Differential patterns of cortical reorganization following constraint-induced movement therapy during early and late period after stroke: A preliminary study

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OBJECTIVE: Constraint-induced movement therapy (CIMT) has been shown to improve upper extremity voluntary movement and change cortical movement representation after stroke. Direct comparison of the differential degree of cortical reorganization according to chronicity in stroke subjects receiving CIMT has not been performed and was the purpose of this study. We hypothesized that a higher degree of cortical reorganization would occur in the early (less than 9 months post-stroke) compared to the late group (more than 12 months post-stroke).

METHODS: 17 early and 9 late subjects were enrolled. Each subject was evaluated using transcranial magnetic stimulation (TMS) and the Wolf Motor Function Test (WMFT) and received CIMT for 2 weeks.

RESULTS: The early group showed greater improvement in WMFT compared with the late group. TMS motor maps showed persistent enlargement in both groups but the late group trended toward more enlargement. The map shifted posteriorly in the late stroke group. The main limitation was the small number of TMS measures that could be acquired due to high motor thresholds, particularly in the late group.

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CONCLUSION: CIMT appears to lead to greater improvement in motor function in the early phase after stroke. Greater cortical reorganization in map size and position occurred in the late group in comparison.

SIGNIFICANCE: The contrast between larger functional gains in the early group vs larger map changes in the late group may indicate that mechanisms of recovery change over the several months following stroke or that map changes are a time-dependent epiphenomenon.

Keywords: Plasticity, recovery, transcranial magnetic stimulation, upper extremity, motor

1. Introduction

Stroke continues to be a major public health concern in the United States, particularly as a cause of disability (Rosamond et al., 2008). However, the mature brain’s ability to reorganize motor representation in response to novel external and/or internal demands may help diminish impairment after stroke (Hallett, 2001; Klein & Jones, 2008; Nudo, 2003). This plasticity is thought of as an enduring morphological and functional change in neuronal properties (Klein & Jones, 2008; Nudo, 2003), which can occur via modification of synaptic strength, axonal sprouting, and altered synaptic activation (Hallett et al., 1993; Kaas, 1991; Nudo, 2003; Pascual-Leone & Torres, 1993). Related research has focused on translating this knowledge to novel rehabilitative approaches that optimize functional recovery after stroke. For example, a series of studies has provided evidence that constraint-induced movement therapy (CIMT) improves motor recovery after stroke. CIMT originated from studies of forearm deafferentation in non-human primates (Taub & Wolf, 1997). CIMT for recovery after stroke consists of restraining the less-affected arm with a mitt for 90% of waking hours for 2-3 weeks, during which time participants engage in daily repetitive and mass practice of sensorimotor tasks. Several small-scale studies applying CIMT in the early (Alberts et al., 2004, Blanton & Wolf, 1999; Dromerick et al., 2000; Page et al., 2005; Ro et al., 2006) or late (Bonifer et al., 2005; Liepert et al., 1998; Milner et al., 1999; Wittenberg et al., 2003) phase after stroke have reported superior results compared with standard rehabilitative methods. A large multi-center trial enrolling 222 subjects who had predominantly ischemic strokes within the previous 3 to 9 months (i.e., the Extremity Constraint Induced Therapy Evaluation [EXCITE] trial) has shown statistically significant and clinically relevant improvements in the motor ability and use of the paretic arm compared with participants receiving usual and customary care (Wolf et al., 2006, 2008). Subjects receiving CIMT within 3 to 9 months post-stroke had greater improvement in motor function compared to subjects receiving identical intervention later than 12 months post-stroke. However, there was no statistical difference in motor function between the 2 groups after 24 months (Wolf et al., 2010).

Current research demonstrates that motor cortical activation and motor recovery after stroke are dynamic processes that depend on the time elapsed from the stroke, motor functional level, site, and size of the lesion (Carey et al., 2006; Foltys et al., 2003; Marshall et al., 2000; Rossini et al., 2003). Previous studies applying CIMT in the late phase of stroke recovery have demonstrated expansion of motor maps as measured by transcranial magnetic stimulation (TMS) (Liepert et al., 2001; Wittenberg et al., 2003). We also demonstrated an increase in motor map size with early phase CIMT compared to the group receiving usual and customary care (Sawaki et al., 2008a). TMS has been used extensively in humans to evaluate brain reorganization associated with simple motor training (Classen et al., 1998; Kaelin-Lang et al., 2005; Sawaki et al., 2003b), motor skill acquisition (Pascual-Leone et al., 1993, 1995), and peripheral (Roricht et al., 1999; Ziemann et al., 1998) or central lesions (Bastings et al., 2002; Liepert et al., 1998; Wittenberg et al., 2003). Because the effect of time after stroke (chronicity) on this type of plastic change has not been thoroughly investigated, we tested the hypothesis that participants early after stroke (3 to 9 months post-stroke) receiving 2 weeks of CIMT would show an increased TMS motor map volume in the ipsilesional primary motor cortex compared with participants receiving the identical intervention late after stroke (more than 12 months post-stroke). We further hypothesized that this increase would persist at the 4-month follow-up. We expected that the degree of map expansion would be positively correlated with improvement in upper extremity motor function.
2. Methods

2.1. Participants

Inclusion criteria were identical to those of the EXCITE trial (Wolf et al., 2006, 2008); and some of the participants of the present study were also enrolled in EXCITE. Briefly, active movement in the paretic arm had to include at least 20 degrees of wrist extension and 10 degrees of extension at the thumb and 2 other digits (Wolf et al., 2006, 2008). To ensure the safe use of TMS and to minimize potential confounding variables, exclusion criteria included: a) a history of seizures, alcohol or drug abuse, psychiatric illness, and/or head injury; b) cognitive deficits severe enough to preclude informed consent; c) a positive pregnancy test or being of childbearing age and not using appropriate contraception; d) ferromagnetic material in the cranium; and e) cardiac or neural pacemakers. After a careful screening process, 17 early participants (3 to 9 months post stroke; age ± SEM: 54.4 ± 3.8) and 9 late participants (more than 12 months post-stroke; age ± SEM: 57.6 ± 3.8) were found eligible for this study. Each individual participant gave informed consent. The protocol was approved by the Institutional Review Boards at each participating site (Wake Forest University, Emory University, and The Ohio State University).

2.2. Study design

Each subject participated in 10 consecutive weekdays of CIMT-based, intensive upper extremity therapy, during which time he/she donned a padded mitt covering the non-paretic hand. The mitt was also worn for at least 90% of waking hours over the 2-week period, including 2 weekends (Wolf et al., 2006, 2008). Treatment focused on unimanual skill acquisition and functional retraining and was based on the principles of intensive task-oriented training (Lawrence, 1980; Taub et al., 1994) that can also be described in terms of motor learning (Kleim & Jones, 2001, Schmidt 1999, Winstein, 1991). Tasks emphasized grasp as well as manipulation and release of objects. Participants also performed general activities related to daily living and fine motor coordination. Task difficulty was progressively increased by using a training strategy in which targets for motor ability goals were kept just beyond the level of performance already achieved (Wolf et al., 2006).

2.3. Outcome measures

Wolf Motor Function Test (WMFT). The WMFT was chosen as the primary clinical outcome measure (Wolf et al., 2001, 2006) and was performed by blinded evaluators at all sites. This test encompasses a battery of 15 time-based tasks and 2 force-based tasks (item 7: lift weight and item 14: grip strength). The WMFT has established reliability and validity and has been used extensively to evaluate upper extremity motor function in CIMT trials (Wolf et al., 2006).

Neurophysiological assessment (TMS). Comparability of TMS data collection techniques across all 3 sites was ensured prior to enrollment of participants. After each institutional research team completed intensive training for TMS data acquisition, data from 2 healthy volunteers and 2 participants with late stroke were acquired at each site. Additionally, 1 healthy volunteer (GW) was tested at the 3 sites to ensure reproducibility. Testing was conducted on 3 occasions (at baseline, at 2 weeks upon completion of intervention, and at 4-month follow-up). Bipolar adhesive monitoring electrodes (H59P, Kendall soft™, Chicopee, MA) were placed over the belly of the extensor digitorum communis (EDC) muscle bilaterally, with the reference electrode placed proximally and inter-electrode distance of approximately 1.5 cm (Wolf et al., 2004). To ensure reproducibility across sites, similar equipment and techniques were used at all three sites. The EDC muscle was selected as the target muscle because it is the primary effector of finger extension, which is one of the minimal motor criteria for inclusion in the study. A template was created for each subject at baseline using a sheet of polyester film to guarantee reproducibility of electrode placements at different time points. Any volume conduction of motor-evoked potentials (MEPs) from neighboring muscles would most likely capture functionally-related wrist extensor activity (Wolf et al., 2004). The electromyographic (EMG) signals were amplified and filtered (band-pass 30 Hz to 1 kHz) using an isolated bioelectric amplifier (James Long Co., Caroga Lake, NY) and fed into a laboratory computer for off-line analysis. Auditory feedback of EMG was used to ensure quiescence of target muscle activity prior to stimulation. TMS was delivered using a Magstim 200 stimulator with a figure-eight coil (Magstim, Whitland, Dyfed, UK). The coil handle was pointed in a posterior direction, yielding approximately posterior-to-anterior current flow across the central sulcus (Brasil-Neto et al., 1992, Kobayashi and Pascual-Leone, 2003) and allowing consistent posi-
tions, the center of gravity is calculated by

\[ \text{Center of gravity mapping:} \text{ The center of gravity (COG) is an estimate of the center of the motor map and is an average of all active location vectors, each weighted by the MEP amplitude at that location (Wassermann et al., 1992). If there are } n \text{ locations, the center of gravity is calculated by } \frac{\sum_{i=1}^{n} (x_i + n \text{MEPs})/n \text{MEVs for the } x \text{ coordinate (COG } x) \text{ and similarly for the y coordinate (COG } y) (Liepert et al., 1998).} \]

\[ \text{Recruitment curves:} \text{ To study changes in cortical excitability in a range relevant to map acquisition, limited recruitment (stimulus-response) curve (RC) measurements were performed (Devanne et al., 1997).} \]

The coil was kept at the hot-spot of the EDC muscle.

The stimulus intensity was increased in 10% steps between 90 and 150% of rMT, and 10 MEPs were recorded at each stimulus intensity. The silent period (SP) is a measure of cortical inhibition that can be measured using a single stimulator (Rossini et al., 1994; Rothwell, 1991). Stimulation was delivered at 150% of aMT during active contraction of the EDC muscle. Five SPs were recorded, and the post-stimulus analysis time was 500 ms (Inghilleri et al., 1993). Duration of SP were visually measured and averaged; trials without consistent background EMG activity were discarded (Chen et al., 1999).

2.4. Data analyses

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and Prism (Graphpad, La Jolla, CA). Statistical analyses were conducted on performance assessment (log WMFT) outcomes (for both paretic and non-paretic sides) and TMS measures (rMT, aMT, nMV, COG x, COG y, RC, and SP for both hemispheres). We compared baseline measures for the two groups (early vs late). The normality of each measure was assessed using the Kolmogorov-Smirnov test. Because of the skewed distribution of the WMFT, a logarithmic transformation was performed on the 15 time-based WMFT measures (Wolf et al., 2005). Student t-tests were used to compare normally distributed measures (either before or after transformations). Transformations did not correct non-normality of aMT, SP, and COG y of the less-affected side; therefore, the non-parametric Wilcoxon rank-sums test was used for these three measures to make comparisons between groups. An analysis of variance (ANOVA) model with repeated measures was fitted to each dependent variable, in order to evaluate group (early vs late) and visit (2-weeks and 4-month) main effects, adjusting for baseline values by including the baseline as a covariate in the model. The interaction effect between group and visit was also included in the initial model. If the interaction was not significant at the level of 0.05, then it was removed from the final model. For all tests, significance level was set at 0.05. The trends for map volume and recruitment curve slope over time were analyzed by least squares regression and group differences analyzed by between-group t-tests.

3. Results

Wolf/Motor Function Test (WMFT): At baseline testing with WMFT, there was no significant difference for
Fig. 1. Effect of constraint-induced motor therapy (CIMT) on Wolf Motor Function Test (WMFT) collected at baseline, at 2 weeks (i.e., completion of intervention), and at 4-month follow-up. A: Log mean of time-based evaluations (scores indicate time to complete tasks; smaller scores indicate greater improvement). Time-based measures in early group showed significant improvement compared with the late group immediately after CIMT ($P = 0.02$). B: Mean of force-based measure (lift weight lb; higher scores indicate more weight lifted). C: Mean of force-based measure (grip strength kg; higher scores indicate more grip strength). Note that both early (solid dots) and late (open dots) stroke groups showed improvement in all performance measures at 2 weeks and at 4-month follow-up. Data are expressed as mean ± SE.

Time- and force-based measures between groups. Both groups improved on time- and force-based measures on the paretic side immediately after CIMT after adjustment for baseline measure; however, the early group showed significantly more improvement on time-based measures ($P = 0.02$, Fig. 1A). At 4-month follow-up, time-based measures showed slightly but significantly slower performances compared with measurements taken immediately after CIMT in early participants ($P = 0.03$, Fig. 1A). The force-based measures (i.e., grip strength and weight lifted) tended to reflect greater improvement in the early than in the late group, but these between-group differences were not statistically significant (Fig. 1B and C). There was no significant difference for time- and force-based measures between groups at 4-month follow-up. Time- and force-based measures remained stable on the less-affected side following the 2-week intervention (Table 1).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>ln meanWFMT (baseline)</td>
<td>0.36 ± 0.04</td>
<td>0.42 ± 0.07</td>
</tr>
<tr>
<td>ln meanWFMT (2-week)</td>
<td>0.32 ± 0.43</td>
<td>0.39 ± 0.09</td>
</tr>
<tr>
<td>ln meanWFMT (4-month)</td>
<td>0.42 ± 0.07</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td>Lift lb (baseline)</td>
<td>17.21 ± 1.01</td>
<td>16.27 ± 1.85</td>
</tr>
<tr>
<td>Lift (2-week)</td>
<td>17.67 ± 0.74</td>
<td>17.00 ± 1.41</td>
</tr>
<tr>
<td>Lift (4-month)</td>
<td>17.53 ± 0.90</td>
<td>18.67 ± 1.21</td>
</tr>
<tr>
<td>Grip Kg (baseline)</td>
<td>30.41 ± 2.81</td>
<td>31.05 ± 3.05</td>
</tr>
<tr>
<td>Grip (2-week)</td>
<td>32.70 ± 2.56</td>
<td>29.60 ± 3.16</td>
</tr>
<tr>
<td>Grip (4-month)</td>
<td>31.99 ± 3.95</td>
<td>28.16 ± 2.17</td>
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Natural Log (ln) Mean of 15 time-based measures and force-based subtests (7 Lift and 14 Grip) collected at baseline, after 2 weeks and at 4-month follow-up. Data are expressed as mean ± SE.

Neurophysiological findings – Ipsilesional hemisphere: No significant between-group differences for TMS measures were found at baseline. An illustration
Fig. 2. Longitudinal changes in motor map volume (A), center of gravity (COG) x (B), and COG y (C) on the ipsilesional hemisphere. Note that both early (solid dots) and late (open dots) stroke groups exhibit increased map volume after 2 weeks and at 4-month follow-up. There is, however, a significantly further posterior shift of COG y from its position at 2 weeks to its position at 4-month follow-up for the late group as compared with that of the early group (Fig. 2C, \( P = 0.01 \)). Additionally, there is a significant difference between COG y of the early versus the late group at 4-month follow-up (Fig. 2C, \( P = 0.02 \)), suggesting a differential pattern of reorganization between the groups.

of these longitudinal changes in TMS motor map volume and location in 2 representative participants is shown in Fig. 3. Both groups had a non-significant trend towards an increased TMS motor map volume of the EDC at 4-month follow-up, but no significant difference in EDC map volume changes was found between the groups at any interval (Fig. 2A). The slope of the trend line for change in map volume over time was negative, on average, in the early group, but positive in the late group, with the difference almost reaching statistical significance (\( p = 0.06 \)). No significant differences were found over time in rMT, aMT and SP in the ipsilesional hemisphere (Table 2). Also, no significant changes were found in RC plots, over time those changes were in opposite directions (Fig. 4). The early group appears to show decreasing excitability in the ipsilesional hemisphere over time while the late group had very little change, but increased overall.

**COG position:** After adjusting for differences in baseline measures, no significant shift was observed in the ipsilesional COG x direction for either group (Fig. 2A). On the other hand, ipsilesional COG y at the 4-month follow-up showed significant differences: 1) in the late group, there was a posterior shift compared with measurements taken immediately after CIMT (\( P = 0.02 \)); and 2) there was a between-group difference, with the late group more posterior than the early group (Fig. 2C, \( P = 0.01 \)). The pattern overall was of little change in COG in the early group and a posterior-lateral shift in the late group.

**Contralesional hemisphere:** Baseline TMS measures of the contralesional hemisphere differed significantly between groups only with regard to map position: COG y for the early group was more anterior (mean ± SE, 2.76 ± 2.28) compared with COG y for the late group (mean ± SE, 0.68 ± 0.33) (\( p = 0.01 \), Table 3). Other TMS measures including rMT, aMT and SP were stable over time and did not differ significantly between groups (Table 3). There was no significant difference between the 2 groups in RC over time. However, the late group appeared to exhibit a higher degree of excitability in response to TMS compared to the early group.
Fig. 3. Longitudinal changes in motor map volume of 2 representative participants. The grid size is 1 cm, and (0,0) is Cz in the 10–20 EEG system. Motor responses at each scalp position are shade-coded by MEP size (relative to the maximal response). Increased motor map volume of ipsilesional hemisphere was observed in both an early subject (top diagrams) and a late subject (bottom diagrams) over a 4-month period. The 4-month follow-up for the late subject showed a significantly posterior shift of the motor map.

Table 2

Measures of the ipsilesional hemisphere in the 2 treatment groups

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<thead>
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<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>rMT (baseline)</td>
<td>64.54 ± 5.62</td>
<td>55.33 ± 5.68</td>
</tr>
<tr>
<td>rMT (2-week)</td>
<td>62.54 ± 4.45</td>
<td>63.40 ± 7.86</td>
</tr>
<tr>
<td>rMT (4-month)</td>
<td>62.00 ± 4.82</td>
<td>52.70 ± 6.95</td>
</tr>
<tr>
<td>aMT (baseline)</td>
<td>58.08 ± 5.94</td>
<td>47.80 ± 4.81</td>
</tr>
<tr>
<td>aMT (2-week)</td>
<td>52.73 ± 5.01</td>
<td>52.50 ± 6.54</td>
</tr>
<tr>
<td>aMT (4-month)</td>
<td>52.27 ± 4.40</td>
<td>48.50 ± 7.18</td>
</tr>
<tr>
<td>SP (baseline)</td>
<td>139.69 ± 10.52</td>
<td>166.49 ± 14.25</td>
</tr>
<tr>
<td>SP (2-week)</td>
<td>154.95 ± 9.46</td>
<td>165.72 ± 19.59</td>
</tr>
<tr>
<td>SP (4-month)</td>
<td>168.19 ± 24.70</td>
<td>177.41 ± 24.52</td>
</tr>
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</table>

Resting motor threshold (rMT), active motor threshold (aMT), and silent period (SP) collected in the extensor digitorum communis (EDC) muscle of the more-affected forearm at baseline (1), after 2 weeks (2), and at a 4-month follow-up (3). Data are expressed as mean ± SE.

Correlation of changes with chronicity: We found a significant correlation between changes in log WMFT and time after stroke, with early time after stroke associated with more decrease in WMFT (F = 10.446, P = 0.01). No significant correlation was found between measures of changes in motor performance (WMFT) and TMS motor map volume (F = 0.181, P = 0.67). No significant correlation was found between changes in TMS map (F = 0.355, P = 0.56), or changes in COG x (F = 2.644, P = 0.12) and chronicity. Recruitment curve slope change was not associated with map volume change (Figs. 5 and 6).

4. Discussion

The goal of this study was to investigate differential patterns of cortical reorganization underlying improved motor function following CIMT during early and late periods after stroke. The results provide evidence that map expansion of the cortical representation of a hand muscle is a consistent phenomenon in both early and late groups while other measurable changes of excitability and inhibition remain stable. However, the therapy-induced cortical reorganization of late stroke participants appears to be greater, as evidenced by a larger posterior shift in motor maps and a more dramatic increase in map size, contrary to our hypothesis.

As noted previously, extensive precedent exists for the use of TMS to measure cortical reorganization underlying improved motor function in humans. For example, Bastings et al. evaluated 12 participants with late stroke and demonstrated that those with
good recovery had larger TMS motor maps recorded from the first dorsal interosseous muscle in the ipsilesional hemisphere when compared with age-matched healthy volunteers (Bastings et al., 2002). Liepert et al. demonstrated expansion of TMS motor maps generated for thenar muscles in people with late stroke receiving CIMT (Liepert et al., 1998). This motor map expansion may be the human correlate of similar expansion in motor maps after intensive motor training of non-human primates with cortical lesions. While interpretation is difficult for a single muscle’s motor map change, without knowing what happens to other muscles, map expansion may represent strengthened connectivity within the motor cortex. In another study, Wittenberg et al reported expansion of ipsilesional and decrease of contralesional TMS motor maps after CIMT in late stroke (Wittenberg et al., 2003). More recently, we demonstrated in the first multicenter trial of CIMT that such therapy can produce statistically significant enlargement of ipsilesional TMS motor maps that persists for at least 4 months in early stroke participants compared with participants receiving standard care (Sawaki et al., 2008b). Note that reanalysis of this data for individual trend over time demonstrated a mean trend that is actually negative, despite the group’s average map size increasing slightly but significantly at each time point.

In the present study, there was a marked improvement in motor function immediately after CIMT in early stroke participants, with a lesser degree of improvement for late stroke participants. Furthermore, contrary to our initial hypothesis, enlargement of the ipsilesional TMS-evoked motor map volume showed no statistically significant differences between early and late groups. However, map volume still nearly doubled for the late group between baseline and 4-month follow-up, with a less notable expansion apparent for the early group and a negative mean trend over time. This negative trend is only in the analysis of the regression line for individual map size over time. This trend of relatively larger functional gains in the early group vs larger map expansion in the late group implies that the role of map expansion as an index of motor recovery may differ according to time elapsed since stroke and is not tightly linked to function. Map size may continue to shrink for several months after stroke, so that earlier intervention affects a map that has not yet fully regressed. Additionally, posterior shift of the COG was signifi-
Table 3

<table>
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<tr>
<th></th>
<th>Early</th>
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<tbody>
<tr>
<td>rMT (baseline)</td>
<td>52.06 ± 3.16</td>
<td>44.22 ± 3.97</td>
</tr>
<tr>
<td>rMT (2-week)</td>
<td>51.31 ± 2.69</td>
<td>44.88 ± 3.05</td>
</tr>
<tr>
<td>rMT (4-month)</td>
<td>52.44 ± 2.52</td>
<td>45.50 ± 2.80</td>
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<tr>
<td>aMT (baseline)</td>
<td>45.28 ± 3.72</td>
<td>36.63 ± 2.99</td>
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<tr>
<td>aMT (2-week)</td>
<td>42.00 ± 2.96</td>
<td>38.83 ± 4.37</td>
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<tr>
<td>aMT (4-month)</td>
<td>45.69 ± 3.02</td>
<td>39.83 ± 3.28</td>
</tr>
<tr>
<td>Motor map area (baseline)</td>
<td>4.87 ± 0.42</td>
<td>4.89 ± 0.86</td>
</tr>
<tr>
<td>Motor map area (2-week)</td>
<td>5.42 ± 0.54</td>
<td>5.49 ± 0.89</td>
</tr>
<tr>
<td>COG x (baseline)</td>
<td>4.62 ± 0.65</td>
<td>5.90 ± 0.46</td>
</tr>
<tr>
<td>COG y (baseline)</td>
<td>4.70 ± 0.27</td>
<td>4.70 ± 0.31</td>
</tr>
<tr>
<td>COG x (2-week)</td>
<td>4.58 ± 0.24</td>
<td>4.72 ± 0.38</td>
</tr>
<tr>
<td>COG y (2-week)</td>
<td>4.65 ± 0.26</td>
<td>4.86 ± 0.42</td>
</tr>
<tr>
<td>COG y (4-month)</td>
<td>2.76 ± 0.37</td>
<td>0.68 ± 0.34</td>
</tr>
<tr>
<td>COG y (4-month)</td>
<td>2.95 ± 0.37</td>
<td>0.26 ± 0.54</td>
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<tr>
<td>SP (baseline)</td>
<td>145.88 ± 14.68</td>
<td>148.08 ± 19.99</td>
</tr>
<tr>
<td>SP (2-week)</td>
<td>151.44 ± 20.65</td>
<td>167.89 ± 8.78</td>
</tr>
<tr>
<td>SP (4-month)</td>
<td>145.84 ± 10.72</td>
<td>162.65 ± 18.67</td>
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Resting motor threshold (rMT), active motor threshold (aMT), TMS motor map area, center of gravity for the x (COG x) and y (COG y) coordinates, and silent period (SP) collected in the extensor digitorum communis (EDC) muscle of the non-paretic forearm at baseline, after 2 weeks, and at a 4-month follow-up. Motor map area expressed in cm². Data are expressed as mean ± SE. *COG y of the contralesional hemisphere of the late group is significantly more posterior than that of the early group at baseline (p<0.01).

The ipsilateral posterior shift of the COG after CIMT in our late group is expected, given prior evidence for such shift (Calautti et al., 2003; Carey et al., 2006; Pineiro et al., 2001; Rossini et al., 1998). For instance, data from Dancause and colleagues, who used microelectrodes to record neuronal activity in adult squirrel monkeys, demonstrated major neuroanatomical reorganization of somatosensory cortical area in response to ischemic infarct to the M1 hand area (Dancause et al., 2005). In the present study, the ipsilateral posterior shift in motor map may well reflect adaptive neuroplastic change expressed as increased activation of the somatosensory cortex in addition to the motor cortex as a form of compensation after prolonged deprivation of activity. Interestingly, Barbay et al. demonstrated that early vs late motor training can yield comparable improvement in motor skills in squirrel monkeys (Barbay et al., 2006); but mechanisms underlying motor recovery associated with motor training were distinct in the acute and late stages. Using intracortical microstimulation applied to primary motor cortex (M1) hand area, the investigators demonstrated that delaying the training results in a significant decrease in the spared-hand representation compared with the early training. They concluded that timing of rehabilitative training can have a differential effect upon reorganization of movement representations in M1 after stroke (Barbay et al., 2006). Posterior shift and expansion of upper extremity motor representation appears to be a consistent finding after stroke in animal models; however, the...
Fig. 6. Ipsilesional changes in center of gravity (COG). “Change 1” denotes 2-week minus baseline; “change 2” denotes 4-month minus 2-week. No correlation was found between changes in COG x, COG y, and chronicity.

association between this shift and motor recovery in humans remains unclear.

Other findings from the present study showed that the contralesional COG y in the early group is anterior to that of the late group at baseline. The anterior localization of contralesional COG y at baseline in our early participants may indicate an early recruitment of certain cortical areas, such as within the dorsal premotor cortex, that goes on to decrease or become less prominent in later stages of recovery. Such a differential change may reflect an aspect of early spontaneous recovery, at which time contralesional dorsal premotor cortex could be more active.

The main limitation of this study is the small sample size of measurable maps in the late group, although this is somewhat mitigated by the literature on map changes in chronic stroke patients receiving CIMT. Also, while we attempted to enroll equal number of early and late stroke participants in this study, sample size was unequal in the 2 groups and could be considered as a confounding factor. At the same time changes of motor function after CIMT in our study were similar to the data reported by Wolf and colleagues in that the early group showed greater improvement compared to the late group.

In summary, comparison in change of TMS motor map and TMS physiology over time demonstrates a disparity between motor map changes and functional improvement. There is a greater sensitivity to change later after stroke, with a suggestion that maladaptive changes that occur late after stroke can be reversed by CIMT. But functional improvement with CIMT is better early (3–9 months) after stroke despite relatively small changes in motor maps.

Acknowledgments

This study was sponsored by NICHD RO1 HD-40984 and partially sponsored by the Cardinal Hill Endowment in Stroke and Spinal Cord Rehabilitation. We thank the therapists, nurses, and research assistants from all sites for invaluable work during data collection. We also extend thanks to Cheryl Carrico, MS, OT/L for help with editing.

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