

# Repetitive Bilateral Arm Training and Motor Cortex Activation in Chronic Stroke

## A Randomized Controlled Trial

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**H**EMIPARESIS REPRESENTS THE dominant functionally limiting symptom in 80% of patients with acute stroke.<sup>1</sup> Within 2 to 5 months after a stroke, patients recover a variable degree of function, depending on the magnitude of the initial deficit.<sup>1</sup> Several studies have demonstrated that recovery is associated with reorganization of central nervous system networks.<sup>2,3</sup> Functional brain imaging of paretic movement during the recovery period has shown recruitment of cortex immediately adjacent to the stroke cavity along with intact cortical areas within the lesioned and in the uninjured contralesional hemisphere.<sup>4,5</sup> The pattern of recruitment depends on the severity of impairment,<sup>6</sup> lesion location,<sup>7</sup> and time since stroke.<sup>8</sup> The factors that initiate and maintain cortical reorganization are not known. Imaging data suggest that circuitry in motor cortices on both sides of the brain is modified during recovery.<sup>2</sup>

**Context** Reorganization in central motor networks occurs during early recovery from hemiparetic stroke. In chronic stroke survivors, specific rehabilitation therapy can improve upper extremity function.

**Objective** To test the hypothesis that in patients who have chronic motor impairment following stroke, specific rehabilitation therapy that improves arm function is associated with reorganization of cortical networks.

**Design, Setting, and Patients** A randomized controlled clinical trial conducted in a US ambulatory rehabilitation program with 21 patients (median [IQR], 50.3 [34.8-77.3] months after unilateral stroke). Data were collected between 2001 and 2004.

**Interventions** Patients were randomly assigned to bilateral arm training with rhythmic auditory cueing (BATRAC) (n=9) or standardized dose-matched therapeutic exercises (DMTE) (n=12). Both were conducted for 1 hour, 3 times a week, for 6 weeks.

**Main Outcome Measures** Within 2 weeks before and after the intervention, brain activation during elbow movement assessed by functional magnetic resonance imaging (fMRI) and functional outcome assessed using arm function scores.

**Results** Patients in the BATRAC group but not in the DMTE group increased hemispheric activation during paretic arm movement ( $P=.03$ ). Changes in activation were observed in the contralesional cerebrum and ipsilesional cerebellum ( $P=.009$ ). BATRAC was associated with significant increases in activation in precentral ( $P<.001$ ) and postcentral gyri ( $P=.03$ ) and the cerebellum ( $P<.001$ ), although 3 BATRAC patients showed no fMRI changes. Considering all patients, there were no differences in functional outcome between groups. When only BATRAC patients with fMRI response were included (n=6), BATRAC improved arm function more than DMTE did ( $P=.02$ ).

**Conclusions** These preliminary findings suggest that BATRAC induces reorganization in contralesional motor networks and provide biological plausibility for repetitive bilateral training as a potential therapy for upper extremity rehabilitation in hemiparetic stroke.

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Even with traditional rehabilitation therapy, 50% to 95% of stroke survivors remain impaired.<sup>9-11</sup> For some patients, recently developed repetitive active training therapies provide additional benefit.<sup>12</sup> Bilateral arm training with rhythmic auditory cueing (BATRAC), a rehabilitation therapy based on the concept that bilateral movement permits interhemispheric facilitation of the limbs,<sup>13</sup> is one such intervention. We previously showed that BATRAC improves arm function in chronic stroke survivors with fixed upper extremity deficits.<sup>14</sup>

We hypothesized that BATRAC may be associated with reorganization of brain regions involved in motor control.

## METHODS

### Study Participants

This study was conducted as part of the University of Maryland School of Medicine, National Institute on Aging—Claude D. Pepper Older Americans Independence Center in collaboration with the Johns Hopkins University Division of Brain Injury Outcomes. All study participants provided informed written consent. The study was approved by the ethics committees of the participating institutions (the University of Maryland School of Medicine, the Baltimore Veterans Affairs Medical Center, and the Johns Hopkins University School of Medicine).

Eligible participants had residual upper extremity spastic hemiparesis following a single cortical or subcortical ischemic stroke. All patients had the ability to move the affected limb (at least partial range antigravity movement) and had completed 3 to 6 months of conventional rehabilitation therapy. Inclusion criteria were adequate language and neurocognitive function to understand instructions. Patients with multiple clinical strokes, a history of other neurological disease, chronic pain, or emotional disorders were excluded.

This article reports findings from a substudy of a larger study designed to examine the effect of BATRAC on function and the retention of functional improvement 4 months after the last

training session. Participants in the larger study were randomized to receive either BATRAC or the control intervention (dose-matched therapeutic exercises [DMTE]) using a stratified block allocation scheme (variable block size, allocation ratio 1:1). All participants included in the larger study were entered into the functional magnetic resonance imaging (fMRI) substudy if they were eligible to undergo MRI (absence of metal implants and claustrophobia). When the fMRI substudy was designed, we were unable to estimate the sample size needed; we knew of no data that could be used to estimate the fMRI activation changes brought about by the BATRAC intervention. We chose to analyze our data at this time based on recent fMRI studies from our group<sup>7,15,16</sup> that indicate that a sample size of approximately 10 patients per group is sufficient to show fMRI activation changes. Data were collected between 2001 and 2004.

The investigators performing training or analyses of fMRI and functional data were blinded to group assignment. Patients were aware of the differences in treatment but were not specifically aware that one treatment was a control because neither the consent forms nor verbal explanations referred to DMTE as a control treatment. Thus, patients could reasonably expect an improvement regardless of treatment group. Baseline fMRI data from 13 patients in the current sample were reported as part of another study.<sup>7</sup>

### Training and Physical Therapy

BATRAC training consisted of hour-long therapy sessions (four 5-minute movement periods interspersed with 10-minute rest periods) 3 times per week for 6 weeks. Upon auditory cues at individually determined rates of 0.67 to 0.97 Hz, participants pushed and pulled bilaterally, in synchrony or alternation, 2 T-bar handles sliding in the transverse plane.<sup>14</sup> DMTE was based on neurodevelopmental principles<sup>17</sup> and included thoracic spine mobilization, scapular mobilization, weight bearing with the paretic arm, and opening a closed fist. DMTEs were administered

in standardized format equal to the time used for BATRAC.

### Outcome Assessment

Within 2 weeks before and after BATRAC or DMTE, patients underwent fMRI of nonparetic and paretic elbow movement, electromyography of biceps and deltoid muscles during elbow movement, and a battery of arm function tests.

**Functional Magnetic Resonance Imaging.** Scanning was performed at the Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Md. Before fMRI scanning, there was a 5-minute period of accommodation to the scanning environment when several cycles of arm movement were performed. A total of 60 coronal blood oxygenation–level dependent (BOLD) weighted scans (echo planar imaging; repetition time, 3 seconds; echo time, 40 milliseconds; slice thickness, 5 mm; 30 scans) covering the entire brain were acquired to access brain activation first from the nonparetic arm and then from the paretic arm. The 60 scans were obtained during 3 cycles of rest (10 images) followed by arm movement (10 images). During imaging, the arm was strapped to a device that limited the movement to a single plane and a defined range of motion. Flexion began at 45° relative to the standard anatomical position, ending at 60° to 75°, and was followed by extension. The range was selected by adjusting the end position according to the patient's movement ability. It was held constant for all tests on an individual patient. Movement was performed in response to a beep given via headsets once every 3 seconds.

The participants kept their eyes closed during scanning. Video monitoring and taping with 2 cameras (one focused on the head, the other on the elbows) allowed us to assess compliance with the requested movement, any mirror movement of the opposite limb, and head motion. No patient showed any overt head movements in these recordings.

A T1-weighted image set was acquired for anatomical localization (3D-MPRAGE sequence; resolution,

1 × 1 × 1 mm<sup>3</sup>). Data from fMRI were processed using the BrainVoyager Software (Brain Innovation BV, Maastricht, the Netherlands). Images were corrected for minimal head motion and changes in image intensity. To allow analyses across individuals, each patient's image set was normalized to the Talairach coordinate space by applying translation, rotation, and scaling in 12 subvolumes. The subvolumes were defined by the Talairach landmarks, anterior and posterior commissures, rostral, caudal, ventral, dorsal, and lateral boundaries of the brain (reference points were selected manually). To facilitate image analyses, all image data from patients with left-sided lesions were flipped about the mid-sagittal plane, such that the affected hemisphere was always the right hemisphere. When combining individual images to obtain a composite functional map, image data were smoothed using a full width-half maximum algorithm with a kernel of 8 mm.

Statistical analysis to identify activated voxels was performed using standard linear regression methods (boxcar design with hemodynamic response modification, independent variable: elbow motion vs rest).<sup>18</sup> Uniform probability thresholds commonly used in comparable studies<sup>6,8</sup> were applied when identifying activated voxels (individual patient:  $P < .001$ , uncorrected for multiple comparisons; composite image maps of multiple patients:  $P < .05$  with Bonferroni correction).

The number of activated voxels in 9 regions of interest was automatically determined using software we developed using Matlab (Mathworks Inc, Natick, Mass). The 9 regions of interest were selected by manually identifying the following anatomical landmarks: medial part of the precentral gyrus, lateral part of the precentral gyrus, postcentral gyrus, cerebellar hemispheres, supramarginal gyrus, supplementary motor area (caudal supplementary motor area between medial precentral gyrus and a coronal plane through the anterior commissure<sup>19</sup>), and superior, middle, and inferior frontal gyri.

Difference maps identifying voxels activated after, but not before, the intervention were constructed for each patient<sup>7,20</sup> and were combined into composite maps by treatment group (BATRAC and DMTE).

**Motor Function.** Upper extremity motor function was measured with the upper-extremity portion of the Fugl-Meyer Motor Performance Test<sup>21</sup> and the Wolf Motor Arm Test<sup>22</sup> (WMAT), during which Wolf time and Wolf weight were measured, and the University of Maryland Arm Questionnaire for Stroke<sup>14</sup> (UMAQS). Additionally, we used dynamometry to measure elbow and shoulder strength (peak force in 3 consecutive trials). The Fugl-Meyer test assesses the ability to isolate movements at each joint and the influence of unwanted synergies on movement. Although there are no published cutoffs, based on our observations patients who are severely impaired score below 25, and those who are moderately impaired score between 26 and 50 out of 66. The WMAT measures functional ability. The Wolf time is the mean time required to perform 14 functional tasks with the paretic arm and hand. Maximum Wolf time is 120 seconds; moderate and severe impairment results in times above 80 and 120 seconds, respectively (S.M.-W., S. Harding, J.W., unpublished data, 2004). The Wolf weight assesses functional strength as the weight that the paretic arm can lift. Moderate and severe impairment correspond to 1 to 2 and 0 kg, respectively. The UMAQS is a self-reported questionnaire that assesses the daily use of the paretic arm in accomplishing activities of daily living on the basis of a 5-point ordinal scale. Moderate and severe impairment correspond to below 35 and 25 out of 50, respectively.

**Electromyography.** To screen for co-contraction or mirror movement of the unimpaired limb, biceps and deltoid activity were recorded bilaterally from surface electrodes while the patient isometrically contracted the hemiparetic limb with either low (force needed to oppose gravity) or maximal force. Elec-

tromyographic (EMG) testing was performed within 2 weeks of each fMRI examination. A *synkinesia index* was computed based on root mean square (RMS) amplitudes:

$$\frac{[(\text{RMS}_{\text{paretic}} - \text{RMS}_{\text{nonparetic}}) / (\text{RMS}_{\text{paretic}} + \text{RMS}_{\text{nonparetic}})]}{}$$

### Statistical Analysis

A series of 6 unpaired *t* tests was used to compare the changes (value after treatment minus baseline) in functional outcome following BATRAC vs DMTE. A comparison of the changes in brain activation induced by BATRAC vs DMTE was performed using repeated-measures analysis of variance (proc MIXED with a REPEATED statement, SAS version 9.1; SAS Institute Inc, Cary, NC).

Separate analyses were performed for the paretic and nonparetic arms. This analysis was designed to test for differences in activation between the arms. Change (value after treatment minus baseline) in volume of brain activation (voxels) was the dependent variable; independent variables included voxel count at baseline, side of brain from which voxel count was obtained (ipsilesional vs contralesional), area of brain scanned (cerebellum, supplementary motor area, and inferior frontal, mid frontal, postcentral, precentral [medial part], precentral [lateral part], superior frontal, and supramarginal gyri), and treatment (BATRAC vs DMTE).

In addition to these main effects, all 2-way and all 3-way interactions (except those including initial voxel count) were included in the model. All 3-way interactions were nonsignificant and were dropped from the models. Because the cerebral cortex is interconnected with the contralateral cerebellum, the designations ipsilesional and contralesional were flipped for the data obtained from the cerebellum to allow for an analysis of activation changes in corticocerebellar networks.  $P \leq .05$  was considered statistically significant.

Akaike information criterion and Schwarz's Bayesian information crite-

rion were used to choose among the 3 covariance structures (none, unstructured, and compound symmetry) used to account for the serial autocorrelation among observations from the same individual. All patients included in the

analyses completed either the 6-week BATRAC or 6-week DMTE interventions.

**RESULTS**

**Baseline Characteristics**

Twenty-six patients were enrolled after a single cortical or subcortical ischemic stroke. Initially, 11 and 15 patients were randomized to BATRAC and control (DMTE) groups, respectively. Four patients (1 in the BATRAC group and 3 in the DMTE group) discontinued the intervention and 1 BATRAC patient cancelled baseline MRI due to claustrophobia, leaving 9 patients in the BATRAC group and 12 in the DMTE group for analysis (12 men and 9 women; mean [SD] age, 61.5 [12.6] years) a median (interquartile range [IQR]) of 50.3 (34.8-77.3) months (range, 10 months-39 years) after stroke (FIGURE 1). There were no significant differences between BATRAC and DMTE groups with respect to age, time since stroke, or baseline functional scores. There were more women in the DMTE group (TABLE 1).

**Brain Activation**

At baseline, there was no difference between voxel counts in the BATRAC and DMTE groups (mean [SE] within-person difference, 11 [114],  $P = .92$ ).

Movement of the paretic arm, but not the unaffected arm, resulted in differential change in the activation of brain regions according to treatment group (treatment group  $\times$  brain area interaction,  $P = .03$  in the paretic arm and  $P = .19$  in the non-paring arm; TABLE 2). In the paretic arm, for BATRAC significant changes in the number of activated voxels were seen in the cerebellum, the postcentral, and the precentral gyri (medial and lateral parts) (TABLE 3). The changes in the cerebellum and medial precentral gyrus remained significant after adjustment for multiple comparisons (critical Bonferroni for 9 comparisons,  $0.05/9$ ;  $P = .006$ ) and were different from the changes in the DMTE group.

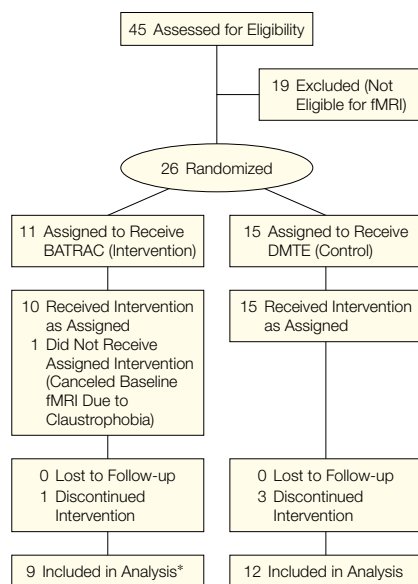
There was a suggestion of differential lateralization of brain activation with movement of the paretic arm but not the nonparetic arm (treatment group  $\times$  side of brain,  $P = .06$  for paretic arm and  $P = .99$  for nonparetic arm; Table 2). Movement of the paretic arm in the BATRAC group led to a significant increase in the activation in the contralesional hemisphere ( $P = .009$ ; Table 3) without any change in the ipsilesional hemisphere (because of the data coding, "contralesional cerebrum and ipsilesional cerebellum"). In the control group, there were no significant changes in the activation of either side of the brain.

The activation maps representing the difference between postintervention and baseline time points visually confirmed significant activation changes in the BATRAC group but not in the DMTE group (FIGURE 2). Six of 9 patients in the BATRAC group showed recruitment of precentral regions (primary motor cortex and premotor area) with and without the postcentral gyri (FIGURE 3). The remaining 3 patients demonstrated no change in activation of precentral, postcentral, premotor areas (Figure 3), and cerebellum (data not shown).

**Mirror Limb Cocontraction**

To determine if changes in contralesional activation patterns were due to involuntary cocontraction in the non-

**Figure 1.** Participant Flow Through the Trial



BATRAC indicates bilateral arm training with rhythmic auditory cueing; DMTE, dose-matched therapeutic exercises; fMRI, functional magnetic resonance imaging.

\*In a secondary analysis on arm function data, 3 patients without fMRI response were excluded.

**Table 1.** Baseline Characteristics

	BATRAC (n = 9)	DMTE (n = 12)	P Value
Age, mean (SD), y	63.3 (15.3)	59.6 (10.5)	.53
Women, No. (%)	2 (22.2)	7 (58.3)	.04
Time since stroke, median (IQR), mo	75.0 (37.9-84.5)	45.5 (22.6-66.3)	.70
Time since completion of conventional rehabilitation therapy, median (IQR), mo	71.8 (33.7-81.4)	40.6 (19.2-61.6)	.71
Stroke location, No. (%)			
Cortical	6 (66.7)	6 (50)	
Subcortical	2 (22.2)	4 (33.3)	.79
Brainstem	1 (11.1)	2 (16.7)	
Left-sided stroke, No. (%)	3 (33.3)	4 (33.3)	>.99
Fugl-Meyer score, mean (SE)*	29.6 (3.5)	28.3 (2.1)	.74
Wolf time, mean (SE), s*	58.6 (10.2)	58.1 (10.0)	.98
Wolf strength, mean (SE), kg*	0.76 (0.45)	0.85 (0.36)	.87
Strength, mean (SE), kg†			
Elbow	11.2 (2.5)	7.4 (1.1)	.14
Shoulder	7.9 (1.2)	7.1 (1.3)	.67

Abbreviations: BATRAC, bilateral arm training with rhythmic auditory cueing (intervention); DMTE, dose-matched therapeutic exercises (control); IQR, interquartile range.

\*See the "Methods" section for descriptions of the Fugl-Meyer and Wolf tests.

†Measured with dynamometry (peak force in 3 consecutive trials).

paretic limb when the paretic arm was moved, the synkinesia index obtained from EMG recordings was analyzed. The index was unchanged (within-group mean [SE] baseline, 0.68 [0.06]; post-BATRAC, 0.82 [0.05]; paired *t* test with 8 *df*, *P* = .08). Additionally, continuous video recordings of elbow movement performed during fMRI scanning did not show any overt mirror movements.

**fMRI Activation and Functional Outcomes**

A comparison of the changes in functional outcome including all patients revealed no significant differences between the groups (TABLE 4). Prior to these analyses we noted that 3 BATRAC patients showed no before-after differences in fMRI activation and we analyzed the functional data with and without these 3 BATRAC patients. Excluding them, we found a significantly greater increase in Fugl-Meyer scores in the BATRAC than in the DMTE group (Table 4). The inferences concerning functional outcome were unchanged when the comparisons were performed using the non-parametric Kruskal-Wallis test.

**COMMENT**

Bilateral repetitive arm training (BATRAC) over 6 weeks induced

changes in movement-related cortical activation patterns in chronic stroke survivors, suggesting cortical reorganization. Increased recruitment was observed in sensorimotor areas of the contralesional hemisphere (precentral gyrus, postcentral gyrus) and in the ipsilesional cerebellum. In patients with such changes arm function improved, supporting our previous observation regarding BATRAC.<sup>23</sup>

Activation in the contralesional hemisphere is frequently seen acutely after stroke in patients without exposure to rehabilitation.<sup>4,5,24-28</sup> The recruitment is commonly explained by an unmasking of uncrossed corticospinal projections,<sup>2</sup> which are silent or latent in the healthy state. Serial functional im-

aging studies show that contralesional recruitment is demonstrable early after stroke and then declines as spontaneous recovery progresses.<sup>8,26,29-31</sup> The functional relevance of contralesional recruitment is unclear.<sup>2,32</sup> Temporary inhibition of the contralesional motor cortex by repetitive transcranial magnetic stimulation does not interfere with paretic hand movement.<sup>33</sup> However, the opposite is reported for contralesional premotor areas.<sup>34</sup> The presence of evoked muscle responses after stimulation of the contralesional motor cortex may occur more often in patients with poor recovery.<sup>35,36</sup> Our data suggest functional relevance to contralesional hemisphere recruitment possibly brought about by BATRAC therapy.

**Table 2.** Independent Variables Predicting Change in Activated Voxels Measured by fMRI\*

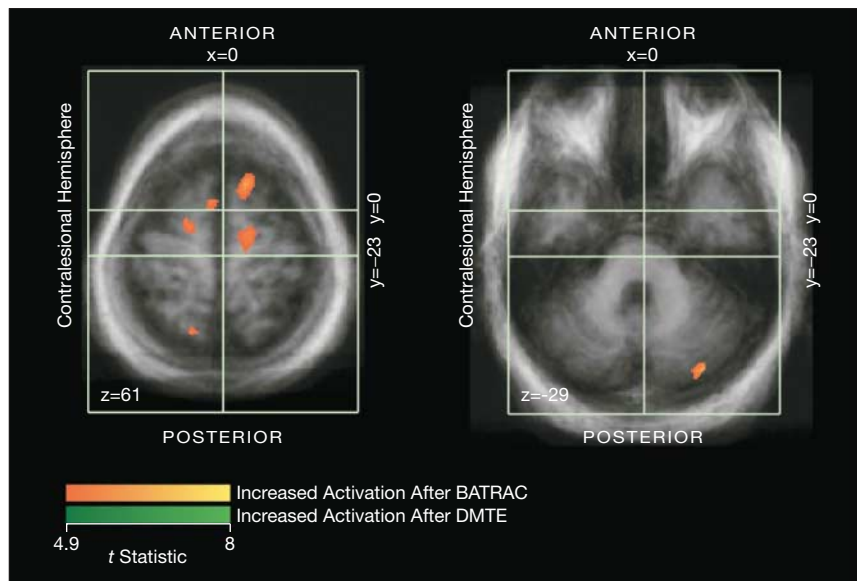
Variable	Paretic Arm		Nonparetic Arm	
	F Statistic	P Value	F Statistic	P Value
No. of voxels at baseline	F <sub>1,330</sub> = 108.7	<.001	F <sub>1,262</sub> = 89.6	<.001
Treatment group	F <sub>1,19</sub> = 2.9	.10	F <sub>1,15</sub> = 1.1	.30
Side of brain (ipsilesional vs contralesional)	F <sub>1,19</sub> = 1.70	.21	F <sub>1,15</sub> = 2.4	.14
Brain area (9 regions)†	F <sub>8,152</sub> = 3.9	<.001	F <sub>8,120</sub> = 0.9	.56
Treatment group × brain area	F <sub>8,152</sub> = 2.2	.03	F <sub>8,120</sub> = 1.4	.19
Treatment group × side of brain	F <sub>1,19</sub> = 4.1	.06	F <sub>1,15</sub> = 0	.99
Brain area × side of brain	F <sub>8,160</sub> = 0.5	.87	F <sub>8,128</sub> = 0.2	.99

Abbreviation: fMRI, functional magnetic resonance imaging.  
 \*The first model examined changes resulting from movement of the paretic arm, the second predicted change in the nonparetic arm. Estimates obtained using repeated-measures analysis of variance including data from 9 intervention and 12 control patients. See the "Methods" section for details.  
 †Cerebellar hemisphere, supplementary motor area, superior frontal, middle frontal, inferior frontal, postcentral, precentral (medial), precentral (lateral), and supramarginal gyri.

**Table 3.** Change in Activated Voxels (Posttreatment – Pretreatment) by Brain Areas and Side of Brain\*

Brain Area	BATRAC		DMTE		Difference	
	Change (SE)	P Value	Change (SE)	P Value	Mean (SE)	P Value
Cerebellum	2752.6 (520.9)	<.001	141.2 (454.6)	.70	2611.4 (691.4)	<.001
Inferior frontal	487.6 (516.3)	.32	37.7 (447.1)	.88	449.9 (683.0)	.51
Middle frontal	494.7 (516.3)	.31	-86.6 (447.1)	.90	581.4 (683.0)	.39
Postcentral	1069.1 (516.6)	.03	345.9 (447.1)	.40	723.2 (683.2)	.29
Precentral (medial)	1829.9 (516.5)	<.001	257.4 (447.1)	.52	1572.5 (683.2)	.02
Precentral (lateral)	1071.1 (516.3)	.03	255.1 (447.2)	.52	816.0 (683.0)	.23
Supplementary motor area	728.8 (516.4)	.14	-111.6 (447.1)	.86	840.5 (683.1)	.22
Superior frontal	0.9 (516.8)	.95	-104.9 (447.4)	.87	105.7 (683.5)	.88
Supramarginal	136.9 (517.3)	.75	-395.8 (448.5)	.42	532.6 (684.7)	.44
Side of brain†						
Ipsilesional	673.0 (424.7)	.13	97.1 (368.1)	.80	575.8 (562.0)	.31
Contralesional	1231.8 (424.7)	.009	-21.9 (368.2)	.95	1253.8 (562.0)	.03

Abbreviations: BATRAC, bilateral arm training with rhythmic auditory cueing (intervention); DMTE, dose-matched therapeutic exercises (control).  
 \*Model predicting change, by treatment group, in the paretic arm. Estimates were obtained using repeated-measures analysis of variance including data from 9 intervention and 12 control patients. See the "Methods" section for details.  
 †For the cerebrum, ipsilesional and contralesional have the usual meaning. For the cerebellum, the terms have been reversed to corticocerebellar networks.

**Figure 2.** fMRI Images Before and After Intervention (All Patients) During Motion of the Paretic Arm

Two axial sections at different z coordinates representing changes of activation are shown. Areas of yellow-orange indicate increased activation after bilateral arm training with rhythmic auditory cueing (BATRAC); areas of green would indicate increased activation in control patients but none were detected (probability threshold  $P < .05$ , corrected for multiple comparisons). In neither group were any areas of decreased activation identified after the intervention. Left panel, Talairach coordinates x, y, z (foci from anterior to posterior): contralateral:  $-5/4/61$  (Brodmann area [BA] 6),  $-17/-7/61$  (BA 6),  $-15/-60/61$  (BA 7); ipsilesional:  $12/14/61$  (BA 6),  $13/-13/61$  (BA 6). Right panel, ipsilesional:  $29/-77/-29$  (posterior lobe of cerebellum). DMTE indicates dose-matched therapeutic exercises (control).

These findings indicate that prior work, describing only the natural history of acute recovery, may have underestimated the role of contralesional sensorimotor cortex in recovery.

Other rehabilitation interventions that focus on the paretic limb (unilateral) are associated with reorganization in the ipsilesional cortices.<sup>37-42</sup> Constraint-induced (forced use) training, in which the nonparetic arm is restrained to enforce task-oriented exercises with the paretic limb, is one such intervention. Although the numerical analysis of voxel counts was not significant, the difference composite map of BATRAC patients—which is more sensitive to small alterations—shows activation changes in the ipsilesional hemisphere. Therefore, this study provides some evidence that BATRAC also recruits ipsilesional motor areas.

Reorganization in the cerebellum is reported to occur after constraint-induced training.<sup>42</sup> We observed a sig-

nificant increase in cerebellar activation after BATRAC. Extensive cerebellar recruitment seems to predict better hand function in stroke patients.<sup>43</sup> Cerebellar recruitment during motor cortex reorganization may occur as a consequence of pathways connecting the cerebrum to the contralateral cerebellum. Therefore, reorganization of corticocerebellar circuits involving contralesional motor cortex and ipsilesional cerebellum may be an important mechanism of BATRAC therapy.

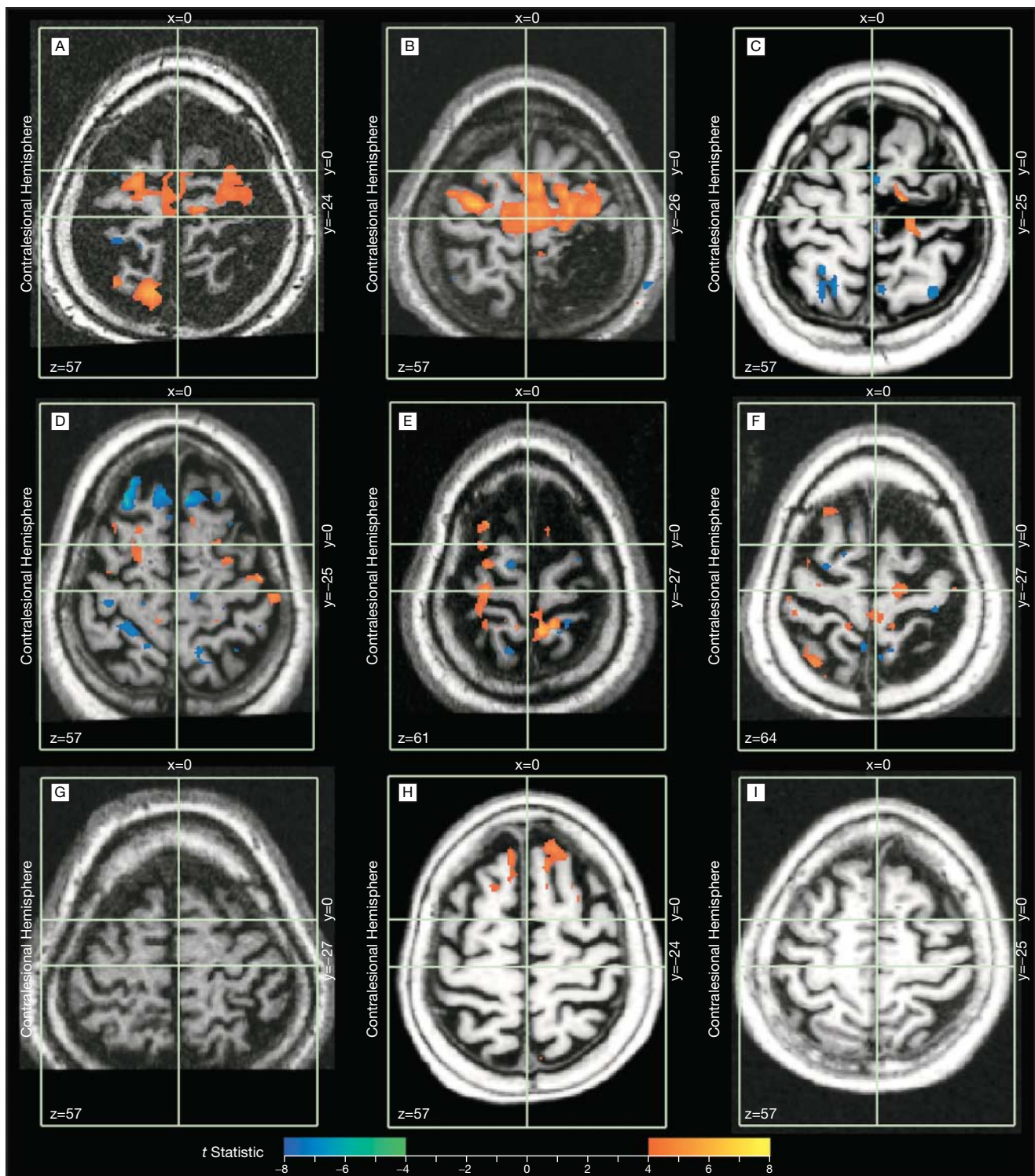
We developed the BATRAC therapy based on the concepts of bilaterality and rhythmicity. Rhythmic training improves spatiotemporal arm control when compared with nonrhythmic training.<sup>44</sup> The rationale for bilaterality is the induction of disinhibition in bihemispheric motor cortices via transcallosal projections.<sup>45</sup> During isolated voluntary movement of the paretic hand, the contralesional motor cortex imposes an abnormally high inhibi-

tory drive onto the ipsilesional cortex,<sup>46</sup> which may contribute to motor impairment.<sup>47</sup> Disinhibition may render cortex in both hemispheres more susceptible to reorganization. After reorganization has occurred (or while it is occurring), its traces are detectable by fMRI activation in response to unilateral movement.

It would be premature to speculate which feature of BATRAC—the bilaterality, rhythmicity, or intensity—is associated with cortical reorganization while DMTE is not. The intensity of elbow training was lower in the DMTE group because this intervention included time devoted to non-elbow tasks such as weight shifting of the trunk and movement of the fingers and wrist. Therefore, the number of repetitions for muscles involved in elbow flexion and extension, the movement assessed in fMRI, was less for DMTE than BATRAC and may be below the threshold to induce measurable reorganization. Additionally, DMTE was mainly based on passive movement (such as mobilization, opening a closed fist with help of the therapist), which might also be a factor contributing to the absence of cortical reorganization in this group.

We previously reported that BATRAC improves arm function.<sup>14</sup> Similarly, the current BATRAC sample (all 9 patients) showed a significant improvement in the Fugl-Meyer score in within-group analysis (12% improvement;  $P = .04$ ). This within-group effect is modest and, while larger than the effect in the DMTE group, it is not statistically different from the within-group change in the DMTE group ( $P < .26$ ). The 9 patients in whom the modest effect in BATRAC was seen included 3 patients who did not exhibit cortical reorganization and who did not improve in any of the functional measures. Based on the lack of evidence of cortical reorganization, we excluded the 3 patients from the between-group comparison and found a significant between-group effect on the Fugl-Meyer score in favor of BATRAC. This suggests that BATRAC may induce cortical reorganization, and that it does not

**Figure 3.** Functional Magnetic Resonance Images Representing the Difference in Activation in Each Patient Undergoing BATRAC



Lesions are on the right side of the brain, probability threshold  $P < .001$ , uncorrected; green-blue indicates decreased activation; yellow-orange, increased. A-F, In 6 of 9 patients, increased activation was seen in the precentral and postcentral gyri (orange-yellow). In a few cases (blue) there was decreased activation. G-I, In 3 patients there was no change in activation of precentral, postcentral, or premotor areas. BATRAC indicates bilateral arm training with rhythmic auditory cueing.

**Table 4.** Change in Arm Function (Posttreatment – Pretreatment) in Both Groups\*

Test	All Patients						Excluding 3 BATRAC Patients Not Showing fMRI Activation Changes			
	BATRAC		DMTE		Difference†		BATRAC		Difference‡	
	No.	Mean Change (SE)	No.	Mean Change (SE)	Mean (95% CI)	P Value	No.	Mean Change (SE)	Mean (95% CI)	P Value
Fugl-Meyer score	9	3.56 (1.44)	12	1.33 (1.17)	2.22 (–1.63 to 6.07)	.24	6	6.17 (0.95)	4.83 (1.02 to 8.65)	.02
Shoulder strength, kg	9	2.47 (1.65)	11	1.37 (0.43)	1.10 (–2.17 to 4.38)	.53	6	3.62 (2.35)	2.26 (–1.55 to 6.07)	.38
Elbow strength, kg	8	0.22 (1.89)	12	1.24 (0.71)	–1.02 (–4.73 to 2.7)	.63	5	1.49 (2.87)	0.25 (–4.25 to 4.75)	.94
Wolf weight, kg	9	0.23 (0.18)	12	0.39 (0.26)	–0.16 (–0.87 to 0.55)	.64	6	0.35 (0.26)	–0.04 (–0.92 to 0.83)	.92
Wolf time, s	9	–3.32 (6.29)	12	–11.09 (8.63)	7.76 (–16.07 to 31.6)	.50	6	–6.14 (9.44)	4.95 (–24.68 to 34.57)	.73
UMAQS	9	2.00 (1.4)	10	1.70 (2.11)	0.30 (–5.18 to 5.78)	.91	6	1.17 (0.65)	–0.53 (–6.56 to 5.50)	.81

Abbreviations: BATRAC, bilateral arm training with rhythmic auditory cueing (intervention); CI, confidence interval; DMTE, dose-matched therapeutic exercises (control); fMRI, functional magnetic resonance imaging; UMAQS, University of Maryland Arm Questionnaire for Stroke (measuring activities of daily living with a 5-point ordinal scale).

\*Unpaired *t* tests were used to compare the groups. An estimate of the pooled variance was used when the 2 groups had equal variance. The Satterthwaite method was used when the variances were unequal.

†Difference between all BATRAC participants vs all DMTE controls.

‡Difference between BATRAC participants (excluding 3 BATRAC participants who showed no change on brain imaging studies) vs all DMTE controls.

help every patient. In addition, the DMTE regimen may also be of some benefit (our failure to show a significant effect may be a type II error because our sample size was small), but if so, this improvement does not appear to be mediated by cortical reorganization. This is only conjecture; studies with larger sample sizes will be necessary not only to evaluate functional benefits but also to understand precisely which factors predict successful BATRAC therapy.

This preliminary study has several limitations. Because our hypothesis was that BATRAC induces brain reorganization, the sample size was chosen based on our experience analyzing fMRI data; it was therefore small to detect changes in arm function that had been demonstrated in a previous study.<sup>14</sup> Second, we do not know the optimal dose of BATRAC or the number of joints and movements that need to be practiced to maximize functional benefits, and therefore, we selected an arbitrary administration schedule. Third, to identify brain activation changes specifically related to BATRAC with its features of bilaterality and repetition, we used a dose-matched active control intervention (DMTE) as opposed to placebo treatment (giving the patient attention but no training) that may have led us to overestimate BATRAC-related activation changes. However, comparing BATRAC to DMTE may result in our un-

derestimating the effect of BATRAC on functional outcome. Our sample size does not allow us to exclude the hypothesis that DMTE may have a salutary effect on some functional outcomes. Another limitation is not having EMG tracking of mirror muscle contractions during fMRI. A change in the degree of mirror contraction or movement of the unimpaired limb during fMRI testing may account for activation changes in the contralesional hemisphere. Because EMG during fMRI is technically difficult and therefore increases patient burden (time and instrumentation), we performed only video recordings during scanning. In these recordings, no overt mirror movements were detected in any of the patients, either before or after the intervention.

## CONCLUSION

In patients with chronic motor impairment after stroke, specific bilateral repetitive upper extremity rehabilitation therapy appears to induce reorganization in bilateral, but mainly in contralesional, hemisphere networks and in cerebellum, and may operate by recruiting these brain areas to provide functional benefits. This association supports the hypothesis that BATRAC improves arm function by inducing reorganization of contralesional motor cortex networks, but it needs to be tested in future studies. The maximal

activation of these networks should be evaluated thoroughly to produce the best possible recovery after stroke.

**Author Contributions:** Drs Luft, Whitall, and Hanley had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Luft, Waller, Whitall, Macko, Goldberg, Hanley.

**Acquisition of data:** Luft, Waller, Whitall, Forrester, Hanley.

**Analysis and interpretation of data:** Luft, Macko, Sorkin, Schulz, Goldberg, Waller, Whitall, Hanley.

**Drafting of the manuscript:** Luft, Macko, Waller, Whitall, Macko, Goldberg, Hanley.

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**Administrative, technical, or material support:** Waller, Whitall, Forrester, Sorkin, Hanley.

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## CORRECTIONS

**Incorrect Wording:** In the Original Contribution entitled "Vaccination Success Rate and Reaction Profile With Diluted and Undiluted Smallpox Vaccine: A Randomized Controlled Trial" published in the September 8, 2004, issue of THE JOURNAL (2004;292:1205-1212), there was incorrect wording in a sentence. On page 1206, under Vaccine Specifics, the third sentence should read ". . . pock forming units per milliliter . . ." instead of ". . . plaque forming units per milliliter . . ."

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### Call for Submissions: Archives of Internal Medicine

The editors of the *Archives of Internal Medicine* seek artistic photographs or photographs of artwork done by *Archives* readers for reproduction on the journal's cover. Submissions must be the author's own work; work that has to do with the themes of medicine is of particular interest. Sculpture, paintings, drawings, photography, fabric art, graphic art, metalwork, crafts, computer art, depictions of medical specimens—perhaps herbs or historical artifacts—and other forms of art are acceptable as long as they can be captured in a photographic submission. No recognizable persons should appear in the image. The image may be black and white or color and at least 3.5 × 5 in (7.6 × 12.7 cm) and no larger than 8 × 10 in (20.3 × 25.4 cm). Digital photographs may be submitted via the *Archives'* Web site (<http://www.archinternmed.com>). Text of fewer than 250 words written by the artist about the work should accompany submissions.