Cortical Reorganization After Modified Constraint-Induced Movement Therapy in Pediatric Hemiplegic Cerebral Palsy

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Constraint-induced movement therapy improves motor function in the affected hand of children with hemiplegic cerebral palsy and results in cortical changes in adults with stroke. This study measured clinical improvement and cortical reorganization in a child with hemiplegia who underwent modified constraint-induced movement therapy for 3 weeks. Clinical, functional magnetic resonance imaging and magnetoencephalography measurements were done at baseline, after therapy, and 6 months after therapy. Modified constraint-induced movement therapy resulted in clinical improvement as measured by the Pediatric Motor Activity Log. Functional magnetic resonance imaging showed bilateral sensorimotor activation before and after therapy and a shift in the laterality index from ipsilateral to contralateral hemisphere after therapy. Magnetoencephalography showed increased cortical activation in the ipsilateral motor field and contralateral movement evoked field after therapy. Cortical reorganization was maintained at the 6-month follow-up. This is the first study to demonstrate cortical reorganization after any version of constraint-induced movement therapy in a child with hemiplegia.

Keywords: constraint-induced movement therapy; cerebral palsy; functional magnetic resonance imaging; magnetoencephalography; synthetic aperture magnetometry

Constraint therapy and modified constraint therapy may work through behavioral changes, cortical changes, or both. Small case series have found cortical changes after cerebral infarction in adult stroke patients by using functional magnetic resonance imaging (MRI) and transcranial magnetic stimulation techniques. However, such changes have not been demonstrated in children after constraint therapy or modified constraint therapy. The purpose of this study was to determine if modified constraint therapy leads to cortical reorganization in a child with hemiplegic cerebral palsy, if cortical changes are associated with clinical improvement, and if changes persist at 6-months of follow-up.

Case Report

Subject

Ethical approval for this study was obtained from Bloorview Kids Rehab and The Hospital for Sick Children, Toronto, Ontario, Canada. The parents and subject gave informed consent and assent to the study. An 8-year-old boy with congenital right hemiplegic cerebral palsy and brain MRI demonstrating left caudate nucleus infarction and left lateral ventricle dilation was enrolled. The baseline neurologic examination was consistent with right hemiplegic cerebral
palsy. The child had normal receptive language and visual acuity. The Gross Motor Functional Classification System\(^{11}\) was at level I and the Manual Ability Classification System\(^{12}\) was at level II for right hand function. The subject had not undergone botulinum toxin type A injections within 6 months of the study and had no prior exposure to constraint therapy or modified constraint therapy.

**Study Design**

Modified constraint therapy included 3 weeks of continuous casting of the unaffected arm and weekly 1-hour occupational therapy. Occupational therapy incorporated standard practice management of cerebral palsy and neurodevelopmental and biomechanical principles and aimed to meet the family’s functional goals for the child. Clinical measures, functional MRI, and magnetoencephalography were done before and after therapy and 6 months later.

**Clinical Measures**

The Pediatric Motor Activity Log was the primary clinical outcome and measured the amount of use and quality of movement of the affected limb. The tool is an adaptation of the adult Wolfe Arm Motor Ability test\(^{13}\) and has been used in previous pediatric constraint therapy studies.\(^{4}\) Other clinical measures included the Quality of Upper Extremity Skills Test,\(^{14}\) the Canadian Occupational Performance Measure,\(^{15}\) the Assisting Hand Assessment,\(^{16}\) and sphygmomanometry.

**Functional Magnetic Resonance Imaging and Magnetoencephalography**

During functional MRI and magnetoencephalography, a standardized motor task (4-finger extension/flexion) was completed for each hand with a specialized splint that provided stability, controlled amplitude, and recorded movements by using fiber optic switches (Figure 1). The amplitude of extension/flexion was determined as 75% of maximum ability at baseline and remained constant for all functional magnetic resonance imaging and magnetoencephalography measurements, despite improved motor skills after therapy, to ensure constant amplitude of movement during all sessions. The forearm was strapped into the splint to provide stability and decrease all movements except the intended finger extension/flexion. The fingers were held together with an individualized removable cast to reduce excessive movements and allow isolated extension/flexion at the metacarpo-phalangeal joints. Fiber optic recorded the presence of movements and documented full range of motion with each movement.

For magnetoencephalography, neuromagnetic activity was recorded using a whole head 151-channel CTF magnetoencephalography system (VSM MedTech Ltd, Coquitlam, BC, Canada) with a sample rate of 625 samples/s and a bandwidth of 0 to 200 Hz. Three fiducial head coils were placed on the subject and provided a reference coordinate system for the recorded magnetoencephalography. Head movement was monitored at the beginning and end of each block of trials. Data were excluded if head movement exceeded 0.5 cm. At the end of each magnetoencephalography data collection, the fiducial coil positions were replaced with MR contrast markers before each functional MRI session. This information was used for co-registration of magnetoencephalography with MRI data. The motor task was done in an event-related design for 100 consecutive trials.

**Figure 1.** The specialized splint device used to standardize the motor task during functional magnetic resonance imaging and magnetoencephalography measurements. The standardized motor task included 4-finger extension/flexion. The angles of the splint were set at 75% of the subject’s maximum extension/flexion at baseline. The angles remained constant for all functional magnetic resonance imaging and magnetoencephalography measurements, despite improved motor skills after therapy, to ensure constant amplitude of movement during all sessions. The forearm was strapped into the splint to provide stability and decrease all movements except the intended finger extension/flexion. The fingers were held together with an individualized removable cast to reduce excessive movements and allow isolated extension/flexion at the metacarpo-phalangeal joints. Fiber optic recorded the presence of movements and documented full range of motion with each movement.
Somatosensory evoked fields were recorded with median nerve stimulation using suprathreshold, constant current, square-wave pulses (3.1-Hz, 0.2-millisecond duration) delivered transcutaneously at both wrists to confirm coregistration and validate cortical activation observed in the region of the central sulcus.

**Functional Magnetic Resonance Imaging Analysis**

For functional MRI, the time course of the data at each pixel was correlated with the square-wave contrast function for motor and rest comparisons using Stimulate software (Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, Minnesota). The threshold for each correlation (r) map was achieved by setting the r value at a level such that only 1% of total activated pixels in the region of interest were displayed. A minimum cluster of 2 contiguous pixels was required. The regions of interest were the four 5-mm contiguous axial slices encompassing and adjacent to the primary motor cortex of the unaffected hemisphere and the corresponding areas in the affected hemisphere. The regions of interest did not include the anterior and posterior poles of these slices. The pixels were identified as either contralateral or ipsilateral to the hand performing the motor task. A laterality index [(contralateral − ipsilateral)/(contralateral + ipsilateral)] was calculated using pixels from all experimental runs.

**Magnetoencephalography Analysis**

Magnetoencephalography data were analyzed by using synthetic aperture magnetometry. The synthetic aperture magnetometry method, first proposed by Robinson and Vrba, is capable of localizing source activity throughout the brain by using a novel spatial filtering algorithm. This method provides estimates of source power that are normalized by brain noise, termed a pseudo-Z statistic. We applied a modified version of the synthetic aperture magnetometry method, termed “event-related synthetic aperture magnetometry,” adapted to observe instantaneous source power with millisecond resolution. This method has been shown to be effective for measuring motor and sensory cortical activity after self-paced movements, and it also provides the ability to create independent time-series waveforms for selected locations of peak activity.

The EMG-recorded movement onset (time = 0 seconds) was marked off-line for each trial and used to re-epoch (−1.5 second to 0.5 second) the magnetoencephalography data. Event-related synthetic aperture magnetometry images of source power were calculated with a 2-mm spatial sampling resolution for broad regions of interest around the hand areas of the sensorimotor cortex, including the premotor cortex and posterior parietal cortices.

The single trial data epochs were used to estimate the data covariance after bandpass filtering from DC to 50 Hz and to baseline the data using the premovement period −1.5 to −0.5 seconds. Event-related synthetic aperture magnetometry images were created at 2-millisecond increments before and after movement onset (−100 milliseconds pre-movement to 200 milliseconds postmovement), and individual images were scanned to find peak activations. To examine source activity over time, an average time series waveform was reconstructed for the entire epoch at locations showing the largest signal power (pseudo-Z). These waveforms were inspected manually to determine the latencies corresponding to peak signal power.

**Results**

**Clinical Measures**

Table 1 summarizes clinical results after therapy. Frequency of use and quality of movement of the hemiplegic hand improved after therapy as measured by the Pediatric Motor Activity Log. Electromyography-derived mirror movement indices demonstrated mirror movements in both hands before and after therapy (indices < 1.0 represent the presence of mirror movements): left hand (before therapy, 0.041; after therapy, 0.159); right hand (before therapy, 0.022; after therapy, 0.080).

**Functional Magnetic Resonance Imaging and Magnetoencephalography**

Figure 2 shows functional MRI results. For right affected hand movement, functional MRI showed increased cortical activation in the contralateral sensorimotor cortex after therapy. This resulted in a shift in the laterality index. Changes were maintained at the 6-month follow-up.

To demonstrate magnetoencephalography activation waveforms, Figure 3 shows 4 main peaks of activity observed in the event-related synthetic aperture magnetometry images overlaid on the subject’s T1-weighted MRI and the corresponding averaged waveforms for movements of the left unaffected hand at baseline. The waveforms show the previously reported components of movement-related magnetoencephalography activity with a slowly rising magnetic field change, or motor field, that reflects activation of the primary motor cortex immediately preceding movement onset. This is followed by a brief reversal of the field pattern after EMG onset, termed movement-evoked field, that has been shown to be associated with sensory feedback arising from the movement itself.

Table 2 summarizes the magnetoencephalography results for the right hemiplegic hand. For right hand movement, increased amplitudes were observed for the contralateral movement evoked field and ipsilateral motor field after therapy. We could not interpret changes at the 6-month follow-up due to excessive head movement during data collection.
Discussion

This is the first report, to our knowledge, of cortical reorganization after modified constraint-induced movement therapy in a child with hemiplegic cerebral palsy. Reorganization was associated with improvement on some clinical measures and persisted at 6 months. Functional MRI showed increased contralateral activity after therapy, with a shift in laterality from the ipsilateral to the contralateral hemisphere. Magnetoencephalography constitutes a unique aspect of this study and provided temporal information about cortical activation before (motor field) and after (movement evoked field) movement onset. These temporal data can delineate the contribution of motor versus somatosensory cortex.19 Magnetoencephalography showed increased contralateral movement evoked field activation (somatosensory cortex) and increased ipsilateral motor field activation (motor cortex) after therapy.

The shift in the functional MRI laterality index to the contralateral hemisphere after therapy in our study is consistent with adult stroke studies7-10 and a single report of a child with hemiplegic cerebral palsy who underwent virtual reality therapy.23 Previous studies, however, were unable to distinguish between motor and sensory activation, whereas magnetoencephalography technology in our study provides this information.

Potential mechanisms for increased contralateral activation after therapy include decreased mirror movements, increased contralateral motor cortex activity, or increased contralateral somatosensory cortex activity. Mirror movements may be partly responsible for activation in the ipsilateral hemisphere; thus, reduced mirror movements after therapy would result in an activation shift from the ipsilateral to the contralateral hemisphere. However, EMG-measured mirror movements did not resolve in our subject after therapy. Motor training during modified constraint therapy

Table 1. Clinical Measures Before and After Modified Constraint-Induced Movement Therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before Therapy</th>
<th>After Therapy</th>
<th>6 Months After Therapy</th>
</tr>
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<tbody>
<tr>
<td>Pediatric Motor Activity Log (amount of use)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.6</td>
<td>4.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Pediatric Motor Activity Log (quality of movement)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5</td>
<td>4.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Quality of Upper Extremity Skills Test&lt;sup&gt;c&lt;/sup&gt;</td>
<td>69.2</td>
<td>68.7</td>
<td>89.4</td>
</tr>
<tr>
<td>Canadian Occupational Performance Measure (performance)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5</td>
<td>8</td>
<td>9.5</td>
</tr>
<tr>
<td>Canadian Occupational Performance Measure (satisfaction)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1</td>
<td>7</td>
<td>9.5</td>
</tr>
<tr>
<td>Assisting Hand Assessment&lt;sup&gt;f&lt;/sup&gt;</td>
<td>68</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>Sphygmomanometry (mm Hg)</td>
<td>102.7</td>
<td>130.7</td>
<td>94.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pediatric Motor Activity Log maximum score is 5.
<sup>b</sup> Quality of Upper Extremity Skills Test maximum score is 100.
<sup>c</sup> Canadian Occupational Performance Measure maximum score is 10.
<sup>d</sup> Assisting Hand Assessment maximum score is 88.

Values in bold highlight clinically important change.
Figure 3. An example of magnetoencephalography temporal measurements in the left unaffected hand. Boxes i-iv show cortical activation measured over time with virtual sensor waveforms. Y-axes show magnitude of activation (pseudo-Z values). X-axes show time in seconds. Time 0 represents movement of the hand detected with electromyography. Change in peak activation (highlighted with color in each waveform) that begins before or with hand movement in each hemisphere (i and ii) represents the motor field (primarily motor cortex). The second change in peak activation in each hemisphere occurs after hand movement (iii and iv) and represents the movement-evoked field (primarily somatosensory cortex). Axial magnetic resonance slices show the cortical locations from where activation measurements were taken.
may lead to increased recruitment and activity of the contralateral motor cortex; however, our magnetoencephalography results do not support this interpretation.

In contrast, our magnetoencephalography results support the third proposed mechanism that modified constraint therapy provides increased sensory input to the affected hand as a result of increased use, which in turn leads to increased recruitment and activity of the contralateral somatosensory cortex. These data are consistent with previous primate studies whereby sensory impairment secondary to dorsal rhizotomy resulted in abnormal motor function.6

Poor sensory input of an extremity is felt to lead to a condition of neglect, decreased use, and ultimately, poor motor function. Of interest is the study of Kristeva et al,24 who found that the electrical motor evoked field counterpart was absent in a deafferented patient who could perform index finger flexions without sensory awareness of the movements. The authors concluded that the movement-evoked field reflects peripheral feedback to the sensorimotor cortex that is necessary to create perceptual awareness of movement. This suggests that modified constraint therapy may contribute to improved hand function through a mechanism that enhances sensory input by way of the somatosensory cortex.

After therapy, magnetoencephalography also showed an increase in the ipsilateral motor field. This activity is most likely related to simultaneous mirror movements of the opposite hand and may simply reflect changes in mirror movement timing. This requires future investigation. It should be noted that an ipsilateral motor field (but not movement-evoked field) is often present in adult controls in the absence of mirror movements19; however, these are always coincident in time with the contralateral motor field. In contrast, we observed that the ipsilateral motor field and movement-evoked field were delayed by 70 to 80 milliseconds with respect to the contralateral motor field. To our knowledge, ipsilateral magnetoencephalography responses in subjects with strong mirror movements have not been previously reported.

Clinical improvement after therapy was demonstrated with parent reports of improved use and quality of movement (Pediatric Motor Activity Log), improved grip strength, enhanced ability to complete bimanual tasks (Assisting Hand Assessment), and progress on identified goals (Canadian Occupational Performance Measure). Only the Canadian Occupational Performance Measure improvement was maintained at the 6-month follow-up. Of interest was that the Quality of Upper Extremity Skills Test, which objectively measures quality of movement, did not show improvement immediately after therapy but did show a gradual and significant improvement during the 6-month follow-up period. We hypothesize that improved quality of movement occurs after increased arm/hand use.

The 6-month clinical results are interesting because the quality of movement of the hemiplegic hand was improved although the spontaneous use of the hemiplegic hand/arm had returned to baseline values. It is possible that improved quality occurred at some time between therapy and 6 months and persisted despite the recurrence of disuse.

It is not clear why the results for quality of movement on the Pediatric Motor Activity Log differed from results of the Quality of Upper Extremity Skills Test. Possibly, parents are better at reporting increased hand use versus improved quality. Parent report for hand quality on the Pediatric Motor Activity Log may therefore be influenced by the more easily scored frequency of use. Further research is needed to validate the pediatric version of the Motor Activity Log and to study the temporal pattern of skill development after constraint therapy.

### Table 2. Magnetoencephalography Peak Activation for Right Hemiparetic Hand Movement

<table>
<thead>
<tr>
<th>Cortical Location</th>
<th>Before Therapy, Mean (SE)</th>
<th>After Therapy, Mean (SE)</th>
<th>Latency Time of Peak (s), mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor fieldb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>1.8 (1.33–2.27)</td>
<td>2.2 (1.79–2.61)</td>
<td>−0.043 (0.040)</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2.3 (1.89–2.71)</td>
<td>3.1 (2.74–3.46)</td>
<td>0.042 (0.028)</td>
</tr>
<tr>
<td>Movement-evoked fieldc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>2.6 (2.19–3.01)</td>
<td>4.1 (3.67–4.53)</td>
<td>0.081 (0.022)</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2.6 (2.16–3.04)</td>
<td>2.2 (1.89–2.51)</td>
<td>0.154 (0.021)</td>
</tr>
</tbody>
</table>

a. Pseudo-Z peak cortical activation.
b. Motor field measurements represent motor cortex.
c. Movement-evoked field measurements primarily represent somatosensory cortex.

Values in bold are different from baseline values in the same location as defined by an absence of overlap in the standard error (SE). Standard errors were calculated from 100 movement trials. Mean latency times for peak activations at each cortical location were measured relative to time 0 (onset of hand movement as measured with electromyography).
Conclusion

This is the first pediatric report of cortical change after modified constraint therapy. Study limitations include a single case and single baseline values. The subject was 8 years postinjury with stable clinical function. Functional MRI and magnetoencephalography findings were consistent with each other. Unique study features include the combination of functional MRI and magnetoencephalography measurements, and standardized motor tasks during functional MRI and magnetoencephalography. Our results support the mechanism of cortical reorganization, specifically activation of the contralateral somatosensory area, for improved function after modified constraint therapy.

Acknowledgments

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References