WHITE MATTER INTEGRITY IN ADULTS WITH HEMIPARETIC MULTIPLE SCLEROSIS GIVEN CONSTRAINT-INDUCED MOVEMENT THERAPY

by

TYLER A. RICKARDS

EDWARD TAUB, COMMITTEE CHAIR
DAVID KNIGHT
VICTOR W. MARK
JOHN RINKER
GITENDRA USWATTE

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MEDICAL/CLINICAL PSYCHOLOGY

ABSTRACT

In adults with chronic stroke and children with cerebral palsy, structural changes in grey matter correlate with clinical improvements due to an efficacious upper-extremity (UE) rehabilitation therapy, Constraint-Induced Movement (CI) Therapy. Changes in white matter following CI therapy have not been observed, but damage to white matter tracts has not been found to decrease motor improvement resulting from this treatment. The objectives of this project were to: 1) evaluate the efficacy of CI therapy compared to complementary and alternative medicine (CAM) treatments on improving impaired UE function in participants with the progressive form of multiple sclerosis (MS), 2) investigate whether white matter integrity is correlated with motor function prior to treatment and improvement due to therapy, and 3) determine if change in white matter tracts is associated with CI therapy. Diffusion Tensor Imaging (DTI) was utilized to quantify white matter integrity.

Eighteen participants with hemiparetic slowly progressing MS received either CI therapy or a set of CAM techniques. Fractional anisotropy (FA) values were calculated over the whole brain prior to and following treatment and tractography was used to isolate the corticospinal tract (CST).

The CI therapy group improved use of the more-affected arm in the life situation that was 4.1 times greater than the CAM group. The groups improved similarly on the
in-laboratory measure of arm function. FA value of the CST was not related to motor function. Pretreatment contralateral CST FA value correlated with motor improvement following CI therapy, but not CAM treatments.

These results confirm the efficacy of CI therapy in improving motor function in individuals with CNS damage. The lack of a relationship between pretreatment motor function and integrity of the CST in individuals with MS may suggest that motor function relates to another structure necessary for motor function and a site of frequent pathology in individuals with MS: the spinal cord. Pretreatment integrity of the CST related to improvement in motor function following CI therapy.

Keywords: Multiple Sclerosis, rehabilitation, MRI, brain, CI therapy, white matter
DEDICATION

This dissertation is dedicated to my parents. You encouraged me so much that I had no choice but to believe that I could do what I wanted to do.
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I am grateful to the members of the dissertation committee for their time and their efforts. I have benefitted from each of your unique areas of expertise. I would like to thank Dr. Edward Taub for his efforts not only on this project but throughout my graduate training. He is a world-class scientist whose work has positively influenced the lives of thousands, including mine. I am proud to have been trained by someone who is so passionate and sincere in his approach to his particular field and science, in general.
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INTRODUCTION

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune, degenerative disorder of the central nervous system (CNS). It affects approximately 400,000 people in the United States and is 2-3 times more common in women than in men (National MS Society, 2011). The manifestation of MS appears to be influenced by both environmental and genetic factors (Goodin, 2010). Degradation of both white matter (WM) (Compston & Coles, 2008) and grey matter (Calabrese, Filippi, & Gallo, 2010) is typical in individuals with MS.

Using the current MS diagnostic criteria (2010 McDonald Criteria), the initial MS attack must be “clinical,” having symptoms that are consistent with MS lasting at least 24 hours. The disease has various subtypes, including: relapsing/remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). The subtypes are classified by the course of the disease. If an individual with MS has recurrent attacks with consistent periods of stability between them, the individual is classified as having RRMS. Those with SPMS show a progressive decline in their condition after evolving from the RRMS subtype. Individuals with PPMS exhibit a progressive decline after the initial appearance of the disease; they show a slower and more consistent decline than those with RRMS (Hurwitz, 2009), and have a disease course similar to SPMS (Kremenchutzky, Rice, Baskerville, Wingerchuk, & Ebers, 2006).

Symptoms commonly associated with MS include: fatigue, numbness, bladder and/or bowel dysfunction, vision problems, pain, cognitive dysfunction, emotional changes, speech and swallowing problems, headaches, seizures, tremor, breathing problems, sexual dysfunction, as well as coordination and general motor problems.
(National MS Society, 2011). Between 25 to 60% of those diagnosed with MS go on to develop tremor and/or ataxia (Koch, Mostert, Heersema, & DeKeyser, 2007) and many have motor problems that are primarily unilateral (Cowan, Ormerod, & Rudge, 1990; Gorman, 2002; Jenkins, Khaleeli, & Thompson, 2008; Kurtzke, 1961; Pendlebury, Lee, Blamire, Styles, & Matthews, 2000). One-half of those with the primary progressive form of MS require assistive devices (e.g., orthotics) within five years of diagnosis (Weinshenker et al., 1989).

CI Therapy

Constraint-Induced Movement (CI) therapy is a behavior-based therapy shown to substantially increase impaired limb function following injury to the CNS. Research with primates (Taub, 1976; 1980) established some of the basic procedures and the key theoretical bases of CI therapy. In these studies, somatosensory deafferentation was carried out by severing all sensory nerve roots innervating a single forelimb. This prevented all afferent input from the limb from reaching the brain. Following this surgical technique, the affected limb was no longer used in the free situation (Mott & Sherrington, 1895). In Taub’s experiments, use of the deafferented limb was induced by two techniques: training (most effectively by the technique termed *shaping*) and physical restraint of the less-affected forearm (summarized in Taub, 1976).

The original essential components of CI therapy developed with deafferented primates have been translated to use in humans: shaping of movements during massed task practice and physical restraint of the less-affected arm, to which has been added a “transfer package” to induce transfer of gains in motor function from the laboratory to the
home setting. Massed practice in the context of CI therapy with adult humans in this laboratory entails training of the more-impaired upper-extremity for multiple hours per day in the laboratory setting on consecutive weekdays for two successive weeks. A protective safety mitt is worn to reduce use of the less-impaired hand for a target of 90% of waking hours during treatment. The padded mitt limits the limb’s ability to perform common tasks but does not compromise safety by preventing individuals from bracing or balancing themselves. The transfer package is critical for maximizing therapeutic gains and neuroplastic effects of the therapy (Gauthier et al., 2008). It includes daily monitoring of use of the more-affected arm in the home environment, problem-solving with a therapist to overcome perceived barriers to using the more-impaired extremity in the home, and home practice of a number of activities of daily living and prescribed exercises that change daily.

CI therapy has been found to produce large, clinically-significant improvements in motor function (Taub et al., 1993; 2006; Wolf et al., 2006). The therapy was first administered to adults with chronic stroke but has since been demonstrated to successfully treat upper-extremity hemiparesis in other populations: traumatic brain injury (Shaw, Morris, Uswatte, McKay, Meythaler, & Taub, 2005), cerebral palsy (Sterling et al, 2013; Taub, Ramey, DeLuca, & Echols, 2004; Taub, Griffin, Nick, Gammons, Uswatte, & Law, 2007; Taub, Griffin, Uswatte, Gammons, Nick, & Law, 2011), and for focal hand dystonia in musicians (Candia, Elbert Altenmuller, Rau, Schafer, & Taub, 1999). CI therapy has also been demonstrated to be efficacious in improving arm function in a small sample (n=5) of individuals with hemiparesis as a result of slowly progressive MS (Mark et al., 2008). However, a comparison between the
efficacy of CI therapy and other treatments frequently sought by individuals with MS has not been performed.

Complementary and Alternative Medicine (CAM) Therapies

One-half to three-fourths of those with MS pursue some form of CAM technique in addition to their conventional treatment to address symptoms like fatigue, depression, and anxiety (Bowling, 2010). CAM techniques sought by adults with MS include aquatic therapy (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012), yoga (Oken et al., 2004), guided imagery (Maguire et al., 1996), and mindfulness training (Grossman et al., 2010). Despite being frequently sought by individuals with MS, the efficacy of these therapies is inconsistent (Bowling, 2011).

Neuroplastic Change: Use-Dependent Plasticity

Prolonged, behaviorally-relevant afferent input can produce structural reorganization in the CNS. In animals, cortical representation zones following loss of sensory input due to somatosensory deafferentation (Kaas, Merzenich & Killackey, 1983) and amputation (Merzenich et al., 1984) are “invaded” by neurons from cortical representation zones of adjacent body parts that are intact. Conversely, increased use of a body part by an animal leads to an increase in the cortical representation zone for that body part (Jenkins, Merzenich, Ochs, Allard, & Guic-Robles, 1990). Similar phenomena occur in humans. Amputation of an arm (Elbert et al., 1994; Flor et al., 1995) has been found to result in invasion of the cortical representation of the removed limb; stroke, which reduces use of a more-affected arm, has been found to cause contraction of cortical
representation zones (Liepert et al., 2000). Moreover, as in primates, increase in extremity use has been shown to increase the size of representation zones (Elbert, Pantev, Wienbrunch, Rockstroh, & Taub, 1995).

*CNS Change in MS*

Examples of CNS structural reorganization in the aforementioned studies were in populations with “static” damage (e.g., amputation, stroke): their CNS alteration occurred at a particular point in time. In individuals with “progressive” diseases (e.g., MS), differences in brain activity patterns relative to those without CNS injury have been shown. For example, examining functional activity of the CNS during a resting state, Liu et al. (2011) showed that a group of participants with RRMS had higher amounts of spontaneous brain activity in the insula/ superior temporal gyrus ipsilateral to the more-impaired upper-extremity compared to controls. This activity correlated positively with scores on the Expanded Disability Status Scale (EDSS). Pantano et al. (2002) similarly found that individuals with hemiparetic MS showed greater functional magnetic resonance imaging (fMRI) activation than controls in motor areas ipsilateral and contralateral to the more-impaired arm during a sequential finger-to-thumb opposition task. In addition, Morgen et al. (2004) found that less task-specific reduction in fMRI activation of motor areas occurs during spontaneous thumb movements in individuals with MS compared to controls who underwent the same training. One study showed a change in white matter structures after training. Ibrahim et al. (2011) showed improvements in WM integrity (fractional anisotropy (FA) value) of the corpus callosum after physical therapy treatment in individuals with MS.
Plasticity Induced by CI therapy

Studies using brain mapping (transcranial magnetic stimulation) and functional brain techniques (electroencephalography, positron emission tomography, fMRI) indicate that a plastic brain change occurs following CI therapy in adults (Könönen et al., 2012; Kopp et al., 1999; Liepert et al., 1998; 2000; Schaechter et al., 2002; Wittenberg et al., 2003) and children (Sutcliffe, Gaetz, Logan, Cheyne, & Fehlings, 2007; Sutcliffe, Logan, & Fehlings, 2009). For example, in adults with chronic stroke, Könönen et al. (2012) found increased fMRI activation in the sensorimotor region and significantly reduced contralateral corticospinal tract conduction time after CI therapy. However, results from functional brain activity studies may be influenced by extraneous factors including the participant’s attention, the task administered, the extent to which the movements employed are controlled, and the other control conditions in the experimental situation. In light of these sources of variability, conclusions from such studies are difficult to interpret. Imaging techniques examining structural plasticity avoid the variability of functional imaging which requires limb movement during the scan.

Experience-related changes in the structure of the brain have also been demonstrated using voxel-based morphometry (VBM). Studies in healthy adults have found that an increase in grey matter (GM) occurred in bilateral mid-temporal regions and the left posterior intraparietal sulcus following three months of juggling practice (Draganski et al., 2004) and in the parieto-occipital junction following forty hours of golf practice (Bezzola, Merillat, Gasser, & Jancke, 2011). In research from this laboratory, as
noted, an increase in GM was found to occur following CI therapy in adults with chronic stroke in sensory and motor areas, and the hippocampus in both hemispheres (Gauthier et al., 2008).

Diffusion Tensor Imaging (DTI)

Since its inception in 1990 (Moseley et al.), DTI has been established as a validated measure of WM integrity (Wakana et al., 2007). DTI is based on the non-random movement of water molecules in the brain. Magnitude of directional diffusion is characterized by a FA value: Large FA values indicate an area in which the diffusion is in a common direction, with lower values indicating more random movement. FA values reflect structural properties at the cellular level including a combination of axon diameter, fiber density, and myelination. Considered collectively, these measures reflect the structural integrity of a tract (Beaulieu, 2009; Jang, 2010).

Plastic change of WM tract integrity (FA value) has been demonstrated following motor-training, such as juggling training in healthy adults (Scholz, Klein, Behrens & Johansen-Berg, 2009) and piano practice in children (Bengtsson et al., 2005). After neurological damage, positive change in WM tracts has been observed following melodic intonation therapy in individuals with stroke with Broca's aphasia (Schlaug, Marchina, & Norton, 2009) and vision training in individuals with a traumatic brain injury (Jaswal, Alkan, Kim, Biswal, & Alvarez, 2010). Additionally, FA value increases in focal regions of the corticospinal tract (CST) have been demonstrated in children with cerebral palsy with spastic quadriparesis after botulinum injection followed by physical therapy (Trivedi et al., 2008).
DTI and Motor Function in MS

In individuals with MS, the relationship between structural properties of the CNS, motor function, and improvement in motor function due to therapy is unclear. Diffusion tensor techniques have detected whole brain and tract-specific changes in the integrity of WM in such individuals due to disease progression (Harrison et al., 2011) as well as therapy (Ibrahim et al., 2011). DTI has also been able to detect WM abnormalities in individuals with MS not present in healthy controls (Bodini, Khaleeli, Cercignani, Miller, Thompson, & Ciccarellia, 2009; Cercignani, Inglese, Pagani, Comi & Filippi, 2001). DTI has also been utilized with this population to identify the relationship between characteristics of CST in the brain and motor function. Pagani, Filippi, Rocca, and Horsfield (2005) found that lesion overlap of the CST was related to poorer motor function in individuals with MS. Several studies have found that the DTI-quantified integrity of the CST was decreased in individuals with MS relative to controls (Ceccarelli et al., 2010; Reich et al., 2008; Wilson, Tench, Morgan, and Blumhardt, 2003).

Specific Aims and Hypotheses

Aim 1: Compare the outcome of CI therapy and a combination of CAM treatments in adults with hemiparetic progressive MS (i.e., progressive MS producing asymmetric motor deficits of the upper extremities).

Hypothesis 1: CI therapy will produce greater improvement in upper-extremity function than the CAM treatment in adults with hemiparetic progressive MS.
Aim 2: Determine whether WM integrity of the CST contralateral to the motor deficit differs from that of the ipsilateral CST at pretreatment in adults with hemiparetic progressive MS before CI therapy treatment.

*Hypothesis 2:* White matter integrity of the CST contralateral to the side of motor deficit will be less than that of the ipsilateral CST before CI therapy treatment.

Aim 3: Determine if either WM integrity of the CST ipsilateral or contralateral to the side of motor deficit, or other pretreatment WM characteristics are related to amount of upper-extremity motor deficit in adults with hemiparetic progressive MS.

*Hypothesis 3:* Prior to treatment, adults with hemiparetic MS with greater integrity of the CST contralateral and ipsilateral to the side of motor deficit will have less motor deficit.

Aim 4: Determine if either WM integrity of the CST ipsilateral or contralateral to the side of motor deficit, or other pretreatment WM characteristics are related to amount of upper-extremity motor improvement following CI therapy in adults with hemiparetic progressive MS.

*Hypothesis 4:* Prior to treatment, adults with hemiparetic MS with greater integrity of the CST contralateral and ipsilateral to the side of motor deficit will have similar improvement in motor function compared to those with lesser CST integrity.
Aim 5: Ascertain whether there is a structural neuroplastic change in the CST, or other WM tract, following CI therapy or CAM treatment in adults with hemiparetic progressive MS.

_Hypothesis 5:_ The CST will show an increase in integrity following CI therapy and not CAM treatment in adults with hemiparetic progressive MS.

_Aim 6:_ If there is structural change in the CST or other WM tract in adults with hemiparetic progressive MS due to CI therapy or CAM treatment (Specific Aim 5), determine if this change correlates with functional motor improvement due to the therapy.

_Hypothesis 6:_ The amount of structural change in the CST following CI therapy will correlate with gains in upper-limb motor function in adults with hemiparetic progressive MS.

**RESEARCH DESIGN AND METHODS**

**Participants**

Eighteen participants with moderate upper extremity hemiparesis over the age of 21 with slowly progressive MS were randomized and received CI therapy or a set of CAM treatments. Participants were obtained from local physician referrals and self-referrals, by newsletters from the Alabama Chapter of the National MS Society, and announcements of this study at Clinicaltrials.gov or the website from this laboratory. Participant characteristics are reported in Table 1. This project was approved by the Institutional Review Board for human research at the University of Alabama at
Birmingham (IRB# X111130009). Informed consent was obtained from each participant.
Analysis for this study was a part of a larger study (“Brain Responses to Rehabilitation in Progressive MS,” IRB #F090415004, Funding Agency: National Institutes of Health, PI: Victor W. Mark, M.D.), which has been approved by this institution’s Institutional Review Board.

**[TABLE 1]**

*Inclusion Criteria*

The inclusion criteria were: 1) moderate upper extremity hemiparesis defined as the ability to lift the more-affected arm from a table to at least shoulder height, extend the digits and wrist at least 10 degrees, and to grasp and release a small object (e.g., a hand towel), 2) functional upper extremity deficit resulting from MS in the opinion of the primary physician, 3) MS in a slowly progressive, non-relapsing phase of disease with no relapses for at least the past 3 months to reduce variability of the course of the disease which could have potentially contributed to ability to participate and respond to therapy (individuals who were formally diagnosed with either primary progressive MS, secondary progressive MS, or relapse-remitting MS were included), 4) Motor Activity Log score less than 2.5/5, demonstrating significantly reduced use of the more-affected arm and potential for improvement with therapy, 5) MiniMental State Exam score equal to or greater than 23/30, and 6) ability to tolerate 3 hours / day of repetitive physical therapy for 10 consecutive weekdays.
Exclusion Criteria

The exclusion criteria were: 1) ferromagnetic metal in the body or any other factor that would preclude MRI scanning, 2) participation in concurrent physical therapy or movement research, or 3) previous CI therapy or forced-use therapy exposure.

Procedures

Clinical measures of motor function and MRI acquisition were performed immediately prior to and following the two week period of either CI or CAM therapy.

CI Therapy

CI therapy consists of four main components: massed practice training of the more-affected arm, training by shaping, a transfer package, and restraint of the less-affected arm. Training of the more-affected arm by shaping (Skinner, 1938; Taub et al., 1994) was done in the lab for three hours each weekday for two consecutive weeks. Tasks used in CI therapy are designed to be functionally-relevant, and include a focus on techniques such as digit dexterity, grasp, or wrist movement. The proportion of time spent in each activity was based upon the opinion of the therapist as to what was likely to benefit the patient, and agreement between the patient and the therapist. Rest periods to prevent excessive fatigue were provided by the therapist on an as-needed basis. The transfer package involves daily monitoring of real-world use of the affected arm, problem-solving with a therapist to overcome perceived barriers to use of the more-affected arm, prescribed home practice of activities of daily living, behavioral contracting, and a diary maintained daily by the participant to record which activities
specified in the behavioral contract were carried out in the home environment. The transfer package requires 0.5 hours per day in addition to the three hours of daily training. Restraint of the less-impaired arm for a target of 90% of waking hours over the duration of treatment was accomplished with a padded mitt which limits the limb’s ability to do common tasks, but does not compromise safety by preventing individuals from bracing or balancing themselves.

**Complementary Therapy**

To control for any gains in motor function that may occur as a result of participant expectancy of improvement due to a therapy, participants in the comparison group received a set of CAM treatments at the UAB Hospital Recreation Center for the same amount of time as participants in the CI therapy group spent doing therapy (3.5 hours / day for 10 consecutive weekdays; 35 hours over two weeks). Therapies were administered under the supervision of a recreational therapist (Terrie Adams, MS, CFS), and included: relaxation exercises, pool therapy, and yoga. These activities were chosen because they were found to be desirable for individuals with MS and are not likely to fatigue them. The proportion of time to be spent in each activity was based upon the participant’s preference, opinion of the therapist as to what was likely to benefit the participant, and agreement between the participant and the therapist. This was also the procedure used for the selection of training activities by the therapist and those participating in CI therapy.
Running head: RELATIONSHIP OF WM INTEGRITY TO CI THERAPY IN HEMIPARETIC MS

Clinical outcome measures

*Motor Activity Log (MAL)*

The MAL is a scripted, structured interview that asks individuals to rate (on an 11-point Likert scale anchored by definitions at six points) the frequency (Amount of Use scale) and quality (Quality of Movement scale) of their more-impaired upper extremity use. It includes thirty activities of daily living, such as opening a drawer or using a fork, among other tasks. The two scales of the MAL (Amount of Use and Quality of Movement) are highly correlated; the Quality of Movement scale was used for this study. This measure has been found to be reliable and valid (Uswatte, Taub, Morris, Light, & Thompson, 2006; Uswatte, Taub, Morris, Vignolo, & McCulloch, 2005; van der Lee, Beckerman, Knol, de Vet, & Bouter, 2004).

*Wolf Motor Function Test (WMFT)*

The WMFT is a reliable and valid measure of prompted movement in the laboratory (Morris, Uswatte, Crago, Cook, & Taub, 2001; Wolf et al., 2006). It assesses the speed of movement of the more-impaired arm on seventeen standard, simple movements or tasks: two involve measuring strength and fifteen involve recording time to completion of a movement task. After the time to complete a task was recorded, it was converted into a “rate”: the number of times the task would be accomplished in 60 seconds (by dividing 60 by the time for completion of that task) (Hodics, Nakatsuak, Uperti, Alex, Smith, & Pezzullo, 2012). An average of the “rates” across all of the timed tasks in this measure was then calculated.
Patient Opinion Survey

Prior to participating in therapy, participants indicated on a scale from 1 (strongly disagree) to 7 (strongly agree) how strongly they anticipated improvement in motor function of their more-impaired upper extremity due to therapy (CI therapy or CAM therapies). Information about anticipated improvement in motor function due to therapy was obtained to indicate whether the expectation to improve differed among participants between the two treatments.

Expanded Disability Status Scale (EDSS)

The EDSS is a physician-administered measure commonly used in individuals with MS to determine degree of functional impairment. Scores on the EDSS range from 0 (Normal Neurological Exam) to 10 (Death due to MS) by 0.5 point increments (Kurtzke, 1983). This measure was administered prior to participation in therapy.

Neuroimaging

Structural DTI images were obtained on a 3.0 Tesla Allegra scanner at the Civitan International Research Center in Birmingham, Alabama. Whole-brain diffusion images were acquired in 32 directions with the following parameters: approximately 38 slices 3mm thick with a 1mm gap between slices, single shot echo planar (EPI), TR = 5600ms, TE =96ms, voxel size = 1.6 x1.6 x 3.0 mm^3, FOV = 210mm and, b value = 1250 s/mm^2.
Diffusion Tensor Imaging

FSL (Smith et al., 2004) was used to create FA maps for each scan and to perform probabilistic tractography for locating the CST. First, imported dicom files were converted to NIfTI-1 format prior to any preprocessing. Second, the image was skullstripped using the Brain Extraction Tool (Smith, 2002) and checked so that parenchyma close to the skull would not be eroded erroneously. Next, after application of eddy current corrections, the diffusion tensor model was “fit” at each voxel and values greater than one replaced with the average of the voxels surrounding it.

Probabilistic tractography was used to isolate each individual’s CST contralateral and ipsilateral to their more-impaired upper extremity. FA values were extracted at each voxel in the area of interest (the CST). Probabilistic tractography is a well-validated technique (Dyrby et al., 2007). The Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) was applied to the images to create all necessary files in FSL (Smith et al., 2004). Creation of a region of interest (ROI) (the CST in this study) requires the application of four types of ROIs to indicate the starting and ending point of tractography: seed ROI, waypoint ROI, exclusion ROI, and termination ROI. The tract starting at the seed ROI must go through the waypoint ROI to be considered. Any pathway going through the exclusion ROI is excluded from analysis, and any tract reaching a termination ROI is stopped at that point. Whole brain and hemispheric analysis of FA value was also performed by thresholding the whole brain diffusion FA data at values greater than 0.20 (Dineen et al., 2008). Voxels with FA values less than 0.20 were excluded from analysis.
Tract-Based Spatial Statistics (TBSS)

Whole brain and CST data were also analyzed employing a voxelwise statistical analysis of the DTI data using TBSS (Smith, 2006). In order to carry out within-participant comparisons from pretreatment to post-treatment and between-group comparisons at pretreatment, a mean FA image from the sample of participants in the current study was created and thinned to make a mean FA skeleton. This skeletonized image represents the centers of all tracts common to the group. Each participant’s aligned FA data was projected onto this skeleton and the resulting data analyzed using voxelwise statistics (Prakash, Snook, Moti, & Kramer, 2010). FA value at each voxel was then able to be calculated for each participant’s pretreatment and post-treatment data.

Data Analysis

Independent-sample t-tests were used to evaluate differences between the groups before treatment in the motor characteristics studied, specifically more-affected arm use (MAL) and more-affected arm motor capacity (WMFT). Mixed repeated-measures ANOVAs for the MAL and the WMFT (separately) were used to examine between-group differences in more-impaired upper extremity change due to therapy. In these models, the repeated measures factor was Time (Pretreatment, Post-treatment); the between subjects factor was Group (CI therapy, CAM therapy). An advantage for one of the treatments was indicated by a significant Time x Group interaction. Changes from pre to post-treatment were also examined within each group using paired t-tests. Correspondingly, the size of the treatment effects were calculated for a between-subjects
effect size \( (d) \) by dividing the difference between a mean score of the two groups (e.g., post-treatment MAL scores) by the standard deviation of the sample. Within-subjects effect size \( (d') \) was calculated by dividing the mean change of a group on a motor measure by the standard deviation of the change (Cohen, 1988). An effect size value of 0.57 is considered large in the meta-analysis literature. Statistical models parallel to those for the motor characteristics were used to test for pre-treatment differences and pre-to post-treatment changes in the neuroanatomical characteristics studied. A paired t-test was conducted comparing the mean FA value of the contralateral and ipsilateral CSTs. Correction for family-wise error (FWE) for the voxel-based method was used. Pearson correlation coefficients were calculated to determine direction, magnitude, and significance of the relationship of mean FA value of CST ipsilateral and contralateral to the more-impaired arm, indicative of WM integrity, and pretreatment function of the paretic upper-extremity. Pearson correlation coefficients were calculated to determine the relationship of mean FA value of CST ipsilateral and contralateral to the more-impaired arm and post-treatment function of the paretic upper-extremity due to therapy while controlling for pretreatment motor function. The relationship between structural improvement and functional improvement was investigated by doing Pearson correlations between functional change due to therapy (in the MAL and WMFT separately) and structural change (in mean FA value of the contralateral and ipsilateral CST separately) from pretreatment to post-treatment separately for both the CI therapy and CAM groups.
RESULTS

Motor Characteristics and Changes after Therapy

Participants in the CI therapy and CAM therapy groups did not differ in any demographic characteristics ($P>0.05$). The CI therapy group had higher Wolf Motor Function Test Rate scores prior to therapy than the CAM therapy group ($t_{(16)} = 2.27; P = 0.04$). MAL scores demonstrated that the CI therapy group showed greater improvement in movements of the more-affected arm in the life situation than the CAM therapy group ($F_{(1,16)} = 27.90; P < 0.001; d = 1.55$; Table 2). The CI therapy group showed a significant improvement in real-world arm use ($t_{(8)} = 9.93; P < 0.001; d' = 3.45$) that was 4.1 times greater than that seen in the comparison therapy patients, although the comparison group also significantly improved on the MAL ($t_{(8)} = 2.30; P = 0.05; d' = 0.77$). Both groups improved on the Wolf Motor Function Test Rate score ($F_{(1,16)} = 27.98; P < 0.001$). No interaction effect was observed, indicating that CI therapy and the CAM therapies were similarly effective at yielding improvements on this laboratory-based measure of motor ability.

[TABLE 2]

Prior to treatment, there was no difference between CI therapy and CAM therapy groups in their anticipation of gains to be made from therapy, as indicated on the Patient Opinion Survey ($t_{(17)} = 0.44; P = 0.67$). In addition, anticipated improvement in motor function did not relate to gains in motor function made following CAM therapy ($r_{(7)}^{MAL} = 0.21; P = 0.59; r_{(7)}^{WMFT} = 0.14; P = 0.72$) or CI therapy ($r_{(7)}^{MAL} = -0.23; P = 0.55; r_{(7)}^{WMFT} = -0.15; P = 0.70$). Pretreatment EDSS did not relate to pretreatment motor function on the MAL ($r_{(10)} = 0.11, P = 0.68$) or WMFT ($r_{(10)} = -0.08, P=0.74$), or gains
made due to therapy in either the CI therapy group ($r_{(7)}^{MAL} = -0.07$, $P=0.85$; $r_{(7)}^{WMFT} = -0.26$, $P = 0.51$) or the CAM group ($r_{(7)}^{MAL} = -0.41$, $P=0.28$; $r_{(7)}^{WMFT} = 0.19$, $P = 0.63$).

**Neuroanatomical Characteristics Before Treatment**

Prior to treatment, there was no difference in FA value of the contralateral or ipsilateral CST between the CI therapy and CAM therapy groups ($P > 0.05$). There was no difference in FA value between the CST contralateral to the more-affected arm (M = 0.4671, SD = 0.0272) and the ipsilateral CST (M = 0.4609, SD = 0.0395) at pretreatment ($t_{(16)} = 0.24; P = 0.81$).

**Relation of Pre-treatment Neuroanatomical Characteristics to Motor Function and to Motor Response to Therapy**

Pretreatment FA values of the ipsilateral and contralateral CST did not correlate with pretreatment hemiparetic arm use on the MAL or the WMFT ($P$ values = 0.13 - 0.58). The correlation of pretreatment contralateral CST FA value and motor improvement on the MAL following CI therapy approached significance ($r_{(7)} = 0.65$, $P = 0.057$). Pretreatment CST FA values of participants in the CAM therapy group did not relate to motor improvement due to therapy ($P$ values = 0.58 - 0.93).

[TABLE 3]  
[FIGURE 1]
White Matter Change after Therapy

There was not a main effect of treatment on the CST FA values ($F_{(1,16)}^{ipsilateral} = 3.55; P = 0.08$; $F_{(1,16)}^{contralateral} = 0.35; P = 0.56$) or interaction effects ($F_{(1,16)}^{ipsilateral} = 1.90; P = 0.19$; $F_{(1,16)}^{contralateral} = 0.95; P = 0.34$), indicating no difference in CST FA value change between the CI therapy and the CAM therapy groups following treatment. Follow-up analyses indicated there was no change in FA of the ipsilateral or contralateral CST following CI therapy ($t_{(8)}^{contralateral} = 0.25, P = 0.81; t_{(8)}^{ipsilateral} = -0.39, P = 0.71$). In the CAM group, there was a moderate reduction in FA of the ipsilateral CST from pretreatment to post-treatment ($t_{(8)} = -2.15, P = 0.06$) and no change in FA of the contralateral CST ($t_{(8)} = -1.23, P = 0.25$). When conducting whole-brain clusterwise voxel analysis (thresholds of $P < 0.2, t_{crit}=2.306$), no change in FA was detected following CI therapy. Negative changes in FA were detected in small clusters of voxels following CAM treatment in the ipsilateral anterior limb of the internal capsule as it projects to the frontal region ($P_{FWE}=0.008; cluster size = 115 voxels$) and posterior ipsilateral cerebral peduncle ($P_{FWE}=0.008; cluster size = 118 voxels$) and are shown in Figure 2.

[FIGURE 2]

White Matter Change & Motor Change Relationships

There was no relationship between treatment change in FA value of the CSTs and change in motor function due to CI therapy ($P$ values $= 0.23 - 0.92$) or CAM treatment ($P$ values $= 0.43- 0.77$). Additionally, there was no relationship between change in FA value
following CAM therapy (of the ipsilateral anterior limb of the internal capsule or ipsilateral posterior cerebral peduncle) and change in motor function.

DISCUSSION

These results confirm the efficacy of CI therapy in improving use of the more-affected arm in daily life in individuals with MS: the CI therapy group showed greater improvement of the MAL than the CAM group. The two groups, however, improved similarly on a laboratory-based measure of motor ability. Pretreatment white matter integrity (FA values) of the ipsilateral and contralateral CST did not correlate with hemiparetic arm use on the MAL or the WMFT before treatment. However, participants with greater pretreatment white matter integrity of the contralateral CST had greater improvement following CI therapy on the Motor Activity Log. There was no change in the CST or any other white matter regions following CI therapy. In the CAM therapy group, there was a moderate reduction in white matter integrity of the ipsilateral CST from pretreatment to post-treatment and reduction in white matter integrity in small regions in the ipsilateral anterior limb of the internal capsule and the posterior ipsilateral cerebral peduncle. These reductions in white matter integrity were unrelated to improvements in motor function made following therapy.

The current study demonstrates that CI therapy is efficacious in improving use of the more-affected arm in daily life in individuals with MS. This confirms findings from a previous study (Mark et al., 2008) in a smaller sample (n=5) which did not have a comparison therapy. In the current study, the CI therapy group had a significantly higher
WMFT score (M = 41.35, SD = 5.51) than the control group (M = 32.50, SD = 10.34) before therapy ($t_{(16)} = 2.27; P = 0.04$), but both groups had similar improvements afterwards. This pattern permits two possible interpretations of the results on the WMFT. One interpretation is that there is a ceiling effect in place, and the results from this sample are not interpretable. In support of this, the CI therapy group’s pretreatment WMFT performance is similar to the post CI therapy performance of a sample of patients with chronic stroke in a recent publication (Taub et al., 2013). The second interpretation is that there is not a ceiling effect. If this is the case, we could conclude that CI therapy and CAM treatments produce similar improvement on the WMFT. In support of this, the groups improved similarly on the measure and there were no correlations between pretreatment motor function and improvement.

WM integrity of the contralateral CST at pretreatment was moderately related ($P=0.06$) to improvement in real-world motor function following CI therapy. In individuals with chronic stroke, improvement on a laboratory measure of motor function following CI therapy has been demonstrated to be related to the amount of healthy-appearing parenchyma (Brain Parenchymal Fraction) at pretreatment (Rickards et al., 2012). However, improvement in real-world and laboratory-measured motor function following CI therapy has been found to be unrelated to integrity of the CST at pretreatment in adults with chronic stroke (Hu et al., 2009; Rijntes et al., 2011; Sterr et al., 2010) or children with cerebral palsy (Rickards et al., unpublished manuscript). In individuals with MS, decreased WM integrity is related to poorer global functional status and more severe symptomology (Rovaris & Filippi, 2007). Therefore, it is possible that
the ability to improve real-world motor function following CI therapy may be attenuated due to a diminished global status of the individual.

Prior to treatment, WM integrity of the CST was unrelated to real-world or laboratory-based motor function. WM integrity of the CST prior to treatment has been found to be related to hemiparetic arm function in adults with chronic stroke (Sterr et al., 2010) and children with cerebral palsy (Rickards et al., unpublished), but this relationship is not well-studied in adults with hemiparetic MS. Some results suggest that CST integrity may be related to motor function in adults with MS (Ceccarelli et al., 2010; Reich et al., 2008). However, pathology secondary to MS is not limited to the brain. One study (Hoing & Sheremata, 1989) found that approximately half of their sample (n=77) had regions of their spinal cord displaying suspected pathology. Additionally, WM integrity of the spinal cord has been related to overall motor function as measured by the EDSS and the MS functional composite scale (Oh et al., 2013).

Change in WM integrity following CI therapy in individuals with MS was not observed in the brain; however it may occur in the spinal cord. Also, structural changes may occur in grey matter, which was not studied here. Increases in grey matter volume that correlate with improvement in everyday motor function has been observed following CI therapy in adults with chronic stroke (Gauthier et al., 2008) and children with cerebral palsy (Sterling et al., 2013). Alternatively, there may be a change in WM integrity in the CST that is masked by the fact that motor fibers of the lower extremities and torso also run in the CST. To address this problem, quantification of the integrity of WM would have to be fiber-specific and at high resolution. The small decline in WM integrity observed in the ipsilateral CST in the CAM treatment group may be due to the
progressive nature of MS. This negative change may have been “stabilized” in the CI therapy group. However, it may also be a spurious finding: the negative change in WM integrity was unrelated to any improvement(s) made in motor function following treatment.

Future studies should include analysis of the structural integrity of the spinal cord, in addition to the brain, to assess whether structural change and/or white matter status in that region correlates with motor function. Increased resolution of MRI scans providing 1.) smaller voxels for analysis and 2.) additional directional data to control for crossing white matter tracts within a given region of interest or individual voxel would be beneficial. However, scan acquisition time must be brief enough to remain tolerable to the participant. Another consideration for future studies is that white matter integrity may relate to capacity to retain gains made from CI therapy. One recent study in individuals with chronic stroke indicated that functional integrity of the CST (measured with fMRI activation) may relate to retention of gains made following CI therapy (Rijnjes, Hamzei, Glauche, Saur, & Weiller, 2011). If this is the case in those with MS, then structural white matter tract integrity might also prospectively indicate which participants would lose their CI therapy-induced gains in motor function over time and might therefore benefit from booster therapy sessions.
References


Running head: RELATIONSHIP OF WM INTEGRITY TO CI THERAPY IN HEMIPARETIC MS


Form 4: IRB Approval Form
Identification and Certification of Research Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: RICKARDS, TYLER
Co-Investigator(s):
Protocol Number: X111130009
Protocol Title: Neuroplasticity Induced by Constraint-Induced Movement Therapy in Adults with Multiple Sclerosis: A Diffusion Tensor Imaging Study

The IRB reviewed and approved the above named project on 1-27-12. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.
RB Approval Date: 1-27-12
Date IRB Approval Issued: 1-27-12

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigator please note:
The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
UAB IRB Approval of Waiver of Informed Consent and/or Waiver of Patient Authorization

Approval of Waiver of Informed Consent to Participate in Research. The IRB reviewed the proposed research and granted the request for waiver of informed consent to participate in research, based on the following findings:
1. The research involves no more than minimal risk to the subjects.
2. The research cannot practically be carried out without the waiver.
3. The waiver will not adversely affect the rights and welfare of the subjects.
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Check one: □ and Waiver of Authorization (below) □ or Waiver of Authorization (below) □ Waiver of Authorization not applicable

Approval of Waiver of Patient Authorization to Use PHI in Research. The IRB reviewed the proposed research and granted the request for waiver of patient authorization to use PHI in research, based on the following findings:
1. The use/disclosure of PHI involves no more than minimal risk to the privacy of individuals
   i. There is an adequate plan to protect the identifiers from improper use and disclosure.
   ii. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention that is otherwise required by law.
   iii. There is an assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The research cannot practically be conducted without the waiver or alteration.
3. The research cannot practically be conducted without access to and use of the PHI.

—OR—

Full Review
The IRB reviewed the proposed research at a convened meeting at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The waiver of authorization was approved by the majority of the IRB members present at the meeting.

Date of Meeting
Signature of Chair, Vice-Chair or Designee

Date

Expedited Review
The IRB used an expedited review procedure because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the waiver of authorization were carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

1-27-12
Date of Expedited Review
Signature of Chair, Vice-Chair or Designee

Date 1-27-12
Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: RICKARDS, TYLER
Co-investigator(s): 
Protocol Number: X11113009
Protocol Title: Neuroplasticity Induced by Constraint-Induced Movement Therapy in Adults with Multiple Sclerosis: A Diffusion Tensor Imaging Study

The IRB reviewed and approved the above named project on 1/16/13. The review was conducted in accordance with UAB’s Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.
IRB Approval Date: 1/16/13
Date IRB Approval Issued: 1/16/13
HIPAA Waiver Approved: Yes

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.
TABLES

Table 1. Participant characteristics.

<table>
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<th>Participant No.</th>
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CI THERAPY

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OVERALL:

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*Note.* CAM = Complementary and Alternative Medicine; EDSS = Expanded Disability Status Scale; RR = Relapse-Remitting MS; PP = Primary Progressive MS; SP = Secondary Progressive MS.
Table 2. Clinical outcomes data for CI therapy and CAM groups.

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Note. 1Cohen’s d’ is a within-subjects measure of effect size. It is the mean change divided by the SD of the change. A value of 0.57 is considered large in the meta-analysis literature.

* = Significant difference (P≤0.05) from pretreatment to post-treatment

** = Significant difference (P≤0.01) from pretreatment to post-treatment

*** = Significant difference (P≤0.001) from pretreatment to post-treatment

† = Significant difference (P≤0.001) between groups.

Table 3. Correlations between FA values at pretreatment and change in motor scores following therapy.

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<th>FA of Ipsilaterial CST</th>
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<td></td>
<td>0.057~</td>
<td>0.332</td>
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<td>Change in WMFT</td>
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<td></td>
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<td>Change in WMFT</td>
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<td></td>
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Note. ~p<.1
FIGURES

**Figure 1.** Correlation between pretreatment FA value of the contralateral CST and change on the MAL following CI therapy.

![Treatment Change Correlation between the MAL and Contralateral CST](image)

*Note.* $*P = 0.057$
Figure 2. Areas of reduction in FA following CAM therapy. On the left is an axial slice (z = -1) showing a portion of the ipsilateral posterior cerebral peduncle; on the right (z = 3) is a region of the ipsilateral anterior limb of the internal capsule extending into the frontal region. Both regions are in red overlaid onto the MNI 152 T1 template image.