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ORIGINAL ARTICLE

Diffusion Tensor Imaging Study of the Response to Constraint-Induced Movement Therapy of Children With Hemiparetic Cerebral Palsy and Adults With Chronic Stroke

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Abstract

Objective: To investigate the relationship of white matter integrity and path of the corticospinal tract (CST) on arm function before and after constraint-induced (CI) movement therapy in children with hemiparetic cerebral palsy (CP) and adults with chronic stroke.

Design: Study 1 used a multiple-baseline pre-post design. Study 2 was a randomized controlled trial.

Setting: Outpatient rehabilitation laboratory.

Participants: Study 1 included children with hemiparetic CP (n=10; mean age ± SD, 3.2±1.7y). Study 2 included adults with chronic stroke (n=26; mean age ± SD, 65.4±13.6y) who received either CI therapy or a comparison therapy.

Interventions: Children in study 1 received CI therapy for 3.5h/d for 15 consecutive weekdays. Adults in study 2 received either CI therapy or a comparison therapy for 3.5h/d for 10 consecutive weekdays.

Main Outcome Measures: Diffusion tensor imaging was performed to quantify white matter integrity. Motor ability was assessed in children using the Pediatric Motor Activity Log—Revised and Pediatric Arm Function Test, and in adults with the Motor Activity Log and Wolf Motor Function Test.

Results: Participants in both studies improved in real-world arm function and motor capacity. Children and adults with disrupted/displaced CSTs and children with reduced fractional anisotropy values were worse on pretreatment tests of motor function than participants with unaltered CSTs. However, neither integrity (fractional anisotropy) nor distorted or disrupted path of the CST affected motor improvement after treatment.

Conclusions: Participants who had reduced integrity, displacement, or interruption of their CST performed worse on pretreatment motor testing. However, this had no effect on their ability to benefit from CI therapy. The results for children and adults are consistent with one another.

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Constraint-induced (CI) movement therapy substantially increases the use of a more affected arm after damage to the central nervous system (CNS) in both children[1-4] and adults.[5-8] One mechanism associated with this outcome is plastic reorganization of the brain. Previous studies[9-13] have found that CI therapy alters brain function associated with movement of the more affected arm, and in addition results in increased gray matter volume in motor areas of the brain and hippocampus in children with cerebral palsy (CP)[14] and adults after stroke.[15]

Several white matter (WM) tract characteristics that can be identified in diffusion tensor imaging (DTI) scans have been found

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to be related to the extent of motor deficit after CNS damage.[16-28] Fractional anisotropy (FA) values derived from DTI scans differ in intact and damaged/interrupted WM tracts.[25] FA values reflect the physical constraints on water diffusion; low values reflect tracts with poor structural integrity. In children with CP, FA values for the corticospinal tract (CST) are significantly lower than in typically developing children[20] and are positively correlated with better performance on motor tasks.[21] In adults with stroke, motor function is diminished by lesions of the ipsilesional CST,[23,24] particularly in the centrum semiovale region of the corona radiata where the CST receives contralesional input via the corpus callosum.[24] In addition, FA values for the CST in adults are strongly positively correlated with motor function in both the acute and chronic periods of stroke.[26-28]

Given the importance of the CST in determining motor function after CNS damage before treatment, we attempted to further determine whether the status of this structure also influences motor outcome after CI therapy, and whether the results would be similar in children and adults. Two separate studies were conducted: one in children with hemiparetic CP given CI therapy (study 1) and another in adults with chronic stroke randomly assigned to receive either CI therapy or a comparison therapy (study 2). All had DTI scans before and after therapy.

Our expectations concerning the outcome of the studies were 2-fold. The first hypothesis related to the clinical effect of CI therapy and posited that CST damage would not prevent either children or adults from benefiting as much as patients without CST damage. This hypothesis was based on previous results from this laboratory in which lesion-symptom mapping (via voxel-based statistics) showed that lesions in the CST did not prevent adults with chronic stroke from benefiting as much from CI therapy as patients without CST damage.[24] We anticipated the same result here with regard to the CST but examined damage in a different way—that is, by inspection of the integrity and path of the tract rather than lesion overlap. The second hypothesis was that CI therapy, matching the increase it produces in gray matter in motor areas of the brain, would increase WM integrity of the CST.

Study 1: Pediatric CI Therapy

Methods

Participants

Ten children between 2 and 8 years of age with hemiparetic CP were recruited from an outpatient CI therapy clinic. Inclusion and exclusion criteria for participation in the 2 studies are detailed in appendix 1. This project was approved by the institutional review board for human research at the University of Alabama at Birmingham. A parent of each participant signed informed consent, and the 7.6-year-old participant signed informed assent. Participants were enrolled from 2009 through 2011.

List of abbreviations:

CI	**constraint-induced**
CNS	**central nervous system**
CP	**cerebral palsy**
CST	**corticospinal tract**
DTI	**diffusion tensor imaging**
FA	**fractional anisotropy**
MAL	**Motor Activity Log**
MRI	**magnetic resonance imaging**
PAFT	**Pediatric Arm Function Test**
PMAL-R	**Pediatric Motor Activity Log—Revised**
WM	**white matter**
WMFT	**Wolf Motor Function Test**

Procedures

Participants were given CI therapy, which consisted of intensive motor training using the technique termed shaping, for 3 hours each weekday for a 3-week (15-d) period in which the child's less affected arm was continuously restrained in a long-arm cast.[2,4] On the last 2 days of treatment, the cast was removed and training focused on bilateral activities. The child's caregivers received a "transfer package" designed to facilitate transfer of therapeutic gains made in therapy to the life situation. The transfer package, taking an additional 0.5 hours per treatment day, included a behavioral contract signed by the parents, steps to induce continuing use of the more affected arm at home, and guidance to overcome perceived problems in using the more affected arm in everyday life.[2,4,7,15,29]

Participants underwent magnetic resonance imaging (MRI) 3 weeks before CI therapy (baseline), immediately before treatment (pretreatment), and immediately after the 3-week therapy period (posttreatment). Comparison of a child's scans at baseline and pretreatment controlled for the possibility that any change in WM integrity during treatment was due to normal brain development. Two measures of real-world motor function, the Pediatric Motor Activity Log—Revised (PMAL-R) and limb preference score of the Pediatric Arm Function Test (PAFT), were administered before and after treatment. The PMAL-R was also given at baseline to control for the possibility that change in motor function that might take place during the 3-week treatment period was due to normal development.

Clinical outcome measures

The PMAL-R[2,4] is a scripted, structured interview with an established reliability and validity[30] in which caregivers rate how well and how often their children use their more affected upper extremity on 22 frequently performed activities of daily living. Since the How Well and How Often scales are highly correlated,[30] only the How Well scale, which will hereafter be referred to as the Arm Use scale, is reported.

The PAFT is a behavioral observation system set in the laboratory to assess motor ability when movement is requested.[2,4,31] For unilateral tasks on the PAFT, children can use either hand, yielding a limb preference score (more affected vs less affected arm), with higher scores indicating greater use of the more affected upper extremity. Scores can range from 0% (no use of the more affected upper extremity) to 100% (use of the more affected upper extremity on all of the activities tested). The limb preference score has convergent validity with the PMAL-R Arm Use scale.[31] One child in the current study was outside the appropriate age range for the test (2—6y) and did not complete the measure.

Magnetic resonance imaging

DTI images were obtained in 45 directions on a 1.5T Philips Intera MRI scanner.[a] To reduce motion within the scanner, children were sedated with propofol[32,33] for the duration of image acquisition (approximately 1h). An intensivist monitored each child