maladaptive role of the iM1 in a chronic subcortical stroke sample displaying severe to mild arm motor impairment. We finally emphasize that although kinematic analysis is time-consuming, when a therapy appears to enhance recovery, the use of a combined movement kinematics-fMRI approach may facilitate distinctions between recovery and compensation at both neural and behavioural levels.

Funding

This work was supported by American Heart Association (0860041Z to Dr. Cirstea). The Hoglund Brain Imaging Center is supported by a generous gift from Forrest and Sally Hoglund and National Institutes of Health (P30 AG035982, P30 HD002528, and UL1 RR033179).

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