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Motor Cortex Activation During Treatment May Predict Therapeutic Gains in Paretic Hand Function After Stroke

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Background and Purpose—Functional brain imaging after stroke offers insight into motor network adaptations. This exploratory study examined whether motor cortical activation captured during arm-focused therapy can predict paretic hand functional gains.

Methods—Eight hemiparetic patients had serial functional MRI (fMRI) while performing a pinch task before, midway, and after 2 weeks of constraint-induced therapy. The Wolf Motor Function Test (WMFT) was performed before and after intervention.

Results—There was a linear reduction in ipsilateral (contralesional) primary motor (M1) activation (voxel counts) across time. The midpoint M1 Laterality Index anticipated post-therapeutic change in time to perform the WMFT. The change in ipsilateral M1 voxel count (pre- to mid-) correlated with the change in mean WMFT time (pre- to post-).

Conclusions—The relationship between brain activation during treatment and functional gains suggests a use for serial fMRI in predicting the success and optimal duration for a focused therapeutic intervention. (*Stroke*. 2006;37:1552-1555.)

Key Words: magnetic resonance imaging ■ rehabilitation

Functional MRI (fMRI) has revealed reorganization in the primary and secondary motor cortices during poststroke recovery and after therapeutic interventions.¹ Few studies have explored the evolution of brain activation in relation to behavioral gains in a “one-to-one” correspondence during a specific rehabilitation intervention.² This exploratory study examined whether the brain activation midway through a 2-week arm-focused intervention might capture adaptations induced by the initial week of training and, in turn, could be used to anticipate post-therapeutic behavioral changes in paretic hand function. If so, this brain-behavior correspondence may offer guidance to determine an optimal duration for task-specific therapy.²

Subjects and Methods

Eight patients with hemiparetic stroke (Fugl-Meyer [FM] motor score 33 to 62) participated. Inclusion criteria were >3 months after stroke, ability to perform the fMRI task, and a minimum of 10° of voluntary wrist and finger extension. Lesions varied in location, but all spared the hand motor representation (M1). No alternative therapy group was studied. Seven healthy volunteers were scanned twice to test the reproducibility of fMRI activation.

Physical Therapy and Functional Measure

All patients received constraint-induced therapy for 2 weeks as defined for the EXCITE trial.³ The Wolf Motor Function Test

(WMFT)⁴ was performed before and after intervention. The behavioral outcome measure consisted of 6 dexterity items from the full 15-item WMFT (Lift Can; Lift Pencil; Lift Paper Clip; Stack Checkers; Flip Cards; Turn Key in Lock) that most directly captured fine motor control. The change in mean WMFT (mWMFT) time for the 6-item subset was correlated with that for the 15-item test ($r=0.98$), indicating reliability and validity for the subset. The pre-mWMFT-post-mWMFT (absolute time) difference was used as a proxy for functional change in motor skill.

fMRI Acquisition

fMRI acquisition parameters were described previously.⁵ fMRI sessions were performed before intervention, midintervention, and after intervention, each with 4 30-s bouts of repetitive pinch alternating with 5 30-s rest periods. The pinch apparatus included a vertical plastic tube connected to a pressure transducer. The task required tube compression with the index and middle fingers against the thumb, creating enough pressure to match 50% of maximum, viewed through goggles as a target line, and paced by auditory cues at 75% maximum rate. These parameters were maintained constant across the 3 sessions. Practice before each fMRI session minimized unwanted movements and deviations from consistent task performance.

Data Analysis

fMRI data were analyzed as described previously.^{5,6} Volumes related to head motion (>2 mm), and associated movements (visually identified from videotape) were excluded. Z statistic images were thresholded at $Z>3.1$, and significant clusters were defined at

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Clinical and fMRI Results (Group Mean)

Measures	Patients (paretic hand) n=8			Healthy Volunteers (right hand) n=7		
		Pre-	Post-			
Age (y)		66±9		56±7		
mWMFT Time (6-item; s)		33.40±37.69 ¹	16.59±22.46 ²	NA		
Difference in M1 activation						
Variables	Side (Patients)	Pre-Mid	Mid-Post	Pre-Post	Side (volunteers)	Scan 1–2
VC Ismean (SE)	Contralateral	-3 (9)	-7 (8)	-9 (13)	Left	-2 (13)
	Ipsilateral	-10 (4) [§]	-9 (8)	-19 (7) [*]	Right	-2 (8)
% SC Ismean (SE)	Contralateral	-0.16 (0.14)	-0.04 (0.14)	-0.20 (0.15)	Left	-0.09 (0.05)
	Ipsilateral	-0.38 (0.27)	0.02 (0.10)	-0.36 (0.31)	Right	-0.08 (0.08)

Ismean indicates least square mean. [§]P=0.06; ^{*}P=0.02.

¹Three patients (6, 7, and 8) had incomplete items that were scored 121s preintervention (patient 6 1 item; patient 7 2 items; patient 8 5 items); ²one patient (8) had 2 incomplete items that were scored 121s postintervention.

P<0.01 (corrected for multiple comparisons). Regions of interest (ROIs) were set in bilateral M1 and dorsal premotor (PMd) areas. Percentage signal change (% SC) and voxel counts (VCs) within each ROI were measured and a Laterality Index [LI=(contralateral-ipsilateral)/(contralateral+ipsilateral)] (contralateral and ipsilateral activation) to the hand movement. LI ranges from -1 [all ipsilateral activation] to 1 [all contralateral activation] was calculated using VC for each ROI. Linear Mixed Model was used for

intersession comparisons of fMRI variables (% SC, VC), pinch pressure, and rate, separately. Individual linear regression analyses were performed between LI, VC (M1 and PMd; independent variable) pre-, mid-, and post- and the post-pre-mWMFT time difference (dependent variable). Pearson correlation coefficient analysis was used to assess the relationship between changes in fMRI measures and changes in mWMFT time. Preintervention fMRI from patients 5 and 6 was technically unusable.

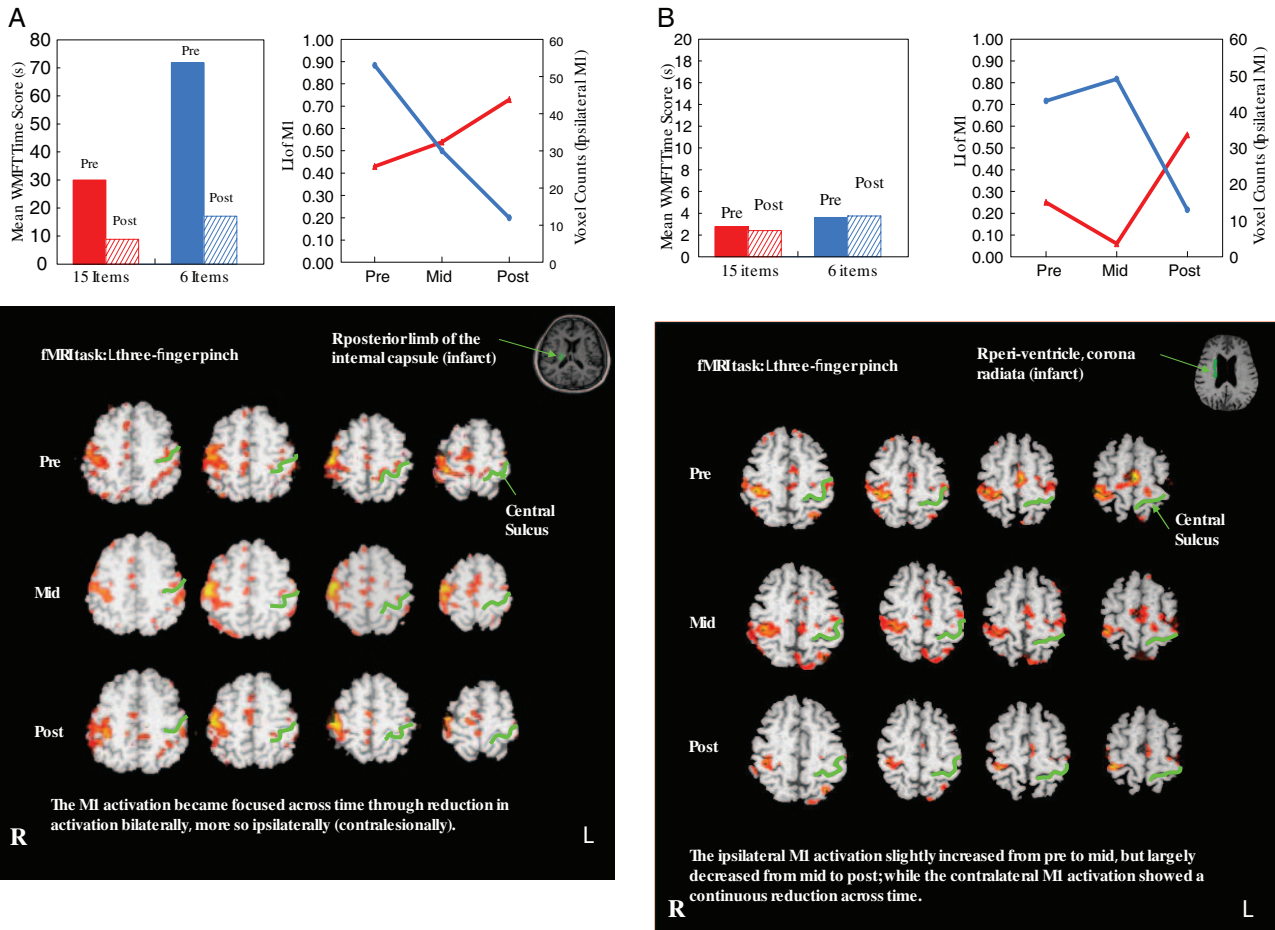


Figure 1. WMFT (top left), LI (red), and ipsilateral VC (blue) for M1 (top right) and serial activation pattern (pre-, mid-, post-) during paretic hand pinch (bottom) for patient 7 (A, female 5 months post, initial FM 45, paretic L) and patient 1 (B, female 12 months post, initial FM 62, paretic L). ▲ indicates LI; ●, VC.

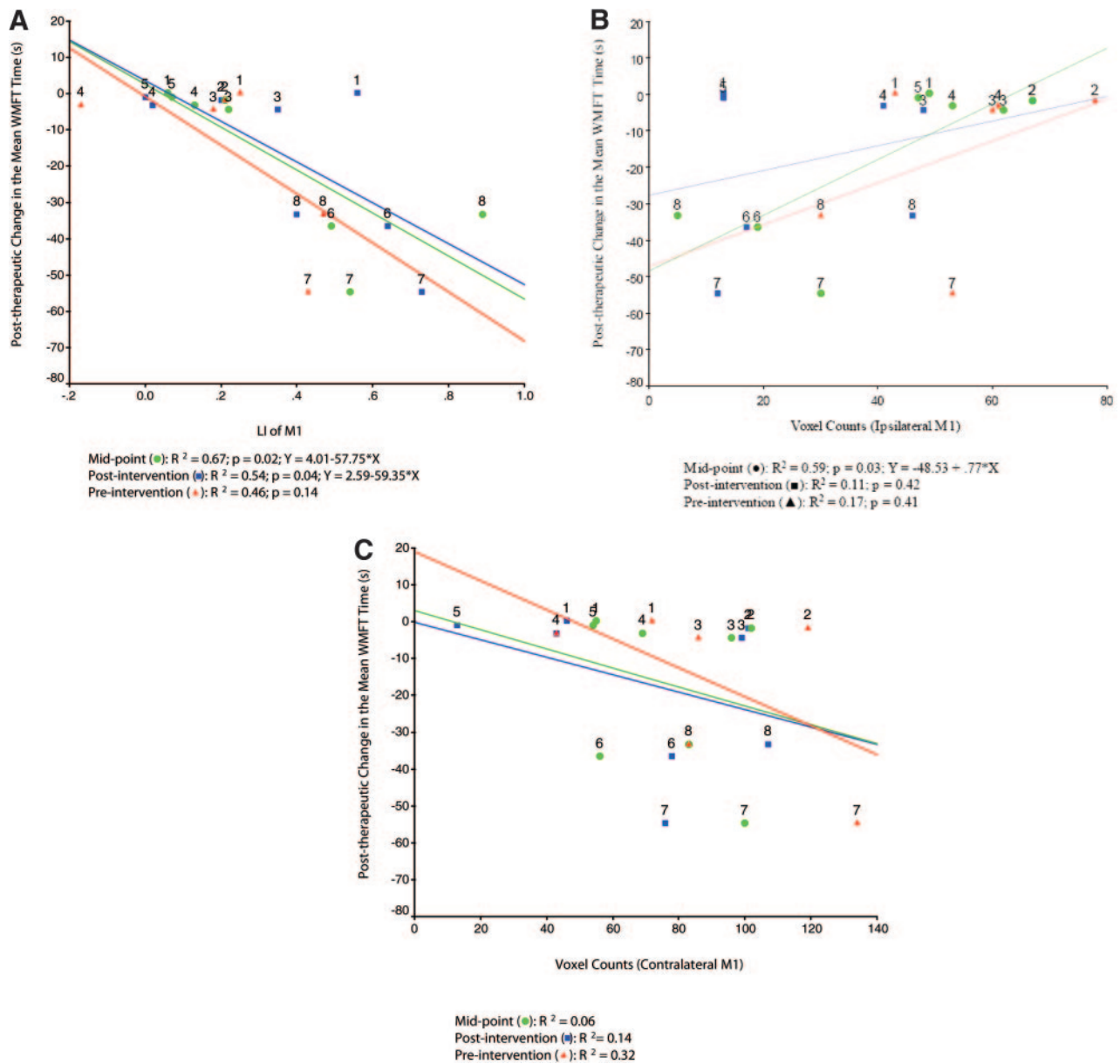


Figure 2. Regression plots for post-therapeutic change in mWMFT time and LI of M1 (A), VC in ipsilateral (B), and contralateral M1 (C). ▲ indicates preintervention; ●, midpoint; ■, postintervention. Patients are numbered.

Results

Prefunctional to postfunctional gains (mWMFT) varied across patients, but the group 6-item time decreased for the paretic hand after therapy ($P=0.03$; Table).

No differences were detected in pinch pressure or rate across sessions ($P>0.1$). Intersession comparisons of M1 activation in healthy volunteers showed no differences (Table). Group analysis for the paretic hand showed a continuous reduction of VC in ipsilateral M1 ($P=0.02$; $P=0.006$ linear trend) across time (Table). No differences in M1 activation across time were found for the less-affected hand ($P>0.1$; data not shown). We observed 4 patterns of LI evolution for M1, including a progressive increase (patients 3, 4, and 7; Figure 1A), a midpoint-only increase (patient 8), a midpoint decrease (patient 1; Figure 1B), and nearly no change (patient 2). Among the 3 showing “progressive increase,” patients 3 and 4 (FM

score 53 and 54, respectively) had either an increase in contralateral or a decrease in ipsilateral M1 activation across time, whereas patient 7 (FM score 45) demonstrated a continuous reduction in bilateral M1 activation but more so ipsilaterally. The “midpoint decrease” in patient 1 (FM score 62), who was well recovered and showed the least functional improvement, was attributed to a pre- to mid- reduction in contralateral M1 activation. The “midpoint-only increase” in patient 8 (FM score 34), who showed the most functional improvement, resulted from a pre- to mid- decrease in ipsilateral M1 activation.

There was no correlation between post-pre change in mWMFT time and change in activation (VC or % SC) in M1 or PMd (ipsilateral or contralateral), except for that between post-pre change in mWMFT time and pre- to mid- change in ipsilateral M1 activation (VC; $r=0.82$; $P=0.05$). The mid-

point and postintervention LI for M1 and midpoint ipsilateral M1 VC, but not that for PMd, did predict the post-pre mWMFT time change (6-item; Figure 2).

Discussion

The midpoint and postintervention LIs for M1 were found to predict paretic hand functional improvement. The midpoint ipsilateral activation (VC) was responsible for this brain–behavior correspondence (Figure 2B). Additionally, the ipsilateral VC (M1) evolved dynamically through progressive focusing during task-oriented training. Moreover, the reduction in ipsilateral M1 activation (VC) after the first week of training correlated with post-therapeutic behavioral improvements.

The small sample size and variability across patients in initial impairment level limit generalizability. Our ability to detect mirror movements from videotape was less accurate than other methods. However, the reproducibility of task performance across sessions in the patients and the similarity of task-related activation in healthy volunteers and in stroke patients for the less-affected hand suggest that these findings are most likely related to adaptive changes in brain activity with therapy and not to confounders such as differences in task performance or to undetected mirror movements. The results warrant further exploration in a larger study.

We selected M1 and PMd based on their reported role in stroke motor recovery.^{1,7} Other areas, such as ventral premotor and supplementary motor areas and cerebellum may also evolve with focused therapy.⁸ The predictive value of M1 activation and the correlates between changes in M1 activation and functional improvements, if replicated in patients across various lesion locations, degrees of impairment, and multiple behavioral assessments, has implications for using serial fMRI as a physiological indicator for “dose–response” interactions during a rehabilitative intervention.² In addition, the relationships among initial impairment level, evolution of M1 activation, and functional gains may help establish the opti-

mal duration of a rehabilitation intervention and lead to a better understanding of adaptive brain–behavior responses to therapy.

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