

# Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Contralesional Primary Motor Cortex on Movement Kinematics and Neural Activity in Subcortical Stroke

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**Background:** Following the concept of interhemispheric competition, downregulation of the contralesional primary motor cortex (M1) may improve the dexterity of the affected hand after stroke.

**Objective:** To determine the effects of 1-Hz repetitive transcranial magnetic stimulation (rTMS) of the contralesional M1 on movement kinematics and neural activation within the motor system in the subacute phase after subcortical stroke.

**Design:** Crossover investigation.

**Setting:** A university hospital.

**Methods:** Fifteen right-handed patients with impaired dexterity due to subcortical middle cerebral artery stroke received 1-Hz rTMS for 10 minutes applied to the vertex (control stimulation) and contralesional M1. For behavioral testing, patients performed finger and grasp movements with both hands at 2 baseline conditions, separated by 1 week, and following each rTMS application. For functional magnetic resonance imaging, patients performed hand grip movements with their affected or unaffected hand before and after each rTMS application.

**Results:** Application of rTMS to the contralesional M1 improved the kinematics of finger and grasp movements in the affected hand. At the neural level, rTMS applied to the contralesional M1 reduced overactivity in the contralesional primary and nonprimary motor areas. There was no significant correlation between the rTMS-induced reduction in blood oxygen level–dependent responses within the contralesional M1 and the degree of behavioral improvement of the affected hand. Overactivity of the contralesional dorsal premotor cortex, contralesional parietal operculum, and ipsilesional mesial frontal cortex at baseline predicted improvement of movement kinematics with the affected hand after rTMS of the contralesional M1.

**Conclusion:** The functional magnetic resonance imaging data suggest that rTMS of the contralesional M1 may normalize neural activation within the cortical motor network after subcortical stroke. Identifying patients suitable for rTMS intervention based on individual patterns of cortical activation may help to implement rTMS in motor rehabilitation after stroke.

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STROKE IS THE MAJOR CAUSE OF long-term disability worldwide,<sup>1</sup> and impaired manual dexterity is common after stroke.<sup>2</sup> Deficits of dexterity may persist despite rehabilitation,<sup>2</sup> constitute a considerable handicap to stroke survivors,<sup>3</sup> and are usually not captured by clinical indices of upper limb function. By contrast, kinematic motion analysis is a sensitive tool to objectively evaluate impaired dexterity after stroke.<sup>4</sup>

Deficits of dexterity after stroke are associated with changes in neural activity within the motor areas of both hemispheres. Stroke affecting 1 hemisphere may

result in increased cortical excitability in the contralesional primary motor cortex (M1).<sup>5,6</sup> Consistent with these data, neuroimaging studies have shown increased activity in the contralesional M1 with movements of the affected hand.<sup>7,8</sup> Within the concept of interhemispheric competition, and considering enhanced inhibition of the lesioned hemisphere by the overactive contralesional hemisphere, reduction in cortical excitability within motor regions of the contralesional hemisphere may help to enhance recovery after stroke.<sup>9,10</sup>

Application of 1-Hz repetitive transcranial magnetic stimulation (rTMS) to the hand area of the M1 reduces the excitabil-

**Table 1. Clinical Details of Stroke Patients**

Patient No./ Sex/Age, y	Stroke Localization	Time From Stroke, mo	Affected Hand	Hand Dominance	MMS Score	NIHSS Score	mRS	ARAT Score	MRC Score	Hamilton Rating Scale for Depression <sup>19</sup>	Sensibility Impairment Score <sup>4, a</sup>
1/F/24	BG	1	Right	Right	30	1	1	40	4	0	10
2/M/37	BG, IC, CR	1	Right	Right	30	3	2	45	5	0	9
3/M/39	IC, CR	1	Right	Right	28	2	1	42	4-5	0	7
4/M/42	CR	1	Right	Right	27	2	1	57	5	0	0
5/M/45	BG	2	Left	Right	29	6	2	47	4-5	0	0
6/F/46	BG, IC	2	Right	Right	30	6	3	45	5	0	0
7/M/47	BG, IC	2	Right	Right	30	2	2	53	4-5	1	7
8/M/48	BG, CR	2	Left	Right	27	4	1	42	4	2	25
9/F/48	IC	2	Right	Right	30	5	3	40	4	3	4
10/F/51	BG, CR	3	Left	Right	28	5	1	44	4-5	0	1
11/M/51	CR	3	Right	Right	28	1	1	47	4-5	1	2
12/M/54	BG, CR	1	Left	Right	29	3	1	45	4-5	2	4
13/M/52	BG, CR	4	Right	Right	30	0	1	47	4	4	4
14/M/53	CR	3	Left	Right	28	1	2	44	4	6	7
15/M/54	CR	1	Right	Right	30	0	0	40	4-5	2	1

Abbreviations: ARAT, Action Research Arm Test<sup>21</sup>; BG, basal ganglia; CR, corona radiata; IC, internal capsule; MMS, mini mental status<sup>16</sup>; MRC, medical research council score of wrist extension<sup>22</sup>; mRS, modified Rankin score<sup>23</sup>; NIHSS, National Institute of Health Stroke Scale.<sup>24</sup>

<sup>a</sup>Rated as previously detailed: 0 indicates normal; greater score indicates more significant impairment; maximum score, 35 points.<sup>4</sup>

ity of corticospinal projections from the site of stimulation.<sup>11</sup> Application of 1-Hz rTMS to the M1 also changes blood flow and excitability in the contralateral M1, and may modulate behavior ipsilateral to the site of stimulation.<sup>12</sup> Recent data show that 1-Hz rTMS applied to the contralesional M1 decreases pathologically enhanced transcallosal inhibition toward the ipsilesional M1, and thereby effects the motor function of the affected hand after stroke.<sup>13,14</sup>

The effects of 1-Hz rTMS of the contralesional M1 on the movement kinematics of both hands in the subacute phase (within 4 months) after subcortical stroke within the middle cerebral artery (MCA) territory were studied. We hypothesized that rTMS reduces neural overactivity in the contralesional motor areas, and at the same time improves the dexterity of the affected hand.

## METHODS

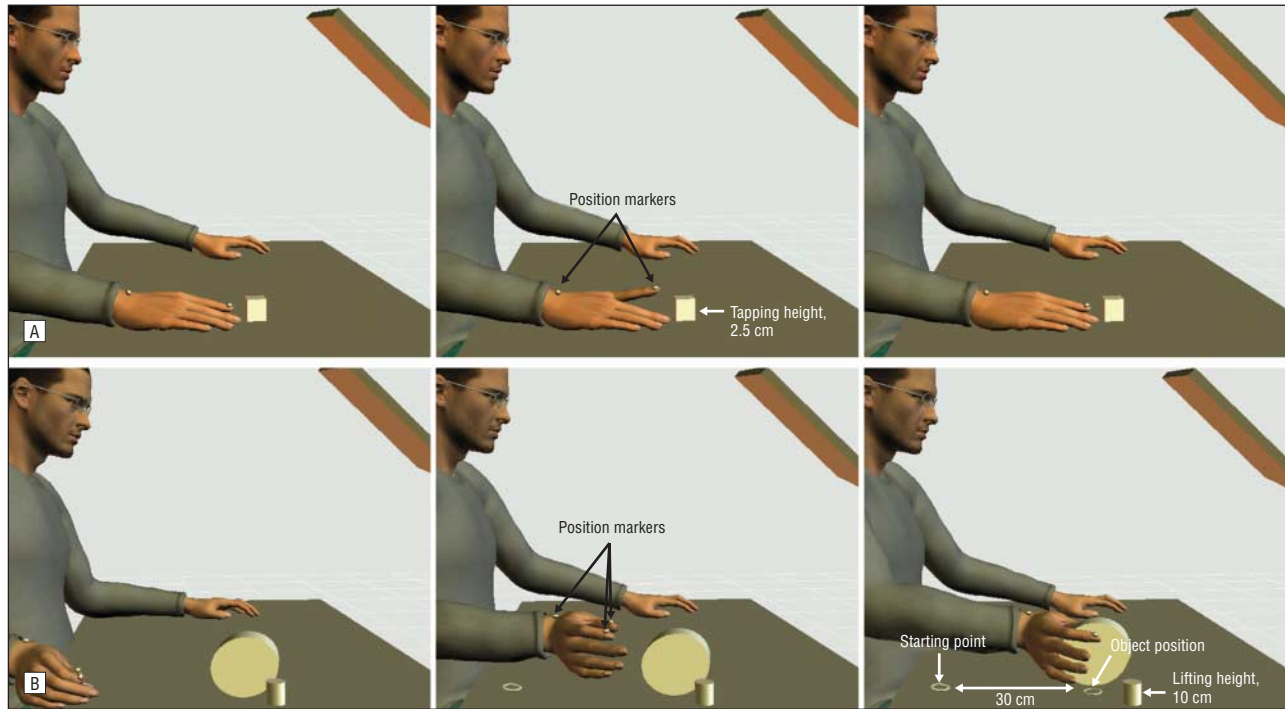
Fifteen adult right hand-dominant<sup>15</sup> patients with a first subcortical ischemic MCA stroke (4 women; mean [SD] age, 46 [8] years; range, 37-54 years) participated. Patients were investigated between 4 weeks and 4 months after stroke, and met the following criteria: (1) location of the ischemic lesion within the MCA territory verified by magnetic resonance imaging, (2) presentation with motor deficits in 1 hand, (3) a score of less than 24 points on the Folstein Mini Mental Status Examination,<sup>16</sup> (4) absence of aphasia that would interfere with the examination, (5) ability to bisect a straight horizontal line within 5% of the midpoint<sup>17</sup> and unimpaired visual fields in both eyes as measured by finger perimetry, (6) negative screening for ideomotor apraxia,<sup>18</sup> (7) absence of relevant depression as suggested by a score of less than 6 points on the Hamilton Depression Scale,<sup>19</sup> (8) ability to complete the experimental protocol with both hands, and (9) absence of mirror movements.<sup>20</sup> The study was approved by the local ethics committee. Informed consent was obtained from each patient prior to participation. **Table 1** summarizes the clinical data.

Patients participated in the behavioral and functional magnetic resonance imaging (fMRI) experiments on 2 days. The sequence of experiments was randomly assigned to each patient and counterbalanced across patients. For the fMRI experiment, patients were tested under 3 conditions: (1) immediately prior to rTMS (baseline condition), (2) following rTMS of the contralesional M1, and (3) following rTMS of the vertex (control stimulation). For the behavioral experiments, participants were tested at 4 time points: (1) 1 week prior to rTMS (baseline 1), (2) immediately prior to rTMS (baseline 2), (3) immediately following rTMS of the contralesional M1, and (4) immediately following rTMS of the vertex. Two baseline conditions were assessed to ensure a stable deficit of the affected hand. The rTMS stimulation conditions were separated by at least 120 minutes and their sequence of application was counterbalanced across patients.

Transcranial magnetic stimulation was performed using a 70-mm figure-of-eight coil and a Magstim Rapid stimulator (Magstim Company, Dyfed, Wales). The coil was placed tangentially over the contralesional M1 at the optimal site, ie, where stimulation at a slightly suprathreshold intensity elicited the largest motor-evoked potential in the contralateral first dorsal interosseus muscle. The resting motor threshold was defined for each participant as the lowest stimulator output that elicited motor-evoked potentials with a peak-to-peak amplitude of at least 50  $\mu$ V in at least 5 of 10 trials. Repetitive transcranial magnetic stimulation was applied to the contralesional M1 at a rate of 1 Hz at 100% resting motor threshold for 10 minutes.<sup>11</sup> Control stimulation was applied by positioning the coil over the vertex, using the identical rTMS frequency and intensity.

## fMRI PROCEDURE

Patients performed hand grip movements with their affected and unaffected hands in the fMRI scanner (Trio 3.0 T; Siemens, Erlangen, Germany). Movements were visually paced at a rate of 1.5 Hz. Intervals of 15 seconds of hand grip movements were followed by periods of motor rest lasting 15 seconds until the next block of movements commenced. Each scanning session comprised 24 activation blocks and 25 baseline



**Figure 1.** Recording of index finger tapping (A) and reach-to-grasp (B) tasks.

conditions. The order of blocks was randomized prior to the scanning session, with the constraint that no more than 3 identical blocks occurred in a sequence. Individual hand movements were visually monitored by an experimenter and videotaped for offline analysis. Repetitive transcranial magnetic stimulation was performed in front of the scanner room, and the time between the end of rTMS and the onset of fMRI was approximately 2 minutes. A gradient echo planar imaging sequence with the following imaging parameters was used: repetition time, 1600 milliseconds; echo time, 30 milliseconds; 26 axial slices; slice thickness, 3.0 mm; in-plane resolution,  $3.1 \times 3.1$  mm; echo planar imaging volumes, 457 for each session. The slices covered a region extending from midprefrontal to the visual cortex. High-resolution T1-weighted images were acquired via a 3-dimensional magnetization-prepared rapid-acquisition gradient-recalled echo sequence with the following parameters: repetition time, 2250 milliseconds; echo time, 3.93 milliseconds; 176 sagittal slices; slice thickness, 1.0 mm; in-plane resolution,  $1.0 \times 1.0$  mm. For all patients, T2-FLAIR (fluid-attenuated inversion recovery) images were acquired to screen for brain lesions not visible on the T1 volume images: repetition time, 9000 milliseconds; echo time, 100 milliseconds; 25 axial slices; slice thickness, 4 mm; in-plane resolution,  $0.9 \times 0.9$  mm.

For imaging data preprocessing and statistical analysis, the Statistical Parametric Mapping 5 software package (Wellcome Department of Imaging Neuroscience, London, England) was used. Images from patients with right-sided lesions were flipped about the midsagittal plane, so that the affected hemisphere corresponded to the left side of the brain for all patients. After realignment of the echo planar imaging volumes for each session and co-registration with the anatomical 3-dimensional image, all volumes were spatially normalized to the standard template of the Montreal Neurological Institute and smoothed using an isotropic kernel of 8 mm full width at half maximum. Boxcar vectors for each condition were convolved with the hemodynamic response function.<sup>25</sup> Movement parameters of the head were used as additional regressors to exclude movement-related variance from the image time series. In the first-level

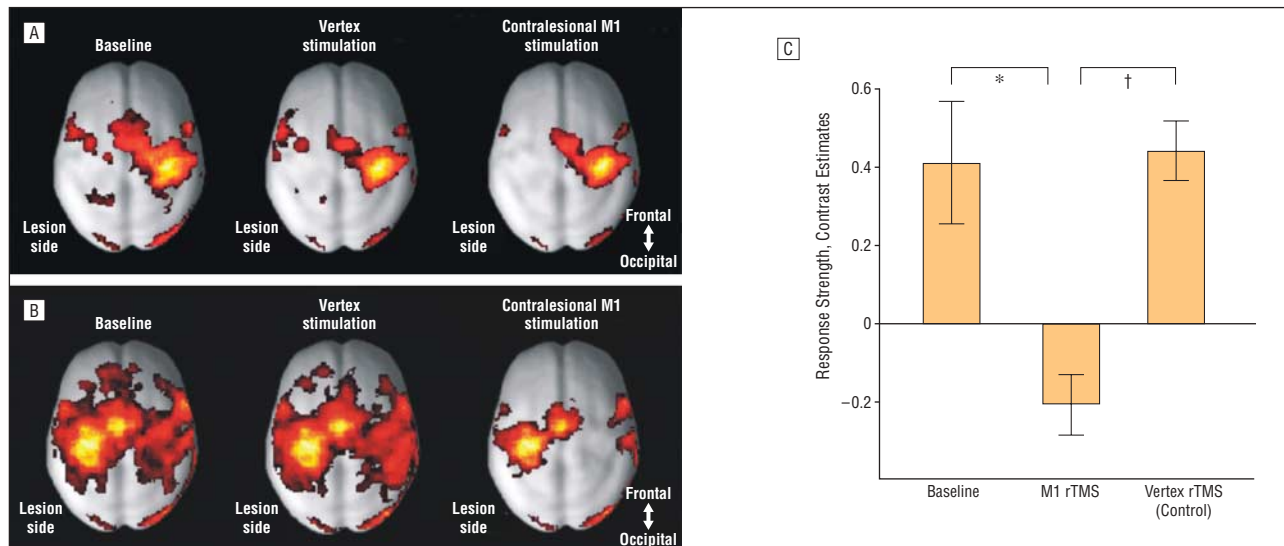
analysis, linear contrast images were computed for the conditions “affected hand vs resting condition” and “unaffected hand vs resting condition” for each patient. These contrast images were entered into a second-level analysis of variance with the factors “intervention” (levels 1, baseline; 2, rTMS of the vertex; and 3, rTMS of the contralesional M1) and “hand” (levels 1, affected hand and 2, unaffected hand). Voxels were identified as statistically significant if their  $t$  values passed a height threshold of  $t = 3.47$  ( $P < .001$ ). Correction at the cluster level was then applied using a threshold of  $P < .05$  (family-wise error corrected for multiple comparisons).

To identify the regions that significantly correlated with rTMS-related improvements in behavior, the percentage of improvement due to rTMS of the contralesional M1 as compared with vertex stimulation was calculated for each behavioral measure. The percentages of improvement for each patient were included in the design matrix as a separate covariate for the contrast “affected hand vs resting condition.” We restricted the correlation analysis to those voxels activated in the main contrast “movements of the affected hand vs resting condition” at an uncorrected threshold of  $P < .001$ . Within this region of interest, significantly correlating voxels were family-wise error-corrected for multiple comparisons ( $P < .05$ , small volume correction).<sup>26</sup> Anatomical localization was assessed using anatomical probability maps.<sup>27</sup>

## BEHAVIORAL PROCEDURE

Patients performed index finger tapping and a reach-to-grasp task with each hand (total duration, approximately 7 minutes; **Figure 1**). Both tasks were recorded using an ultrasonic motion analyzer.<sup>4</sup>

Index finger tapping was performed as quickly as possible. Movement amplitude was 2.5 cm. Three 5-second trials were performed with each hand. To quantify movement performance, the following parameters were obtained:<sup>4</sup> (1) movement frequency (in Hertz), (2) peak movement velocity (in millimeters per second), and (3) peak movement amplitude (in



**Figure 2.** Illustration of neural activity within the cortical motor areas for stroke patients during hand grip movements with either the unaffected (A) or affected hand (B) vs rest prior to an intervention (baseline), following repetitive transcranial magnetic stimulation (rTMS) of the vertex, or rTMS of the contralesional primary motor cortex (M1). Significant clusters are projected on the Statistical Parametric Mapping smoothed average template ( $P < .05$ , family-wise error corrected on the cluster level). C, Bar graphs extracted from peak voxel in contralesional M1 demonstrate a significant decrease in neural activity only after rTMS of this anatomical site, but not of the vertex, compared with baseline, prior to an intervention.  $*P < .01$ .  $\dagger P < .001$ .

millimeters). All parameters were averaged across all trials for each participant. During the reach-to-grasp task, patients placed the hand on a starting mark with thumb and index finger touching (Figure 1B). Patients reached for a cylindrical object (diameter, 9 cm; width, 4 cm; weight, 350 g), grasped it between the tips of the index finger and thumb, lifted it 10 cm above the table, and held it for 3 seconds before placing it back. Ten such movements were performed by each patient with each hand. Patients were directed to perform movements quickly but accurately. For each reach-to-grasp movement, the following parameters were obtained:<sup>4</sup> (1) peak of vertical wrist position (in millimeters), (2) peak of vertical wrist velocity (in millimeters per second), (3) movement time of the wrist (in milliseconds), (4) peak grip aperture (in millimeters), (5) peak velocity of grasp aperture (in millimeters per second), and (6) time of peak grip aperture as the percentage of movement time. All parameters were averaged across all trials performed by each participant. Repeated analyses of variance were calculated for each parameter with the factors “hand” (levels 1, affected hand and 2, unaffected hand) and “intervention” (levels 1, baseline 1; 2, baseline 2; 3, control rTMS of the vertex; and 4, rTMS of the contralesional M1). Post hoc pair-wise comparisons between conditions were performed using *t* tests. A *P* value of .05 was considered significant after Bonferroni correction for multiple comparisons.

## RESULTS

### fMRI PROCEDURE

**Figure 2** demonstrates the neural effects evoked by hand grip movements for the baseline condition, rTMS of the vertex, and rTMS of the contralesional M1, all compared with no movement ( $P < .05$ , corrected for multiple comparisons on the cluster level). For movements of the unaffected hand in the baseline condition (Figure 2A), neural activity was lateralized to the contralesional hemisphere with peak activity within the contralesional M1. Additional significant neural activ-

ity was found in the supplementary motor area, bilateral ventral cortex, dorsal premotor cortex (dPMC), and in occipital visual areas 1 through 5. Movements of the affected hand in the baseline condition (Figure 2B) exhibited neural activity in a similar distribution within the ipsilesional hemisphere, but were associated with additional and more widespread activity in the frontal and parietal areas. Movements of the affected hand were associated with significant neural activity in the contralesional hemisphere, with clusters of activation around the central sulcus, precentral gyrus, and inferior parietal cortex.

Repetitive transcranial magnetic stimulation of the vertex or contralesional M1 did not significantly change activity patterns compared with baseline for movements of the unaffected hand (Figure 2B). In contrast, for movements of the affected hand, stimulation of the contralesional M1 caused a significant reduction in brain activity in the contralesional hemisphere, compared with stimulation of the vertex ( $P < .01$ ) or to baseline ( $P < .001$ ) (Figure 2C). Stimulation of the contralesional M1 reduced and focused neural activity in the ipsilesional hemisphere similar to that of the contralesional hemisphere for movements of the unaffected hand.

### BEHAVIORAL PROCEDURE

Frequency ( $F_{1,14} = 7.5$ ,  $P < .01$ ) and peak velocity ( $F_{1,14} = 15.3$ ,  $P < .001$ ) of index finger tapping with the affected hand were smaller at each baseline condition and after rTMS of the vertex compared with performance of the unaffected hand (Figure 3). The performance deficit of the affected hand was stable, as suggested by similar frequencies and peak velocities at each baseline condition ( $P \geq .4$  for each comparison). After rTMS of the contralesional M1, both the frequency ( $F_{1,14} = 9.6$ ,  $P < .001$ ) and peak velocity ( $F_{1,14} = 6.6$ ,  $P < .02$ ) of index finger tap-

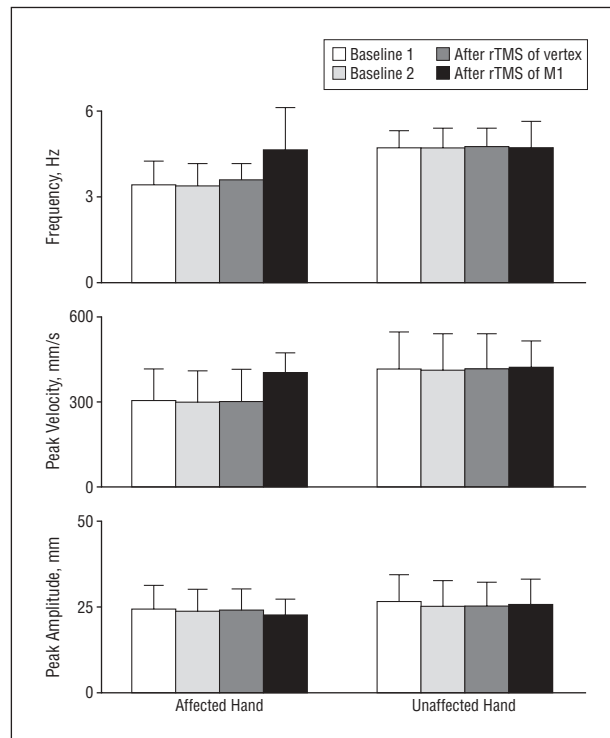
ping with the affected hand increased to values comparable with those obtained from movements of the unaffected hand, regardless of intervention ( $P \geq .4$  for each comparison). A significant “hand”  $\times$  “intervention” interaction on both the frequency ( $F_{1,14}=14.6, P < .001$ ) and peak velocity ( $F_{1,14}=18.2, P < .001$ ) supports this view. With respect to peak amplitudes of index finger tapping, neither of the factors “hand” or “intervention,” nor their interaction, developed significant effects.

Peak wrist velocity ( $F_{1,14}=57.3, P < .001$ ), peak velocity of grasp aperture ( $F_{1,14}=42, P < .001$ ), and time of peak grasp aperture ( $F_{1,14}=58.9, P < .001$ ) were all smaller, and movement times were longer ( $F_{1,14}=42.1, P < .001$ ), for reach-to-grasp movement with the af-

ected hand at both baseline conditions and after rTMS of the vertex, compared with the unaffected hand (**Table 2**). There was no significant difference between peak wrist velocities, movement times, peak velocities of grasp aperture, times of peak grasp aperture, and peak wrist position for movements performed with the affected hand at each baseline condition ( $P \geq .1$  for each comparison), suggesting a stable deficit. After rTMS of the contralesional M1, peak wrist velocities ( $F_{1,14}=17, P < .001$ ), peak velocities of grasp aperture ( $F_{1,14}=12.5, P < .01$ ), and times of peak grasp aperture ( $F_{1,14}=42, P < .001$ ) for movements of the affected hand all increased to values similar to those observed for movements of the unaffected hand (Table 2). Movement times for movements with the affected hand decreased after stimulation of the contralesional M1 ( $F_{1,14}=47, P < .001$ ) to values similar to those observed for movements with the unaffected hand (Table 2). A significant interaction of “hand” and “intervention” on peak velocity of grasp aperture ( $F_{1,14}=21, P < .001$ ), movement times ( $F_{1,14}=9.4, P < .01$ ), and times of peak grasp aperture ( $F_{1,14}=47, P < .001$ ) supports this notion.

#### CORRELATION BETWEEN BASELINE fMRI ACTIVITY AND rTMS-INDUCED CHANGES IN BEHAVIOR

Activity strengths at baseline (ie, prior to rTMS) that indexed a positive correlation with a subsequent rTMS-induced increase in tapping frequency of the affected hand were found in the contralesional precentral gyrus (dPMC, Brodmann area 6,  $r=0.89$ ), ipsilesional mesial frontal cortex (pre-supplemental motor area,  $r=0.90$ ), and contralesional parietal operculum (area OP1, SII,  $r=0.90$ ) ( $P < .05$ , corrected for multiple comparisons; **Figure 4**). That means a higher blood oxygen level-dependent (BOLD) activity in these areas at baseline was associated with a relevant improvement in finger tapping performance after rTMS treatment of the contralesional M1. There was no significant correlation between the rTMS-induced reduction in BOLD response within the contralesional M1 and the degree of behavioral improvement in the affected hand following rTMS.

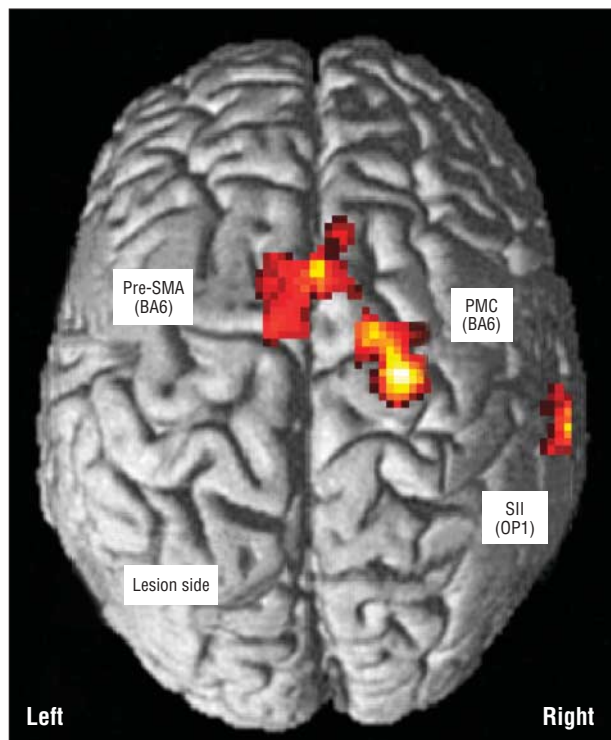


**Figure 3.** Mean (SD) of the frequency, velocity, and amplitude of index finger tapping with the affected and unaffected hands at both baseline examinations, after repetitive transcranial magnetic stimulation (rTMS) of the vertex, and after rTMS of the contralesional primary motor cortex (M1).

**Table 2. Kinematic Measures Obtained From Index Finger Tapping and Reach-to-Grasp Movements**

Hand Conditions	Mean (SD)					
	Peak Wrist Position, mm	Peak Wrist Velocity, mm/s	Movement Time, ms	Peak Grasp Aperture, mm	Peak Velocity of Grasp Aperture, mm/s	Movement Time of Peak Grasp Aperture, %
Affected hand						
Baseline 1	112 (29)	557 (121)	1569 (395)	46 (13)	135 (31)	52 (8)
Baseline 2	114 (30)	565 (123)	1699 (329)	46 (13)	129 (30)	53 (6)
rTMS of vertex	114 (25)	546 (98)	1591 (421)	44 (16)	127 (31)	51 (11)
rTMS of contralesional M1	116 (21)	656 (147)	1002 (186)	50 (10)	213 (35)	76 (60)
Unaffected hand						
Baseline 1	118 (32)	689 (113)	1108 (190)	46 (14)	226 (54)	68 (7)
Baseline 2	120 (30)	692 (118)	1079 (177)	46 (14)	222 (44)	74 (5)
rTMS of vertex	120 (22)	713 (104)	998 (207)	48 (10)	222 (43)	72 (8)
rTMS of contralesional M1	120 (26)	758 (129)	919 (158)	49 (9)	219 (38)	71 (8)

Abbreviations: M1, primary motor cortex; rTMS, repetitive transcranial magnetic stimulation.



**Figure 4.** Nonprimary motor areas in which overactivity prior to an intervention was significantly correlated with improvement of finger tapping frequency of the affected hand following repetitive transcranial magnetic stimulation of the contralesional primary motor cortex were contralesional dorsal premotor cortex (PMC), ipsilesional pre-supplementary motor area (pre-SMA), and contralesional parietal operculum (SII). BA indicates Brodmann area; OP, parietal operculum.

#### COMMENT

Application of 1-Hz rTMS to the contralesional M1 significantly reduced neural overactivity in contralesional motor areas, focused activity in ipsilesional motor areas, and improved movement kinematics of the affected hand in subcortical MCA stroke.

Overactivity in contralesional primary and nonprimary motor areas occurs early after stroke, indicating recruiting of these brain regions after the vascular incident.<sup>7,8</sup> This is in line with our data that reveal overactivity in the ipsilesional and contralesional dPMC, supplementary motor area, parietal cortex, and contralesional M1 for movements of the affected hand. Longitudinal studies demonstrated that initial task-related overactivity in motor-related brain areas are followed by a reduction over time in those stroke patients who eventually recover completely.<sup>8,28</sup> We show that downregulation of excitability within the contralesional M1 early after stroke may normalize neural activity within motor areas of both hemispheres, and improves dexterity of the affected hand.

Disruption of the contralesional dPMC by means of transcranial magnetic stimulation has been found to impair performance of simple motor tasks in long-term stroke patients.<sup>29,30</sup> The ipsilesional dPMC also appears to take on an executive motor role in long-term stroke patients with significant motor impairment.<sup>28</sup> These data highlight the role of the dPMC in hand motor recovery after stroke. We extend earlier findings by demonstrat-

ing that increased recruitment of contralesional dPMC (Brodmann area 6), contralesional parietal operculum (SII), and ipsilesional mesial frontal cortex (pre-supplementary motor area) activity early after stroke indicates significant improvement of dexterity after rTMS treatment. There was, however, no significant correlation between the rTMS-induced reduction in BOLD response within the contralesional M1 and the degree of behavioral improvement in the affected hand.

Stroke patients experience changes in motor cortex excitability with abnormally high interhemispheric inhibition from the contralesional hemisphere toward the ipsilesional M1 for movements of the affected hand.<sup>6,9</sup> Reduction of excitability of the contralesional M1 by inhibitory rTMS is effective in improving hand function after stroke. Our conclusion is that the inhibition of cortical excitability induced by 1-Hz rTMS correlates with a reduction in neural activation and causes a release of the ipsilesional motor areas from transcallosal inhibition. This interpretation is supported by earlier intervention studies. Compared with sham stimulation, 1-Hz rTMS of the contralesional M1 shortened both simple and choice reaction times and improved performance of the Purdue pegboard test with the affected hand within 12 months after subcortical stroke.<sup>13</sup> Application of 1-Hz rTMS to the contralesional M1 accelerated the development of pinch force between index finger and thumb in 10 patients more than 6 months following subcortical stroke, whereas sham stimulation did not change performance in another group of 10 stroke patients with comparable demographic and clinical data.<sup>14</sup>

#### CONCLUSIONS

Our imaging data demonstrate that the rTMS-mediated changes in neural activity go beyond a focal effect on the level of the motor cortex, but may elicit complex changes in functional network architecture. Overactivity of contralesional dPMC, contralesional parietal operculum, and ipsilesional mesial frontal cortex at baseline suggested improvement might occur with movement kinematics of the affected hand after rTMS applied to the contralesional M1. However, the amount of reduction in BOLD response within the contralesional M1 after rTMS did not correlate with the degree of behavioral improvement of the affected hand. Longitudinal studies on larger samples are now needed to confirm these results and evaluate the duration of the rTMS effect on both neural activity and behavior.

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Nowak, Grefkes, Dafotakis, Eickhoff, Küst, Karbe, and Fink. *Statistical analysis*: Nowak, Grefkes, Dafotakis, and Eickhoff. *Administrative, technical, and material support*: Nowak, Grefkes, Dafotakis, Küst, Karbe, and Fink. *Study supervision*: Nowak and Fink.  
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