Structural Neuroplastic Change After Constraint-Induced Movement Therapy in Children With Cerebral Palsy

abstract

Research from the present laboratory with adult stroke patients showed that structural neuroplastic changes are correlated with clinical improvements due to constraint-induced movement (CI) therapy. This pilot study evaluated whether comparable changes occur in children receiving CI therapy. Ten children (6 boys) with congenital hemiparesis (mean age: 3 years, 3 months) underwent MRI scans 3 weeks before, immediately before, and immediately after receiving 3 weeks of CI therapy. Longitudinal voxel-based morphometry was performed on MRI scans to determine gray matter change. In addition, the Pediatric Motor Activity Log-Revised was administered at these time points to assess arm use in daily life before and after treatment. Children exhibited large improvements after CI therapy in spontaneous use of the more-affected arm ($P < .001$, $d' = 3.24$). A significant increase in gray matter volume occurred in the sensorimotor cortex contralateral to the more-affected arm ($P = .04$); there was a trend for these changes to be correlated with motor improvement ($r = 0.63$, $P = .063$). Trends were also observed for increases in gray matter volume in the ipsilateral motor cortex ($P = .055$) and contralateral hippocampus ($P = .11$). No significant gray matter change was seen during the 3 weeks before treatment. These findings suggest that CI therapy produces gray matter increases in the developing nervous system and provide additional evidence that CI therapy is associated with structural remodeling of the human brain while producing motor improvement in patients with disabling central nervous system diseases.

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KEY WORDS
CI therapy, neuroplasticity, rehabilitation, cerebral palsy, hemiplegia, neuroimaging

ABBREVIATIONS
CI therapy—constraint-induced movement therapy
fMRI—functional MRI
PMAL-R—Pediatric Motor Activity Log-Revised
VBM—voxel-based morphometry

Ms Sterling contributed to the study concept and design and helped with acquisition of data, analysis of MRI scans, data management, statistical analysis, interpretation of results, drafting of the manuscript, and approved the final manuscript as submitted; Dr Taub helped with conceptualization and design of the study, was involved with drafting of the manuscript and interpretation of the data, and approved the final manuscript as submitted; Dr Davis was involved with conceptualization and design of the study, helped with analysis of MRI scans, provided medical supervision of MRI scanning and rehabilitation procedures, helped with interpretation of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted; Mr Rickards helped with conceptualization and design of the study, was involved in acquisition of data, analysis of MRI scans, data management, statistical analysis and interpretation of the data, and approved the final manuscript as submitted; Dr Gauthier contributed to the study concept and design, was involved in acquisition of data, helped with analysis of MRI scans, was involved in the interpretation of the data, provided critical revisions of the manuscript, and approved the final manuscript as submitted; Ms Griffin helped with acquisition and interpretation of the data, provided critical revisions to the manuscript, and approved the final manuscript as submitted; and Dr Uswatte was involved in developing the study concept and design, helped with data management, statistical analysis, and interpretation, provided critical revisions to the manuscript, and approved the final manuscript as submitted.

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Constraint-induced movement (CI) therapy has been found to be efficacious in producing improvements in use of a more-affected upper extremity after central nervous system damage in adults.\textsuperscript{1–3} Using the same basic method, large improvements have also been demonstrated in young children with cerebral palsy.\textsuperscript{4–6} Different variants of pediatric CI therapy have also yielded positive results (summarized until 2008 in ref 7).

In adults with chronic stroke, a substantial plastic reorganization of the brain has been found to occur after CI therapy. Initial studies used functional brain measures (transcranial magnetic stimulation, electroencephalography, positron emission tomography, functional MRI [fMRI]).\textsuperscript{8–12} More recently, it has also been found by using voxel-based morphometry (VBM) that CI therapy produces structural brain changes, specifically an increase of gray matter volume of sensorimotor cortex, more anterior motor areas, and hippocampus on both sides of the brain.\textsuperscript{13} These changes correlated with greater improvement in motor outcomes.\textsuperscript{13} In this pilot study, we used VBM to assess gray matter change in the brains of 10 children as a result of CI therapy.

**PATIENT PRESENTATION**

**Patient Presentation and Diagnosis**

Ten children with congenital hemiparesis, aged 2 years, 1 month, to 7 years, 6 months (mean: 3 years, 3 months; SD: 1 year, 6 months), were recruited through the Pediatric CI Therapy Program at Children’s of Alabama. Six of the cases were boys, and 2 children had left-sided motor deficit (Table 1). Inclusion/exclusion criteria are presented in the Supplemental Information.

**Intervention and Measures**

Participants underwent MRI scans 3 weeks before receiving CI therapy (baseline), immediately before treatment (pretreatment), and immediately after the 3-week treatment program (posttreatment). Comparisons of scans at baseline and pretreatment were used to control for the possibility that there would be any substantial spontaneous change in gray matter due to brain development. At each of the 3 testing occasions, the Pediatric Motor Activity Log-Revised (PMAL-R), a scripted, structured interview designed to assess spontaneous use of the more-affected arm in the life situation,\textsuperscript{4–6,14,15} was also administered. This validated measure of clinical outcome in daily activities is described in the Supplemental Information.

CI therapy consists of intensive motor training using the technique termed shaping for 3 hours each weekday for a 3-week (15-day) period in which the child’s less-affected arm is continuously restrained in a long arm cast.\textsuperscript{4–6} On the last 2 days of treatment, the cast is removed and training is focused on bilateral activities. The child’s caregivers receive a “transfer package” designed to facilitate transfer of therapeutic gains made in therapy. The transfer package, taking an additional 0.5 hour per treatment day, includes a behavioral contract, steps to induce continuation of use of the more-affected arm at home, and guidance to overcome perceived problems in using the more-affected arm in everyday life.\textsuperscript{2,6,13}

T1 MRI scans were obtained on a 1.5T Phillips Intera MRI scanner at Children’s of Alabama. All children were sedated with propofol before undergoing MRI.\textsuperscript{16,17} Longitudinal VBM was performed in Matlab 2010\textsubscript{ rb} (Mathworks, Natick, MA) by using SPM8 software (Wellcome Department of Cognitive Neurology, London, United Kingdom) to determine changes in gray matter resulting from CI therapy. The procedures used were similar to those previously used with adults\textsuperscript{15,18,19} (see Supplemental Information for details).

**Outcome**

All of the cases showed large improvements in clinical outcome from pre- to posttreatment but little or no improvement from baseline to pretreatment (control phase; see Table 2). For the participants as a group, paired t tests revealed gains in amount and quality of use of the more-affected arm for daily activities after completing CI therapy (PMAL-R Arm-Use scale; \( t_{(9)} = 10.18, P < .001, d^* = 4.0 \)). Results of the limb preference measure of the Pediatric Arm Function Test\textsuperscript{20} were consistent with observed improvements on

<table>
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<tr>
<th>ID No.</th>
<th>Gender</th>
<th>Age, y, mo\textsuperscript{a}</th>
<th>Side of Motor Deficit</th>
<th>Lesion Size, mm\textsuperscript{b}</th>
<th>Lesion Location</th>
<th>Damage to CST</th>
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</tr>
</tbody>
</table>

CST, corticospinal tract; F, female; M, male.
\textsuperscript{a} Mean age: 3 years, 3 months (SD: 1 year, 6 months).
\textsuperscript{b} Mean lesion size: 2740.4 mm\textsuperscript{3} (SD: 4784 mm\textsuperscript{3}).
Cluster-wise analysis revealed an increase after CI therapy in gray matter volume in the sensorimotor cortex contralateral to the more-affected arm ($P = .04$; cluster size = 18 203 voxels). There was also a trend for an increase in gray matter volume in the ipsilateral sensorimotor cortex ($P = .055$; cluster size = 12 004 voxels). Voxel-wise analysis showed a trend for an increase in gray matter volume within individual voxels in the contralateral hippocampus ($P = .1$). A cortical surface–rendered image of the results of the whole-brain analysis of gray matter change for both children in this study and adults in earlier work13 are presented in Fig 1. There was a trend for a positive correlation between gray matter increase in the contralateral sensorimotor cortex and motor improvement on the PMAL-R ($r = 0.59, P = .09$) (Fig 2). Motor improvement and change in gray matter were not significantly related to the age of the participants. Significant gray matter increases were not seen between the baseline and pretreatment measurements.

### DISCUSSION

Children who received CI therapy showed increases in gray matter in the sensorimotor cortex contralateral to the arm targeted during rehabilitation, ie, the more-affected arm. Trends were also observed for increases in gray matter volume in the ipsilateral sensorimotor cortex and contralateral hippocampus. These structural changes in the brain were accompanied by large improvements in spontaneous arm use in daily life. The absence of significant change in either motor scores or gray matter volume in the 3 weeks preceding treatment makes it unlikely that the motor and gray matter volume increases that occurred during the 3-week treatment period were due to growth and development. It is not possible to make a causal attribution regarding the 2 processes, because the gray matter increase could be a cause or an effect of increased motor ability and behavioral change, or it could simply be an independent accompaniment. However, the trend observed for a correlation between increases in gray matter volume and magnitude of motor improvement raises the possibility of a causal relationship.

Previously, evidence that children experience substantial neuroplasticity during CI therapy was limited to 2 small functional neuroimaging studies. A single case report described increased cortical activation in the contralateral and ipsilateral motor fields after CI therapy using magnetoencephalography.21 In another study, fMRI laterality indices were shifted contralaterally among 4 participants post–CI therapy.22 The current study is the first to examine whether structural neuroplastic reorganization occurs during rehabilitation in a pediatric population.

The presence of gray matter changes after pediatric CI therapy is consistent with the results of adult stroke patients15; however, the pattern is somewhat different. After CI therapy in adults, diffuse gray matter change is seen, whereas more focal increases occur in children. This finding is consistent with previous research, which has shown that, compared with children, adults show significantly more widespread cortical activation when a manual task is performed including not only bilateral sensorimotor cortices as in children but parietal and supplementary motor areas as well.23

Increases in gray matter volume are seen bilaterally in sensorimotor areas in adults13 and in this study in children. The recruitment of existing but normally less active ipsilateral pathways has also been revealed through the use of functional (electroencephalography, fMRI) and structural neuroimaging techniques in adult patients receiving CI therapy.8,10,13 Bilateral effects indicate that, in addition to increasing structural integrity of the contralateral brain areas that are typically most involved in movement of the
more-affected arm, CI therapy may activate an alternate motor network that includes the less-affected sensorimotor cortex. This region may aid recovery by assuming motor functions typically carried out by the brain areas that were directly injured. Reorganization of the motor system has also been found to occur spontaneously in some patients with congenital hemiparesis so that there is greater involvement of the ipsilateral hemisphere during paretic limb movement. CI therapy may promote additional adaptations of ipsilateral motor pathways. Substantial recovery of motor function occurs after CI therapy after hemispherectomy in children, additionally indicating that the less-affected hemisphere can assume functions typically carried out by the other hemisphere.

The observed increase in gray matter could be due to one or more of several different processes: an increase in dendritic arborization and/or synaptic density, gliosis, angiogenesis, or neurogenesis. Research in animal models of CI therapy has found significant axonal growth and focal cerebral neurogenesis along with functional improvement. It would therefore be of value to additionally examine the structural and biochemical changes that may occur with functional improvement after CI therapy in humans.

This preliminary study indicates that an efficacious rehabilitation intervention, CI therapy, can result in structural changes in the damaged brains of young children. The motor improvement and changes in gray matter after CI therapy observed here are similar to those observed previously in adults. Both children and adults show large increases in spontaneous use of their more impaired upper extremity in daily activities after CI therapy. In addition, children who received CI therapy showed gray matter increases in some of the same brain regions as adults, namely sensorimotor cortices and the hippocampus. These changes occurred bilaterally in both populations and the magnitude of the gray matter change was similar. The territorial extent of neuroplastic change appears greater in adults than in children; this pattern is consistent with the development of the motor system.
Confirmation of these findings from a small number of children with the use of a within-participant control procedure is now desirable in a larger number of children with a separate control group and random assignment. In addition, given that clinical improvements persist at 6 months\(^6\) and 1 year\(^6\) posttreatment, it would be important in future work to determine whether neuroplastic changes also persist over time. It should be noted that this study does not indicate that pediatric CI therapy is the only pediatric rehabilitation treatment that produces marked neuroplastic changes. It could be that other pediatric rehabilitation treatments also have this effect, although this has not as yet been demonstrated. It would be of value for future research to assess this possibility.

REFERENCES


(Continued from first page)

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