THE STATUS OF WHITE MATTER IN PATIENTS WITH HEMIPARESIS GIVEN CI THERAPY: A DIFFUSION TENSOR IMAGING STUDY

by

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

BIRMINGHAM, ALABAMA

2009
ABSTRACT

While attempts have been made to identify the cause and mechanism of motor deficit and subsequent recovery, there are several aspects of hemiparesis, especially in the chronic phase of acquired brain injury, that are still unclear. This study used diffusion tensor imaging (DTI) to study the role of white matter in upper extremity motor function in chronic hemiparesis, especially after administration of an efficacious therapy, Constraint-Induced Movement Therapy (CI therapy). This therapy has been proven effective in treating chronic motor deficit and has recently been associated with structural changes in the gray matter tissue in the brain. The goal of this study was to determine if DTI could identify structural brain changes in white matter of chronic stroke patients with motor deficit. In addition, a small number of patients were given CI therapy in a preliminary study to determine the relation of white matter damage to CI therapy outcome.

In eighteen chronic hemiparetic patients fractional anisotropy (FA) values were calculated over the whole brain, before and after either CI therapy or comparison therapy, and tractography was utilized to isolate the CST.

Results indicate that in the hemisphere contralateral to a hemiparetic limb there was a significantly reduced integrity of the white matter fibers compared to the ipsilateral
hemisphere. This was not only the case before CI therapy, which was expected, but it was also the case after CI therapy treatment. CI therapy did not increase the integrity of the CST.

A decrement in motor ability was found in patients with a distorted/disrupted CST. We hypothesize that the alterations in the path of the CST are indicative of a large reorganization of the brain due to the presence of lesions or hydrocephalus ex vacuo. This large scale reorganization could have interfered with the normal functioning of motor circuits. This finding may suggest that motor deficits after damage to the brain are not related to the integrity of the CST alone. The more important factor might be the strength of the entire motor circuitry in which the CST is only one participant.

Keywords: Constraint-Induced Movement therapy, hemiparesis, stroke, multiple sclerosis, magnetic resonance imagine, diffusion tensor image
DEDICATION

This dissertation is dedicated to…

My parents for their unending support and patience,

My friends for their extraordinary understanding,

And my loving husband for caring for me and making me laugh.
ACKNOWLEDGEMENTS

I would like to thank Drs. Taub, Uswatte, and Mark for mentoring me through the years.

Also to all the students who have come and gone throughout the years and provided their
time, help, and support.

Special thanks to Lynne Gauthier. We taught each other so much and became friends in
the process.

Thanks to my committee for their time and effort in guiding me through this process.

Finally, my thanks to the American Heart Association for funding this project through
0715450B Predoctoral Fellowship.
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<td>APB</td>
<td>abductor pollicis brevis</td>
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<td>BET</td>
<td>brain extraction tool</td>
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<tr>
<td>CI therapy</td>
<td>Constraint-Induced Movement therapy</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CST</td>
<td>corticospinal tract</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
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<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
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<tr>
<td>EPI</td>
<td>echo planar imaging</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>EXCITE</td>
<td>Extremity Constraint Induced Therapy Evaluation</td>
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<td>FA</td>
<td>fractional anisotropy</td>
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<tr>
<td>FOV</td>
<td>field of view</td>
</tr>
<tr>
<td>FSL</td>
<td>Functional Magnetic Resonance Imaging Software Library</td>
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<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>GM</td>
<td>gray matter</td>
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<td>MAL</td>
<td>Motor Activity Log</td>
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<td>MCMC</td>
<td>Markov Chain Monte Carlo</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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MS  multiple sclerosis
NifTI-1  Neuroimaging Informatics Technology Initiative
PDD  principle diffusion direction
PDF  probability density function
ROI  region of interest
SENSE  Sensitivity Encoding
SPM  statistical parametric mapping
TE  echo time
TR  repetition time
VBM  voxel-based morphometry
WM  white matter
WMFT  Wolf Motor Function Test
INTRODUCTION

According to the Center for Disease Control (NCHS, 2005), stroke is the third leading cause of death and the second leading cause of limitations in activity in the United States. Multiple sclerosis (MS), a chronic demyelinating disease of the central nervous system (CNS), is the leading cause of non-traumatic disability in young adults (Anderson et al., 1992), with progressive MS increasing in severity into middle and late adulthood. While both diseases have different causes and mechanisms of damage, the resulting clinical presentation and changes in behavior can be very similar. Hemiparesis has been seen in patients with MS (Cowan, Ormerod, & Rudge, 1990; Mark et al., 2008a) and is a common lasting effect of stroke (Lawrence et al., 2001) that greatly limits the ability of patients to live a normal and productive life.

Although both MS and stroke’s disabilities have been extensively studied, CNS factors directly influencing the severity of the hemiparesis found in both and the effect of brain plasticity on recovery still need more clarification. This study focused on these topics by investigating the integrity and path of the corticospinal tract (CST) following stroke and possible structural plasticity using a magnetic resonance imaging (MRI) technique called diffusion tensor imaging (DTI). CI therapy, which has been proven effective in treating hemiparesis in the chronic phase, was used to facilitate motor improvement and possibly brain plasticity. To our knowledge this is the first study to use DTI in studying the effects of an efficacious treatment for hemiparesis in the stroke and MS population.
Constraint-Induced Movement Therapy

CI therapy is a neurorehabilitation technique aimed at treating upper extremity motor deficit. It was derived from basic research with monkeys who were given surgical deafferentation of a single forelimb (Taub, 1976; Taub, 1980; Taub, Harger, Grier, & Hodos, 1980). Following this procedure, monkeys did not use the affected limb in the free situation (Mott & Sherrington, 1895). However, they were induced to use the deafferented extremity by one of two general techniques: 1) restricting movement of the intact limb for 7 or more days; 2) training the deafferented arm, particularly with the technique termed shaping. Shaping requires that progressively more difficult movements be made after performance criteria for simpler movements are achieved. As a result of these techniques a formerly useless limb was converted into a limb that was used extensively.

CI therapy for humans with chronic hemiparesis involves the same methods including intensive training of the more-affected limb through shaping, combined with a set of techniques to promote the transfer of treatment gains to the life situation (“transfer package”). This is usually done while restricting the movement of the less-affected limb (Taub et al., 1993; Taub, Uswatte, & Elbert, 2002; Taub, Uswatte, & Pidikiti, 1999). As a consequence of the treatment, the motor function of the patients’ impaired extremity increases in the life situation as well as in laboratory assessments (Uswatte, Taub, Morris, Barman, & Crago, 2006).

CI therapy is the only rehabilitation technique shown to be efficacious in treating chronic stroke hemiparesis and has also been applied to several other diseases such as MS (Mark et al., 2008a), cerebral palsy (Taub et al., 2007; Taub, Ramey, DeLuca, & Echols,
2004), and traumatic brain injury (Morris & Taub, 2001). There is more evidence for its
efficacy for the treatment of motor deficit to extremities after damage to nervous system
than any other therapy. It has been shown to produce motor improvements in the
laboratory and real-life situations (Mark & Taub, 2004; Taub et al., 1993; Taub, Pidikiti,
DeLuca, & Crago, 1996; Taub et al., 1999). The result has been reproduced in numerous
laboratories (Bonifer, Anderson, & Arciniegas, 2005a; Bonifer, Anderson, & Arciniegas,
2005b; Dettmers et al., 2005; Miltner, Bauder, Sommer, Dettmers, & Taub, 1999), has
undergone placebo controlled trials (Taub et al., 1993; Taub et al., 1996; Taub et al.,
2006a), and recently been tested in a multi-site randomized national clinical trial, the
Extremity Constraint Induced Therapy Evaluation (EXCITE) (Winston et al., 2003; Wolf
et al., 2006). EXCITE included two hundred and twenty subacute patients (3-9 months
post-event) who were randomly assigned to either a CI therapy group or a group
receiving usual and customary care. Results from this study indicated significantly larger
improvements in more impaired arm function in the CI therapy group than the control
subjects and this difference was sustained over the 1-year of follow-up (Wolf et al.,
2006).

Mechanisms

While we have proof that CI therapy is efficacious in treating chronic hemiparesis,
the exact mechanisms that illustrate why these specific techniques might be effective in
recovery are still only partially explained.
Learned Non-Use

One possible mechanism for CI therapy’s effect is based on the hypothesis that hemiparesis not only arises directly from neurologic damage but also has a learning component and that CI therapy can be utilized to overcome this learned behavior. Taub and colleagues observed in deafferented primates that, when forced, the animals manipulated the affected extremity but did not do so spontaneously (Taub, 1980; Taub et al., 1980). In the chronic phase, the animals had the potential to use both arms, but that potential was unrealized; they relied entirely on the intact arm to complete tasks. The same phenomenon is seen in stroke patients in which the ability to use the arm is present yet the patient employs only the less affected arm in most tasks (Andrews & Stewart, 1979). Several converging lines of evidence suggested that nonuse of a single deafferented limb is a learning phenomenon called learned non-use, involving a conditioned suppression of movement (Holmberg, Ringblom, & Wadell, 1998; Taub, 1980; Taub, Uswatte, Mark, & Morris, 2006b). Immediately after neurologic damage, patients are confronted with the extreme difficulty or inability to use the arm. The more affected arm can often not be effectively used during the acute and early sub-acute periods leading to a decrease in the cortical representation of the more affected limb, which in turn could make movement more demanding and effortful (Taub, 1980; Taub et al., 2006b). Attempts at limb use are met with punishment in the form of a failure to succeed at anything an individual tried to do with the limb, which could lead to a conditioned suppression of attempts to use the limb. During stroke recovery, motor ability begins to return to normal; however, patients are hypothesized to retain the learned behavior of neglecting the affected arm. Therefore, there is a gap between what the
patient is capable of doing and what the patient does spontaneously in regards to arm manipulation. This disparity can be overcome by using CI therapy. By forcing the use of the involved extremity and positive reinforcement, the conditioned suppression can be overcome (Taub, 1980; Taub et al., 2006b).

**Brain plasticity**

As stated above, after damage to the motor areas of the brain there is a reduction in the representation area associated with motor control. Another possible mechanism for CI therapy’s benefits is to overcome this reduction by increasing the representational area devoted to the affected limb by neuroplastic mechanisms. In the 1980’s, research from Michael Merzenich and colleagues (Kaas, Merzenich, & Killackey, 1983; Merzenich et al., 1983; Merzenich et al., 1984) demonstrated the phenomenon of *injury-related brain plasticity* in which physically-induced changes to the extremities resulting in reduced afferent input affect their representation area in the brain. By removing the afferent inputs from the second and third digit of owl monkeys, Merzenich showed that representation areas of surrounding digits “invaded” the now deafferented cortical region (Merzenich et al., 1983). A similar study, in which entire digits were amputated instead of just the afferent inputs, showed again an expansion of the cortex representing the remaining intact digits into the cortical territory of the amputated digits (Merzenich et al., 1984).

Jenkins and colleagues (1990) provided evidence for a different type of brain plasticity, *use-dependent brain plasticity*. Instead of removing afferent inputs from the extremities, they showed that increasing the input by modifying behavior could also elicit a change in the brain. Monkeys were trained to perform “behaviorally relevant” tasks in
which one or more digits received increased tactile stimulation, resulting in an increased cortical representation area of the stimulated digits and a modification of the representation boundaries among the digits.

Recent advances in neuroimaging methods have allowed researchers to confirm noninvasively the presence of use-dependent and injury-dependent brain plasticity in humans. For example, increased cortical representation areas of the digits of both Braille readers (Sterr et al., 1998) and musicians (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995) have been identified using magnetic source imaging as an example of use-dependent increases. Not only can changes in representation areas be identified in humans by functional imaging techniques but it has been possible to observe structural changes in the tissue itself due to increased inputs. Maguire and co-workers (2000) showed that with increased driving time and knowledge of the city, London cab drivers had an increased posterior hippocampal volume, an area that is associated with learning spatial information. Draganski and colleagues (2004) showed that physical coordination tasks, such as juggling have a similar effect on the brain. In particular their studies indicate an increase in the density of gray matter in the anterior occipital regions of the cortex.

Although several studies have provided evidence for both use-dependent and injury-dependent brain plasticity, we are only beginning to understand the effect of brain plasticity after central nervous system damage and its possible role in rehabilitation. Functional changes in regional brain activity have previously been shown to occur as a result of CI therapy, including changes in excitability (Liepert et al., 2000), rate of metabolism (Wittenberg et al., 2003), and blood flow rate (Schaechter et al., 2002).
Liepert and colleagues (2000) used transcranial magnetic stimulation to map the cortical representation area of the abductor pollicis brevis (APB), an important muscle in the hand. Following CI therapy they found a near doubling of the excitable area of the APB in the infarcted hemisphere. Behavioral changes were found to parallel the expansion of representation area. In a related study, Kopp and colleagues (1999) used electroencephalography (EEG) dipole modeling of steady-state movement-related cortical potentials to locate the activation source associated with movement of the affected upper extremity. The main area of activation shifted from the ipsilesional hemisphere to the contralesional hemisphere after three months experience in increased post-treatment use of the more affected arm. Both of these studies provided the first pieces of evidence to suggest that CI therapy produces a change in the brain and that these changes are directly related to the patient’s behavior.

The use of functional magnetic resonance imaging (fMRI) has also identified the presence of neuroplasticity due to CI therapy. Levy et al. (2001) investigated brain changes after CI therapy in two chronic stroke patients. While this study was limited in sample, they did find difference in activation from pre- to post-therapy; however these areas were not common between the patients. In a later study by Johansen-Berg and colleagues (2002), differences were found in bilateral cerebellum, somatosensory cortex, and premotor cortex of the lesioned hemisphere which were related to measure of motor ability. Although many other fMRI studies have investigated the effect of CI therapy on brain function (Dong, Dobkin, Cen, Wu, & Winstein, 2006; Greenberg et al., 2004; Hamzei, Liepert, Dettmers, Weiller, & Rijntjes, 2006; Szaflarski et al., 2006), there has yet to be a strong consensus regarding sites of increased activation.
Structural imaging

One requirement of most functional imaging methods, which identifies localized brain activity, is the necessity of patient interaction, sometimes physical activity, during data acquisition. In the area of movement disorders, such as hemiparesis, movement patterns between patients can vary significantly, which could explain why there seem to be inconsistencies in the areas of increased activation. Structural imaging on the other hand requires no patient activity and therefore might be the preferable method to identify neuroplasticity events common to all patients.

Voxel-Based Morphometry

Voxel-Based Morphometry (VBM) is a whole-brain imaging technique that identifies differences in the density of gray matter using T1 weighted anatomical MRI (Ashburner & Friston, 2000; Ridgway et al., 2008). Recently Gauthier et al. (2008) reported structural brain changes following CI therapy using VBM techniques. Longitudinal VBM was performed on patients undergoing CI therapy and a Comparison therapy. Groups receiving CI therapy showed profuse increases in gray matter in sensory and motor cortices both contralateral and ipsilateral to the affected arm, as well as in bilateral hippocampi. Furthermore, increases in gray matter were significantly correlated with increases in spontaneous use of the affected extremity in activities of daily living in the life situation.
Diffusion Tensor Imaging

DTI is a relatively new structural imaging technique that is sensitive to the in vivo Brownian motion of water molecules in the brain. This diffusion is not completely random, or isotropic, but instead is anisotropic meaning that the water has a dominant direction of diffusion. Fractional anisotropy (FA) quantifies the magnitude of directional water movement. An area of the brain in which water diffuses at a high rate in a common direction is represented by large FA values and therefore has a higher probability of being part of a large axon bundle than areas with lower FA values.

DTI has already been validated (Burgel et al., 2006; Ciccarelli et al., 2003; Wakana et al., 2007) and utilized in normal populations to correlate the integrity of white matter tracts with certain behavioral outcomes. For example, in a recent study the amount of piano playing was found to be correlated with increased integrity of the corticospinal tract (CST), arcuate fasciculus, and the corpus callosum (Bengtsson et al., 2005). DTI has also aided the study of medial temporal lobe epilepsy by detecting abnormalities in the hippocampus in which diffusion in the ipsilesional hippocampus differed significantly from the contralesional hippocampus. There was also a difference in diffusion between epileptic patients and normal controls (Yu, Li, Yu, Wang, & Xue, 2006). In the stroke population, this technique has been utilized to establish relationships between tract integrity and the amount of spontaneous recovery of clinical function (Cho et al., 2007a; Konishi et al., 2005; Parmar, Golay, Lee, Hui, & Sitoh, 2006), identify Wallerian degeneration in the corpus callosum (Gupta et al., 2006), and demonstrate improvements in white matter years after stroke (Wang et al., 2006). It has
been paired with fMRI to help explain functional changes in the brain related to spontaneous stroke recovery (Jang et al., 2005).

Corticospinal Tract

Several studies have identified possible factors influencing the amount of motor deficit after stroke (Brott et al., 1989; Kim et al., 2008; Lee, Han, Kim, Kwon, & Kim, 2005; Schiemanck, Post, Witkamp, Kappelle, & Prevo, 2005; Warabi, Inoue, Noda, & Murakami, 1990); however, the majority of these studies were conducted in the acute or sub-acute stroke phase (ending 6 months to 1 year post-stroke). Very little information regarding this relationship was obtained for the chronic phase (more than 1 year post-stroke). A previous study from this laboratory investigated the influence of lesion volume on motor ability in chronic hemiparetic stroke patients. The results of that study indicated that the size of the lesion is not related the amount of motor deficit in the chronic phase. Gauthier et al. (2009) found that lesions located in the CST where the corona radiata intersects with fibers coming from the corpus callosum were associated with poor motor ability. This suggests that the important factor is not how big the lesion is but what structures are damaged. The CST, therefore, seems to be an important factor in analyzing motor deficit. To test this hypothesis, the present research focused on the CST specifically.

The corticospinal or pyramidal tract was first identified in the late 1800s by such investigators as Turck (1852) and Flechsig (1876). This collection of fibers originates in several areas of the cerebral cortex (Davidoff, 1990) and descends to the spinal cord with a decussation in the medulla. It contains axons associated with motor control arising in
the primary motor, premotor, supplementary motor, and somatosensory areas. We
focused on the CST for three main reasons. First it is the main fiber tract transmitting
signals from motor areas of the cerebral cortex downwards to the spinal cord. Second, it
is a very tightly packed bundle of fibers that is easily identified in the posterior limb of
the internal capsule (England, Netsky, & Adelman, 1975) and the cerebral peduncle
(Turck, 1852). Last it was implicated in Gauthier et al. (2009) as a location associated
with greater motor deficits.

Objectives

Previous CI therapy studies have shown that neuroplastic changes occur in
response to therapy using functional brain imaging techniques (Liepert et al., 2000;
Schaechter et al., 2002; Wittenberg et al., 2003). Gauthier et al. (2008) showed that CI
therapy could also produce a structural change in the brain involving an increase in gray
matter. In this study we attempted to determine whether there are also structural changes
in the white matter following CI therapy and to identify the general association of
hemiparesis with CST structure. Until this point, the great majority of hemiparetic
imaging studies reported in the literature were centered on the acute and subacute periods
after the acquired brain injury, specifically stroke, with little study of chronic
hemiparesis. It was previously assumed that chronic patients plateaued in their motor
recovery and as a result it was not of great importance to study this population. CI
therapy research has prompted revision of this view. Through the use of CI therapy large
improvements in motor function can be produced years after onset. This laboratory has
worked with many chronic patients and has the unique opportunity to study the brains of
patients years, sometimes decades, after the incident. The use of an efficacious therapy in conjunction with MRI techniques is novel and to our knowledge this study is the first time DTI has been used to analyze brain plasticity due to CI therapy. In addition, it is one of the few studies of the effects of hemiparesis on the white matter in stroke and progressive MS prior to the administration of therapy in the chronic phase.

**Specific Aims**

**Aim I.** To determine the extent to which chronic hemiparesis is associated with altered integrity of the CST contralateral to the motor deficit relative to the integrity of the CST ipsilateral to the motor deficit at *pre-treatment*.

**Aim II.** To determine whether the integrity of the CST contralateral to the motor deficit at *pre-treatment* is related to the amount of motor ability and spontaneous arm use at *pre-treatment*.

**Aim III.** To determine whether the integrity of the CST contralateral to the motor deficit at *pre-treatment* is related to the amount of change in motor ability and spontaneous arm use from *pre- to post-CI therapy*.

**Aim IV.** To evaluate whether CI therapy improves the integrity the CST contralateral or ipsilateral to the motor deficit from *pre- to post-treatment* and to determine if the amount of change in CST integrity from *pre- to post-treatment* is related to the amount of motor recovery due to CI therapy.

Although the specific aims above are focused on the integrity of the CST, we are also interested in the whole-brain white matter integrity and whether the paths of the CST were disrupted or distorted. An exploratory analysis re-evaluated the specific aims above
using the whole-brain white matter integrity as our primary measure. We also conducted an analysis to determine how a stroke can distort the path (independent of integrity) of the CST and whether a distorted/disrupted CST is predictive of decreased motor ability at pre-treatment and magnitude of the treatment change due to CI therapy.

RESEARCH DESIGN AND METHODS

Participants

Fifty-one chronic (> 1 year) stroke patients and 11 progressive MS patients were recruited between 2004 and 2008 to participate in studies aimed at 1) identifying the relative importance of the different components of CI therapy and 2) evaluating the overall benefits of CI therapy in the MS population (Mark et al., 2008a). Of these patients, diffusion images were obtained from 22 patients (21 chronic stroke, 1 progressive MS). Referrals to these programs came from UAB Hospital clinicians, stroke support groups, advertisements, and webpage contacts. Individuals were screened by the therapists using a structured telephone interview and a physician and therapist evaluated those patients who were found likely to be eligible in terms of the inclusion/exclusion criteria listed below. During this evaluation potential subjects underwent a cognitive test battery that consisted of the Folstein Mini-Mental State Examination (Folstein, Robins, & Helzer, 1983), Zung depression scale (Zung & Durham, 1965), and the Token Test of the Multilingual Aphasia Examination (Benton & Hamscher, 1983). While not intended to be a comprehensive neuropsychological assessment, the administration of these tests by the therapists helped determine which individuals had cognitive deficits that could have impeded their ability to understand and appropriately follow directions for motor tests,
questionnaires, and treatment. Therapists measured active range of motion of the more involved upper extremity using a standard goniometer and made additional clinical observations. The University of Alabama at Birmingham’s Institutional Review Board for human research approved protocol X070914001 (PI: Christi Perkins Hu). Qualifying patients provided signed informed consent.

Inclusion and Exclusion Criteria

The exclusion criteria were: 1) less than one year post-stroke; no upper limit regarding amount of time post-stroke; 2) refusal to have MRI scans pre- and post-treatment or the presence of metal inclusions in the body; 3) frailty, insufficient stamina, fatigue, or severe ataxia that prevented the patient from carrying out the requirements of the therapy (based on clinical judgment); 4) medications were not exclusionary except in the following cases: a. participation in any experimental drug field study, b. Botox injections to the more-affected upper extremity less than three months prior to participation, c. baclofen or dantrolene taken at the time of study; 5) excessive pain in any joint of the more-affected extremity that could limit ability to cooperate with the intervention (based on clinical judgment); 6) serious cognitive deficits as indicated by a Folstein Mini-Mental State Examination score of less than 24 (Bleecker, Bolla-Wilson, Kawas, & Agnew, 1988); 7) an inability to follow test instructions, using as a guide a score of 36 or below on the Token Test of the Multilingual Aphasia Examination (Benton et al., 1983); 8) serious, uncontrolled medical problems (e.g., cardiovascular, severe rheumatoid arthritis, serious joint deformity of arthritic origin, symptomatic cancer or renal disease, any kind of end-stage pulmonary or cardiovascular disease, senility or a
deteriorated condition due to age, uncontrolled epilepsy) as judged by the medical
director; 9) motor problems that are not primarily unilateral; 10) other neurological or
musculoskeletal conditions affecting upper extremity function; 11) 17 years old or
younger; 12) a history of traumatic brain injury as indicated by caregiver or self-report or
the medical records; 13) active range of motion not meeting the following levels: \( \geq 45^\circ \) of
abduction and flexion at the shoulder, extension at the elbow \( \geq 20^\circ \) from a \( 90^\circ \) flexed
starting position, extension at the wrist \( \geq 10^\circ \), extension of all metacarpophalangeal and
interphalangeal (either proximal or distal interphalangeal) joints \( \geq 10^\circ \) in the fingers, and
\( \geq 10^\circ \) of extension or abduction of the thumb.

Interventions

All patients received three and a half hours of therapy for ten weekdays over two
consecutive weeks with two additional days at pre-treatment and again at post-treatment
for testing. Patients were randomly assigned to two groups with two different forms of
treatment: CI therapy or a Comparison therapy.

CI therapy group.

This group received therapy that consisted of all three main components of CI
therapy: an intensive in-laboratory training program for the more involved arm, a number
of behavioral techniques (collectively called the “transfer package”) used to enhance the
transfer of motor improvement of the more affected arm from the laboratory to the life
situation, and a restraint device (a protective safety mitt) placed on the less involved hand
for a target of 90% of waking hours to help prevent use of the less affected arm. The
behavioral components consisted of a Behavioral Contract, Daily Diary, and daily administration of the Motor Activity Log (MAL; seeing Behavioral Testing section). A Behavioral Contract was used to plan a patient’s day in relation to which arm, the more affected or less affected, was to be used to accomplish different activities of daily living. Patients recorded these activities in a Daily Diary, which was reviewed by the therapist. The MAL is a structured interview that measures the amount and quality of use of the more affected arm in the life situation. Problem solving was used in conjunction with reviews of the MAL and Daily Diary to help subjects overcome perceived barriers to the use of the impaired upper extremity in the life situation. The review process reminded patients of the activities for which they should be using their more affected hand. The transfer package makes the patient accountable for the use of their more affected hand. These behavioral components were paired with two types of intensive training: shaping and repetitive practice. Repetitive practice involved the repeated completion of functional tasks for a specific time period set by the therapist. Shaping involved making simple motor activity progressively more difficult to challenge the ability of the patient (Skinner, 1938; Taub et al., 1994). It is a widely used behavioral training technique in which a desired motor or behavioral objective is approached in small steps, by successive approximations (Morgan, 1974; Risley & Baer, 1973; Skinner, 1938; Skinner, 1968). Shaping was given at an intensity of 25 trials per hour with each trial lasting 30 seconds in sets of 10 trials for each task. Coaching on improving the quality, skill and range of movement was also given on at least 90% of attempts. The time required for each set of 10 trials to be completed was recorded as was the performance of all other activities (e.g., rest breaks, bathroom breaks, and meal time).
The purpose of the restraint device on the less affected hand was to prevent a patient from using this extremity for the activities of daily living. This device allowed for free movement of the affected arm while restricting the use of the hand and fingers in activities of daily living. Moreover, the less-affected limb was free to maintain balance through being swung during ambulation and could be used for protective responses in the event of a fall.

Comparison therapy group

The Comparison therapy group received only in-laboratory intensive training of the more involved arm involving shaping or repetitive practice. Patients wore the mitt only when they were in the laboratory. They were not given any components of the “transfer package”. The in-laboratory training was performed at the same intensity as the CI therapy group, which ensured that both groups spent the same amount of time with the therapist during training.

Behavioral Testing

Past research concerning stroke motor ability suggests that laboratory motor tests indicate a rehabilitation patient's maximum motor ability, but that patients frequently do not make full use of that ability in the life setting (Andrews et al., 1979; Taub et al., 1993; Uswatte & Taub, 1999). There is often a very large gap between the two, and CI therapy has the effect of reducing that gap. Thus, to measure the full result of CI therapy, two motor tests were needed: one to measure the maximal amount of motor ability (Wolf Motor Function Test) and one to measure what the patient actually does in the home
situation (Motor Activity Log). These were the two primary measures of clinical outcome.

**Motor Activity Log**

The MAL is a structured, scripted interview that measures the amount and quality of use of the more affected arm in the life situation (Taub et al., 1999; Uswatte, Taub, Morris, Light, & Thompson, 2006; Uswatte, Taub, Morris, Vignolo, & McCulloch, 2005; Van der Lee, Beckerman, Knol, de Vet, & Bouter, 2004). It consists of 30 questions relating to activities of daily living with two different zero to five scales, one for Amount of Use and one for Quality of Movement. During the interview the patients were asked to rate how much and how well they used the more affected arm over a specified time period. This test has a strong, established reliability and validity (Uswatte et al., 2005; Van der Lee et al., 2004). Given that the two scales of the MAL are highly correlated (Uswatte & Taub, 2004), we will use only the Quality of Movement scale for this study.

**Wolf Motor Function Test**

The Wolf Motor Function Test (WMFT) is a motor ability test conducted in the laboratory consisting of 17 items, two of which involve strength measures and 15 of which involve timed performance on various tasks. The first half of the test involves simple limb movements, primarily of the proximal musculature; the second half of the test involves tasks performed in the life situation using the distal musculature. Performance time was measured by the therapist administering the test and patients are told to complete the movement as fast as possible (Morris, Uswatte, Crago, Cook, & Taub, 2001; Wolf et al., 2001). The
performance time was recorded as a \( \log^2 \) transformation of the mean time in seconds. This compressed the times that were near the maximum time limit of 120 seconds. Therefore a patient who improved from ten seconds to five seconds was represented by a larger treatment outcome than a patient who improved from 120 seconds to 115 seconds. This \( \log^2 \) transformation provided the amount of compression needed to accurately portray patient progress (see Appendix 2 of Mark, Taub, Perkins, Gauthier, & Uswatte, 2008b).

**Imaging**

Patients underwent imaging one day before the start of therapy and one day after the completion of therapy on a clinical Philips 3 Tesla (Intera, Philips Medical Systems, Bothell, WA) scanner. Two imaging pulse sequences were run aimed at acquiring data regarding 1) brain structure and 2) directional diffusion of water.

*Anatomical Imaging*

*Acquisition Parameters.* Whole-brain structural images were acquired with the following parameters: approximately 130 slices 1mm thick containing no gaps between slices with a 6 element phase array SENSE head coil, T1 Turbo-field Echo, TR (repetition time) = shortest, TE (echo time) = 4.60 ms, matrix size = 240 x 240 and reconstructed = 256 x 256, voxel size = 1.04 x 1.05 x 1.00 mm\(^3\), field of view (FOV) = 250mm, and flip angle = 8°. The slices of the axial scans were set parallel to the orbital-meatal line.

*Diffusion Imaging*

*Acquisition Parameters.* Whole-brain diffusion images were acquired in 16 directions
with the following parameters: approximately 40 slices 4mm thick with a 1mm gap between slices, a 6 element phase array SENSE head coil, single shot echo planar (EPI), TR = shortest, TE = 87ms, matrix size = 112 x 112 and reconstructed = 128 x 128, voxel size = 2.05 x 2.62 x 4 mm\(^3\), gap between slices = 1mm, FOV = 230mm, b value = 1000 mm/s\(^2\) and flip angle = 90°. There were two changes to the protocol during the study. Patient 14 (see Table 1) had a DTI scan with no gaps between the slices and a slice thickness of 3.5mm. Due to scanner upgrades, imaging data from patient 22 were acquired using an altered DTI protocol (TR = 10s, TE = 72ms, maximum b-value = 800s/mm\(^2\), slice thickness = 2mm, gap between slices = 0mm, number of averages = 2).

Anisotropy. The general method of acquiring DTI images begin with the application of a radio frequency pulse, which makes protons spin in phase. A magnetic gradient is also applied in which the field is varied linearly causing the spins to dephase along this gradient direction. A “refocusing” radio frequency pulse is then applied which induces the protons to spin in the opposite direction. This refocusing is absolute only if the proton does not move along the gradient between these two pulses. If the proton moves parallel to the gradient, the spin is not refocused completely and leads to a decrease in the magnitude of the signal. Direction of diffusion can be determined by comparing the signal after the first pulse and after the refocusing pulse. However, if only one gradient direction is applied, we will be able to obtain information of water diffusion in one direction only. In order to understand the flow of water in three dimensional space, several images need to be acquired in which the gradient direction is modified for each acquisition. The more gradient directions that are applied, the more specific the
information is regarding the directionality of water diffusion.

The direction of water cannot be described simply by a single number. Instead a diffusion tensor is used to describe water movement along each direction and the relationship of one direction to the other. These diffusion tensors can be displayed at each voxel as ellipsoids (Figure 1) that identify the direction of water diffusion as vectors (eigenvectors, \( u \)) and the magnitude of the diffusion in each direction (eigenvalues, \( \lambda \)). A voxel with completely isotropic water movement would have equal eigenvalues (\( \lambda_1 = \lambda_2 = \lambda_3 \)) while a voxel with anisotropic diffusion would have one eigenvalue larger than the other two (\( \lambda_1 > \lambda_2 = \lambda_3 \)). Fractional anisotropy (FA) quantifies the directional diffusivity of water movement. An area of the brain in which water diffuses at a higher rate in a common direction is represented by large FA values and has a higher probability of being part of a large axon bundle than areas with lower FA values.

\[ \lambda_1, \lambda_2, \lambda_3 \]

*Figure 1.* Illustration of molecular diffusion and the resulting eigenvectors. In the first panel, since there is no directionality to the movement, the eigenvalues are equal to each other (\( \lambda_1 = \lambda_2 = \lambda_3 \)). The second panel describes the random movement of a molecule that is bound by a tube structure that could signify an axon cell membrane. While the movement is still random, the constriction results in an eigenvalue larger than the rest (\( \lambda_1 > \lambda_2 = \lambda_3 \)).

The three main causes of anisotropy in axons can most likely be attributed to the confinement of intracellular and extracellular water diffusion by any or all of the following: axonal membrane, packing density of axons, or myelin sheaths (Beaulieu, 2002). Intracellular water is prevented from diffusing perpendicular to the fiber by the
outer cell membrane, while extracellular water diffusion is also limited by the tightly packed parallel axons that create a fiber bundle. Further barriers are introduced by myelin sheaths, which surround the axon with several lipid bilayers. These bilayers prevent water from escaping out of the axon and also constrain the myelin’s own intracellular water. These constraints on water diffusion give rise to a directional water flow (Beaulieu, 2002). It was previously thought that the intracellular microtubules and neurofilaments also added to this directional water flow. This idea was shown to be wrong in a study by Beaulieu and Allen (1994) in which microtubules were depolymerized and axonal transport was inhibited. The result indicated a preservation of FA values indicating that intracellular transport structures do not have a significant role in anisotropic diffusion.

Several studies have been conducted to establish the most important factor for creating directional diffusion (Huppi et al., 1998; Moseley et al., 1990; Neil et al., 1998; Thomsen, Henriksen, & Ring, 1987; Wimberger et al., 1995). While myelin was initially thought to be the main source of anisotropy, it is now known that demyelinated axon fibers still exhibit some directional diffusion. A study by Gulani (2001) examined the spinal cord of X-linked recessive Wistar rat mutants which have a CNS that is nearly demyelinated. Diffusion imaging of the rat showed only a 20% drop in FA. Therefore, the axonal membrane and packing density are the main factors in producing directional diffusion while myelin can act to enhance or modify the diffusion.

Because axonal membranes and the packing density of axons are main factors influencing FA, it can be used as an index of white matter integrity. If the directional flow of water is caused by limiting perpendicular water flow induced by cell membranes as explained above, any disruption in those membranes would affect the diffusion of
water. If damage to the brain were to disrupt an axon, either by directly damaging the cellular membranes or by cellular degeneration, the water diffusion would be altered and therefore a drop in FA would be observed. Therefore the FA values can serve as an index of fiber integrity. A reduction in FA values has been identified in the stroke population by Pierpaoli (2001) and Werring (2000). These decreased values were interpreted as being evidence for Wallerian degeneration of axons. This type of degeneration was first described in the late 1800’s by A.V. Waller (1850) after cutting the glossopharyngeal and hypoglossal nerves in a frog. It was characterized by two main processes: axon fiber disintegration and demyelination. In terms of diffusion, the disintegration of axon fibers and demyelination remove the constraints that induce anisotropic diffusion. The result of these actions would reduce the FA values in the region of degeneration.

Tractography. Tractography is a process by which the axon bundles can be visually reconstructed based on vector maps created from the eigenvectors. Some methods of tractography are initiated in a seed voxel and progress in the direction of the principle vector, ending when the FA value drops below a predetermined threshold or turns at an angle more acute than the predetermined threshold. This method of tractography, termed deterministic tractography, results in one tube-like visualization of the CST in which only the areas of maximum likelihood are identified (Mori & van Zijl, 2002). In all diffusion data there will be areas of uncertainty based on noise and artifacts. Areas of high uncertainty, such as areas in which there are crossing fibers or damage, are normally associated with low FA values. The major drawback to deterministic tractography is the inability to track fibers through areas of low FA due to the fact that these methods do not
take uncertainty considerations into the tractography method. An alternative tractography method, called probabilistic tractography, does deal with uncertainty by not simply generating the tube-like pathway of the CST, but instead creating a distribution of all possible pathways and weighting them based on their likelihood (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Behrens et al., 2003). In order to obtain data on the likelihood of a tract location, a Markov Chain Monte Carlo (MCMC) is run to build distributions on the diffusion parameters. An MCMC is an algorithm for sampling from probability distributions based on a Markov Chain in which a sequence of random steps is taken in a probability distribution. An integral describing some sort of information (in this case information regarding diffusion) at the current step is combined with the next integral in a random path, looking for a step with a high contribution to the current integral. Probability density functions (PDF) are created which represents the probability distribution in terms of integrals of the principle diffusion direction (PDD) at each voxel. A random voxel of the seed region of interest (ROI; details of this are given below) is chosen and the integral is noted. The surrounding voxels are evaluated to identify which ones have a high contribution, or correlation, to the previous integral. From those voxels with a high contribution, the next voxel (or the next step) is chosen at random. The integral from the previous voxel and this new voxel are combined. Using this new integral, the process begins again by evaluating the surrounding voxels which are evaluated in terms of their contribution to the current voxel’s integral. This process is repeated until five thousand iterations are completed. This adjustment of probability distribution integrals is called posterior probability; it allows the five thousand iterations of the process to progress much more rapidly than other types of sampling schemes.
We chose to use the method of probabilistic tractography for three reasons. First the patients included in this study had substantial brain damage. This damage was evident in structural MR images as hypointensities caused by excess water in the tissue or filling necrotic spaces. The increased concentration of water in the damaged tissue would be seen as a decrease in FA (Yang et al., 1999). Deterministic tractography requires limits in minimum FA and acuteness of angle to be set to guide tracking. In normal brain tissue, a significant drop in FA would usually signify the absence of axon bundles, thereby, refining the localization of the target tract. In damaged brains, however, a drop in FA might not indicate the absence of an axon bundle. Several instances have been documented in which axon bundles have proceeded through damaged tissue in which there was a significant drop in FA. By using probabilistic tractography, no limits on FA are required and each voxel is analyzed for its probability for containing the tract in question. Along with a low FA threshold, deterministic methods require an angle limit which restricts tracking the bundle if it should curve away from its current trajectory. In our damaged brains, however, there are times when changes in anatomical structure could cause axon tracts to be altered. In these instances, the probabilistic method would still be able to localize tracts without the angle restriction of other methods. Finally the output of probabilistic tractography is more than simply an image of tube-like structures. It instead creates a probabilistic map covering the entire brain in which the likelihood of each voxel belonging to the tract in question is analyzed. After filtering this with a given probability value, the area of the brain containing the targeted axon bundle is identified as simply a ROI and can be overlaid and used to localize the tract on several different modalities (i.e. anatomical scans, diffusion scans, normalized brains, etc.).
Data Analysis

Preprocessing

FSL or fMRIB Software Library (Smith et al., 2004) was used to create FA maps for each scan and to perform probabilistic tractography for locating the CST. An FA map is a matrix in which each cell contains an FA value that is associated with a voxel in the brain. DTI images went through a four-stage preprocessing process before being analyzed. First the images were converted from the storage format of Digital Imaging and Communications in Medicine (DICOM; http://medical.nema.org/) to the Neuroimaging Informatics Technology Initiative (NifTI-1; http://nifti.nimh.nih.gov/) data format required by the FSL analysis software. Due to the fact that DTI images are acquired one gradient direction at a time, the resulting sixteen-direction data were separated into sixteen separate image-sets. These three-dimensional images were then converted to one four-dimensional image where the fourth dimension is gradient direction. The third preprocessing step masked the skull from the four-dimensional image using the Brain Extraction Tool (BET) provided in FSL to remove any non-parenchymal tissue. The final preprocessing step corrected for eddy currents. When high intensity diffusion gradients are rapidly switched, shear and stretch artifacts are produced which are different for each gradient direction. Magnification and pixel shifts can also result and all artifacts are different for different gradients (Jezzard, Barnett, & Pierpaoli, 1998). FSL uses affine registration to correct both the eddy current and head motion using the image with no diffusion gradients as the reference volume (Jenkinson, Bannister, Brady, & Smith, 2002).
**Fractional anisotropy**

After preprocessing, diffusion tensors \( \mathbf{D} \) were calculated at each voxel. We utilize tensors because the diffusion of water cannot be defined simply by one vector; instead it is a complex relationship among three different vectors. The movement of protons in diffusion images can be described by nine components, each associated with different axes \((xx, yy, zz, xy, xz, yx, yz, zx)\) and by placing these components in a 3x3 matrix, a diffusion tensor can be calculated (see Equation 1).

\[
\mathbf{D} = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{xy} & D_{yy} & D_{yz} \\
D_{xz} & D_{yz} & D_{zz}
\end{pmatrix}
\]

(1)

From these tensors, ellipsoids can be created along with eigenvalues, eigenvectors (similar to what is presented in Figure 1), and fractional anisotropy (FA) values (see equation 2).

\[
FA = \sqrt{\frac{1}{2} \left( \sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2} \right)}
\]

(2)

Due to artifacts in the acquisition of the image, some eigenvalues can be calculated as negative numbers (Koay, Carew, Alexander, Basser, & Meyerand, 2006). This in turn creates FA values that are greater than one. To correct this error we used a post tensor-estimation method that replaces the erroneous FA value with a value based on the average of all surrounding voxels. The resulting FA image was viewed as a gray scale brain in which darker shades represent lower FA values. This same image can be viewed as a color map (Figure 2) using the eigenvector directions to identify fibers running right-left (red), anterior-posterior (green), and rostral-caudal (blue).
The FA map includes both the white matter and gray matter. To isolate the white matter portion of the brain, we segmented the anatomical image using the Statistical Parametric Mapping (SPM) toolbox in MATLAB (v. 7.5; http://www.mathworks.com; http://www.fil.ion.ucl.ac.uk/spm) that uses intensity values as well as standard brain templates to label voxels as gray matter, white matter, or cerebrospinal fluid (CSF).

**Figure 2.** Whole brain FA color maps of patient 22. In the axial view, fibers running right-left are red, anterior-posterior are green, and rostral-caudal are blue. The double white arrows indicate the internal capsule, which contains the CST. Single yellow arrows outline areas of brain damage due to stroke.

This technique labels each voxel with three probability values: the probability the voxel contains gray matter, the probability the voxel contains white matter, and the probability the voxel contains CSF. Some voxels contained a portion of gray matter and white matter, which would be indicated by a high probability value corresponding to the presence of gray and white matter and a low probability value corresponding to the presence of CSF. To deal with these partial volumes, voxels containing more than 50%
white matter were labeled as white matter. From these segments we created a dichotomous image in which voxels equaling one indicated the presence of white matter and voxels equaling zero indicated the absence of white matter and the presence of gray matter, CSF, or background. The white matter image was used to filter the FA map in order to include only FA values from the voxels containing white matter. The resulting white matter-only image was then separated into two hemispheres, and FA distributions were analyzed for each hemisphere separately. Ratios were also calculated in which the FA values for the white matter contralateral to the motor deficit were compared to the FA values for the white matter ipsilateral to the motor deficit (see Histogram Analysis section for a description of the distribution analysis and ratio calculations).

*Probabilistic tractography*

Probabilistic tractography requires the creation of four ROIs to indicate the starting and ending point of tractography: seed ROI, waypoint ROI, exclusion ROI, and termination ROI. The seed ROI is the starting point for this process; while the waypoint ROI acts as an inclusion criterion. Tracts coming from the seed ROI must pass through the waypoint ROI in order to be included in the analysis. Exclusion ROI simply excludes any pathway entering this area, while termination ROIs stop the tractography when the path enters this area.

Using the FA color maps and knowledge of standard neuroanatomy, we created a seed ROI encompassing the posterior limb of the internal capsule on an axial slice where the basal ganglia, thalamus, and internal capsule are also all clearly visible. Since the CST ascends through the internal capsule in the rostral direction, the area should appear
blue. The resulting seed ROI was viewed on both the FA color map and the structural T1 weighted image to ensure correct placement. In some brains with extensive damage and abnormal neuroanatomy, seed ROIs were adjusted in size or position to isolate a CST that had been distorted due to the presence of a lesion or hydrocephalus *ex vacuo*. The cerebral peduncles were also traced on the FA color map starting at the level with the largest expansion of the cerebral peduncle in the midbrain; this was used as a waypoint. Seed and waypoint ROIs were created for the left and right hemisphere separately. Exclusion ROIs were created on the FA color map at the midline of the brain to prevent the inclusion of crossing fibers from the corpus callosum. Termination ROIs were also created on the FA color map to terminate tractography at junction of brain tissue and skull. The tractography in one hemisphere began in the seed ROI and proceeded in both directions. By selecting the posterior limb of the internal capsule, which has been shown to contain the axons descending from the arm area of the primary motor cortex (Englander et al., 1975; Morecraft et al., 2002), other descending fibers were excluded from the tractography. The waypoint image in the cerebral peduncle added another layer of certainty to guarantee that other fibers descending through the midbrain which are not part of the CST or are destined for the cerebellum were not included. The end product was two images, one for each hemisphere, with intensity values indicating the number of times the tracking procedure passed through that voxel. Several voxels were zero, which indicates a 0% chance of it being part of the fiber tract; voxels with the highest number of passes were the most probable location for the CST. The resulting CST image was limited to voxels in which the tracking procedure passed through at least 1000 times before dichotomizing these images. The two resulting images contained voxels in which
intensity values equal to one indicated the presence of the CST and zero indicated an absence of the CST.

In order to isolate FA values from the CST only, we overlaid the two CST images with the whole brain FA map. Any voxel in the FA map that has a value of zero in the CST tractography map was eliminated. This produced an FA map of only the CST from each hemisphere individually from which FA values could be obtained. Since the presence of a fluid filled lesion would dramatically affect the FA of an area, any portion of the CST that was overlapped by a lesion was eliminated.

**Histogram Analysis**

In order to analyze the distribution of FA values in both the whole brain white matter and CST areas only, histograms of FA values were created using in-house Matlab codes in which FA values were segregated into 100 equally spaced bins. To compare distributions between subjects, the frequency of occurrences in each FA value bin was divided by the total white matter voxel count resulting in a standardized frequency count (Figure 3). To quantify the central tendency, the mean FA value was calculated for each hemisphere and CST separately.

Ratios were created (CST FA ratio) which indicated the possible difference in mean FA of the affected CST relative to the undamaged side. The CST FA ratio was calculated by dividing the mean FA of the CST contralateral to the motor deficit by the mean FA of the CST ipsilateral to the motor deficit. A CST FA ratio near one would indicate that the central tendency of FA values for the CST contralateral to the motor deficit is the same as the central tendency of FA values for the CST ipsilateral to the
motor deficit. A CST FA ratio less than one would indicate that the CST contralateral to the motor deficit contains smaller values than the CST ipsilateral to the motor deficit. Previous studies providing data on normal FA values from healthy volunteers indicate no differences between the mean FA values from each hemisphere (Wakana et al., 2007; Yu et al., 2008). Ratios were also created for the white matter segment of the brain (WM FA ratio) in which the mean FA of the hemisphere contralateral to the motor deficit was compared to the mean FA of the hemisphere ipsilateral to the motor deficit.

![Histograms of FA values](image)

**Figure 3.** Distribution of FA values illustrated by histograms. (A) FA values are separated into 100 bins. The y-axis indicates the number of occurrences of that particular FA value. (B) The same data is now plotted as a frequency polygon that can be used to visually compare different distributions. The y-axis is normalized by dividing the number of voxels for each FA value by the total number of voxels.

**Distorted/Disrupted Corticospinal Tract**

When analyzing the effect of acquired brain injury on the CST, a distortion or disruption of the tract might be just as important as the integrity of the tract. While FA
can convey important information concerning the cohesiveness of axon bundles, it does little to indicate changes in physical path of the fiber bundle. Based on previous studies focused on the CST by Parmar et al. (2006) and Cho et al. (2007a), we classified the patients into three categories according to how the path of their CST was affected by brain damage: 1) distorted, 2) disrupted, or 3) unaltered. The CST in the affected hemisphere was compared to both the CST in the unaffected hemisphere and neuroanatomical templates to determine which category was appropriate. A CST in the affected hemisphere with a path similar to that of the CST in the unaffected hemisphere and similar to that of established normal neuroanatomical templates was categorized as unaltered. Based on a study by Kunimatsu et al.(2003) in which a CST tractography was actually observed passing through an infarct in the posterior internal capsule, patients whose CST passed through lesioned or damaged tissue but was unaltered structurally were also included in the unaltered category. A CST in the affected hemisphere in which tractography was incomplete indicated a disrupted tract. To determine whether the patient’s CST was distorted, the distance between the two CSTs was measured using the following method. Each patient’s diffusion image and CST image were first normalized to a standard brain template provided by FSL. On each axial slice the center of gravity of the CST in both hemispheres was identified using an in-house Matlab code. The centroid of the left CST was flipped to the right hemisphere and the distance between the centroid of the right and left CST was measured on each slice which contained the CST (Figure 3). The mean distance between the two centroids was calculated for each participant. The distances ranged from 1.2mm to 8.3mm ($SD = 1.8$). Seventy percent of the 17 participant sample had distortions less than 2.9mm. The next data point indicated a distance of
3.4mm suggesting a break in the distribution. A second method of identifying distortion was used in which the CST was labeled as either distorted or not distorted based on a qualitative inspection of the brain with the rater blinded to patient information and centroid distance. When comparing the distance between the centroids with this visual inspection, the five participants with an obvious distortion in the CST and surrounding brain area also had distances between centroids of 3mm or more. A CST was categorized as *distorted* if the mean distance between the two centroids was more than 3mm based on the clear break in the distribution of the data and corroborated with visual inspection of the brains.

![Figure 4. Demonstration of CST distortion calculation.](image)

**Figure 4.** Demonstration of CST distortion calculation. Right and left CST are identified in red. The centroid is identified in each CST cross-section on every slice that it appears. The centroid of the left CST is flipped to the right side and the distance between the right (yellow dot) and left (red dot) centroid is calculated.

RESULTS

Patient Characteristics

Twenty-two (21 stroke, 1 MS) of the original 62 patients underwent DTI scanning. Stroke patients (8 male) had a mean age of 65 years (range = 44 to 87 years, $SD = 12.3$) and were 4.2 (range = 1 to 20 years, $SD = 5.7$) years post-event. The progressive MS patient (female; 60 years old) had experienced disease onset 20 years earlier and had her last relapse at least 3 months prior to entering the program. Fifteen patients were premorbidly right handed and 7 were premorbidly left handed. Twelve patients had
dominant side hemiparesis. Demographic characteristics and motor scores did not differ significantly between the patients receiving Comparison therapy \((n = 14; \text{Table 1})\) and the patients receiving CI therapy \((n = 8; \text{Table 2})\).

Table 1

**Demographic characteristics for patients in the Comparison therapy group**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (yrs.)</th>
<th>Chronicity (yrs.)</th>
<th>Premorbid Hand Dominance</th>
<th>Side of Hemiparesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>60</td>
<td>1.0</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>79</td>
<td>1.0</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>83</td>
<td>6.8</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>63</td>
<td>1.3</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>59</td>
<td>4.8</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>6 a</td>
<td>Female</td>
<td>54</td>
<td>1.1</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>87</td>
<td>1.0</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>72</td>
<td>12.7</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>80</td>
<td>1.2</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>10 a</td>
<td>Female</td>
<td>78</td>
<td>11.3</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>50</td>
<td>1.3</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>12 a</td>
<td>Female</td>
<td>67</td>
<td>1.3</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>46</td>
<td>20.4</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>52</td>
<td>12.0</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td><strong>Summary</strong> b</td>
<td>5 Male</td>
<td>66.4 (13.5)</td>
<td>5.5 (6.2)</td>
<td>11 Right</td>
<td>5 Right</td>
</tr>
</tbody>
</table>

\(a\) Patients excluded due to artifacts in diffusion images

\(b\) Summary indicates either the mean \((SD)\) or the sum of “Male” or “Right” responses
The diffusion scans from five patients (6, 10, 12, 15, and 21; Table 1 & 2) contained large artifacts and they were therefore excluded from all further analysis. The final sample included seventeen stroke patients and one progressive MS patient with six patients in the CI therapy group and eleven patients in the Comparison therapy group.

Table 2

Demographic characteristics for patients in the CI therapy group

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (yrs.)</th>
<th>Chronicity (yrs.)</th>
<th>Premorbid Hand Dominance</th>
<th>Side of Hemiparesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15(^a)</td>
<td>Male</td>
<td>72</td>
<td>1.8</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>75</td>
<td>1.5</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>58</td>
<td>1.0</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>18</td>
<td>Female</td>
<td>70</td>
<td>1.0</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
<td>60</td>
<td>1.0</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>20(^b)</td>
<td>Female</td>
<td>60</td>
<td>20.0</td>
<td>Left</td>
<td>Left</td>
</tr>
<tr>
<td>21(^a)</td>
<td>Female</td>
<td>60</td>
<td>1.8</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>22</td>
<td>Male</td>
<td>44</td>
<td>3.1</td>
<td>Right</td>
<td>Right</td>
</tr>
</tbody>
</table>

Summary\(^c\)

|            | Male | 62.4 (9.9) | 3.9 (6.5) | 4 Right | 2 Right |

\(^a\) Patients excluded due to artifacts in diffusion images
\(^b\) Patient’s diagnosis was progressive multiple sclerosis
\(^c\) Summary indicates either the mean (SD) or the sum of “Male” or “Right” responses

Clinical Outcome

The clinical results are summarized in Table 3. Repeated measures analysis identified a significant improvement on the MAL from pre- to post-treatment for both
groups combined \(F_{(1,10)} = 122.44, p < 0.001\); however, patients in the CI therapy group \(n = 5\) when compared to the comparison therapy group \(n = 7\) showed a significantly greater improvement on the MAL \(F_{(1,10)} = 7.59, p < 0.05\). For both groups combined, the improvement in WMFT performance time scores was not significant, nor was the difference in gains between groups.

Table 3

*Clinical Outcomes for CI Therapy and Comparison Therapy Patients*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Change</th>
<th>Effect Size ((d')^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CI therapy b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAL</td>
<td>1.4 (1.0)</td>
<td>3.0 (1.1)</td>
<td>1.6 (0.2)(^c)</td>
<td>8.0</td>
</tr>
<tr>
<td>WMFT (^d)</td>
<td>1.5 (1.3)</td>
<td>1.3 (1.6)</td>
<td>-0.2 (0.4)</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Comparison therapy e</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAL</td>
<td>1.5 (0.7)</td>
<td>2.5 (0.7)</td>
<td>1.0 (0.5)(^c)</td>
<td>2.0</td>
</tr>
<tr>
<td>WMFT (^d)</td>
<td>1.0 (1.1)</td>
<td>0.8 (1.0)</td>
<td>-0.2 (0.3)</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Note. Values are mean \((SD)\).

\(^a\) Cohen’s \(d'\) is a measure of within group effect size. It is the mean change from pre- to post-treatment divided by the \(SD\) of the change. By convention 0.57 is a large effect size.

\(^b\) \(n = 5\)

\(^c\) Signifies a significant difference between the CI therapy and Comparison therapy group \((p < 0.05)\).

\(^d\) Reported as a log\(^2\) transformation of the mean time in seconds

\(^e\) \(n = 7\)

Fractional Anisotropy

*Pre-treatment*

The mean FA of the CST across all participants was 0.38 (range = 0.29 to 0.50, \(SD = 0.05, n = 16\), patient 13 excluded due to an inability to track the affected CST). The mean FA of the white matter segment of the brain across all participants was 0.30 (range
= 0.23 to 0.41, \( \text{SD} = 0.04 \) at pre-treatment. The mean FA value for the white matter segment of the brain at pre-treatment was similar to what has been found in previous studies of cerebrovascular disease (Mori et al., 2008; Zhou et al., 2008). There were no significant differences between the CI therapy and comparison therapy group in CST or white matter segment mean FA values.

**Hemispheric Differences in Fractional Anisotropy**

Paired t-tests revealed a significant hemispheric difference in the mean FA values of the white matter segment of the brain at pre-treatment \((t_{(16)} = 3.59, p < 0.001; \text{Figure } 5\text{B})\). The mean of FA values in the affected hemisphere was 0.29 (\( \text{SD} = 0.05 \)) while the mean of FA values in the unaffected hemisphere was 0.30 (\( \text{SD} = 0.04 \)). A similar result was found when analyzing the hemispheric difference between the unaffected and

![Figure 5](image_url)

*Figure 5.* Histogram curves averaged across all participants illustrating the difference in FA distribution between the affected and unaffected hemispheres. There is a significant hemispheric difference in the mean FA values of the unaffected and affected CST (A; \( t_{(15)} = 5.23, p < 0.001 \)) and white matter segment of the brain (B; \( t_{(16)} = 3.59, p < 0.001 \))
affected CST ($t_{15} = 5.23, p < 0.001$; Figure 5A). For this analysis one patient was excluded due to the absence of a traceable CST. The mean of FA values of the affected CST was 0.35 ($SD = 0.04$) while the mean of FA values of the unaffected CST was 0.40 ($SD = 0.04$).

**Probabilistic Tractography of the Corticospinal Tract**

Probabilistic tractography of the corticospinal tract was successfully completed on all CSTs in the unaffected hemisphere (Figure 6). While some tracts in the affected hemisphere had been distorted by lesion or hydrocephalus *ex vacuo*, all but one fiber bundle was successfully located. No CST was identifiable in patient 13 due to extreme hydrocephalus *ex vacuo* and the location of the lesion (Figure 7).

*Figure 6.* Probabilistic tractography results from patient 20 overlaid onto a standard template brain. (A) Three-dimensional rendering of a standard brain template with the corticospinal tract identified in red. (B) Axial, (C) coronal, and (D) sagittal slices of the standard brain show the same corticospinal tract in three planes. Crosshairs are set at the same voxel for all three images.
Figure 7. Illustration of an unsuccessful CST tractography in patient 13. There is a clear distortion of the brain, as shown in the structural scan (A), in which hydrocephalus ex vacuo and the lesion have distorted the brain to the point that the internal capsule and all subcortical nuclei are unidentifiable. (B) The corticospinal tract is identified in red overlaid onto the diffusion image. Crosshairs for each scan are centered on the lesion in the same general axial plane.

Fractional Anisotropy and Motor Scores

No significant correlations were found between the pre-treatment MAL or WMFT scores and pre-treatment CST FA ratios ($p$ values $> 0.1$, Table 4) or WM FA ratios ($p$ values $> 0.2$, Table 4). Hierarchical regressions, in which pre-treatment CST FA ratios were related to post-treatment motor scores while controlling for pre-treatment motor scores and group assignment, indicated no significant relationship between pre-treatment CST FA ratios and the change in motor scores from pre- to post-treatment ($\Delta R^2$'s $< 0.04$, $p$ values $> 0.1$, Table 5). There was also no relationship between the post-treatment motor scores and WM FA ratio after controlling for pre-treatment motor scores and group assignment ($\Delta R^2$'s $< 0.06$, $p$ values $> 0.1$, Table 6).
Table 4

Correlations between pre-treatment motor scores and pre-treatment FA ratios

<table>
<thead>
<tr>
<th></th>
<th>CST FA Ratio (^a)</th>
<th>WM FA Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r) (p)</td>
<td>(r) (p)</td>
</tr>
<tr>
<td>MAL</td>
<td>0.04 0.9</td>
<td>-0.06 0.8</td>
</tr>
<tr>
<td>WMFT (^a)</td>
<td>-0.41 0.1</td>
<td>-0.34 0.2</td>
</tr>
</tbody>
</table>

Note. \(n = 17\)

\(^a\) Patient 13 excluded from analyses associated with CST FA or WMFT due to an inability to track the affected CST and missing WMFT data

Changes in Fractional Anisotropy Due to CI therapy

Due to the absence of post-treatment diffusion scans, 6 patients of the original 17 were excluded from any analysis dealing with changes in the brain from pre- to post-treatment. Of the remaining 11 patients, 4 received CI therapy and 7 received the comparison therapy. Because of this reduced sample size, it was not possible to arrive at clear conclusions concerning the effect of CI therapy on white matter or CST mean FA.

For the combined group, there was no significant difference between the CST FA ratio at pre-treatment and the CST FA ratio at post-treatment \((t_{(10)} = -0.341, p = 0.74)\). This was also the case when comparing WM FA ratios at pre- and post-treatment for the combined group \((t_{(10)} = 0.905, p = 0.387)\).

An ANCOVA analysis found no between-group difference in CST FA ratios from pre- to post-treatment \((F_{(1,8)} = 0.959, p = 0.18, \text{one-tailed})\). Similar analyses were conducted for the mean FA from the affected CST and unaffected CST separately. There was again no change in the FA values from pre- to post-treatment in either the affected CST \((F_{(1,8)} = 0.161, p = 0.35, \text{one-tailed})\) or the unaffected CST \((F_{(1,8)} = 0.409, p = 0.27,\)
Table 5

*Multiple regression of treatment outcome on CST FA ratio*

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>t</th>
<th>p</th>
<th>$F^{a}$</th>
<th>$p^{a}$</th>
<th>$R^{2a}$</th>
<th>$\Delta^{b}R^{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Activity Log</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>3.87</td>
<td>&lt; 0.01</td>
<td>18.95</td>
<td>&lt; 0.01</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy score</td>
<td>0.85</td>
<td>5.79</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.38</td>
<td>2.60</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>-0.56</td>
<td>0.59</td>
<td>14.96</td>
<td>&lt; 0.01</td>
<td>0.85</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Pre-therapy</td>
<td>0.85</td>
<td>6.15</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.38</td>
<td>2.77</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CST FA Ratio</td>
<td>0.20</td>
<td>1.47</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wolf Motor Function Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>-0.99</td>
<td>0.35</td>
<td>59.02</td>
<td>&lt; 0.01</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy score</td>
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<td>10.66</td>
<td>&lt; 0.01</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.02</td>
<td>0.16</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>-0.32</td>
<td>0.76</td>
<td>35.17</td>
<td>&lt; 0.01</td>
<td>0.93</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Pre-therapy</td>
<td>0.97</td>
<td>8.88</td>
<td>&lt; 0.01</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.01</td>
<td>0.14</td>
<td>0.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CST FA Ratio</td>
<td>0.02</td>
<td>0.20</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Dependent variable is post-treatment motor scores

* Indicates the variance accounted for by the entire group of variables in Step 1 and Step 2 independently

** Indicates the variance accounted for by Step 2 over and above the variance from Step 1
Table 6

*Multiple regression of treatment outcome on WM FA ratio*

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>t</th>
<th>p</th>
<th>F</th>
<th>p</th>
<th>R²</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Activity Log</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>3.87</td>
<td>&lt; 0.01</td>
<td>18.95</td>
<td>&lt; 0.01</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-therapy score</td>
<td>0.85</td>
<td>5.79</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.38</td>
<td>2.60</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>-1.39</td>
<td>0.20</td>
<td>16.85</td>
<td>&lt; 0.01</td>
<td>0.86</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Pre-therapy</td>
<td>0.85</td>
<td>6.45</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>0.32</td>
<td>2.35</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM FA Ratio</td>
<td>0.24</td>
<td>1.80</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Wolf Motor Function Test** |      |       |       |     |    |      |     |
| Step 1                   | -0.99| 0.35  | 59.02 | < 0.01| 0.93|
| Pre-therapy score        | 0.96 | 10.66 | < 0.01|     |    |      |     |
| Treatment Group          | 0.02 | 0.16  | 0.87  |     |    |      |     |
| Step 2                   | 0.82 | 0.44  | 38.54 | < 0.01| 0.94| 0.01 |     |
| Pre-therapy              | 0.93 | 9.26  | < 0.01|     |    |      |     |
| Treatment Group          | 0.04 | 0.45  | 0.67  |     |    |      |     |
| WM FA Ratio              | -0.89| -0.87 | 0.41  |     |    |      |     |

Note. Dependent variable is post-treatment motor scores

*Indicates the variance accounted for by the entire group of variables in Step 1 and Step 2 independently

*Indicates the variance accounted for by Step 2 over and above the variance from Step 1*
one-tailed) while controlling for group assignment. Using a similar ANCOVA design, no difference was found between pre- and post-treatment WM FA ratios ($F_{(1,8)} = 0.536, p = 0.242$, one-tailed).

Path of the Corticospinal Tract

Ten of the original 17 patients were categorized as having a CST unaltered by brain damage. Two patients were categorized as having a disrupted CST, three were categorized as having a distorted CST, and two patients had both a disrupted and distorted CST. Since the categories of disrupted CST and distorted CST are not mutually exclusive, these were merged into one group. The resulting two groups consisted of patients with a CST unaltered by brain damage ($n = 10$) and patients with a CST that was changed by brain damage resulting in either a disrupted or distorted CST or both ($n = 7$).

The mean MAL and WMFT scores of the unaltered CST group were significantly better than the mean MAL and WMFT of the changed CST group. The mean pre-treatment MAL score for the unaltered CST group was 1.50 ($SD = 0.85$) and for the changed CST group was 0.83 ($SD = 0.40$; $t_{(15)} = -1.9, p = 0.04$, one-tailed). The mean pre-treatment WMFT score for the unaltered CST group was 1.00 ($SD = 1.08$) and for the changed CST group was 2.04 ($SD = 1.09$; $t_{(15)} = 1.9, p = 0.04$, one-tailed).

DISCUSSION

While attempts have been made to identify the cause and mechanism of motor deficit and subsequent recovery of hemiparesis, there are several aspects, especially in the chronic phase of acquired brain injury, that are still unclear. The goal of this study was to
determine the relation of chronic hemiparesis to white matter integrity in contralateral and ipsilateral hemispheres and to determine if CI therapy could significantly alter the integrity. Analyses were also carried out to determine if disruptions or distortions in the path of the CST were related to motor ability.

No relationship was found between the integrity of white matter or CST and the amount of motor deficit prior to treatment. This finding is similar to that of Mark et al. (2008b) in which the volume of the lesion in chronic stroke patients was found to be not related to the amount of motor deficit at pre-treatment. This was one of the few studies investigating the relationship of lesion volume and motor deficit in the chronic phase of stroke. In contrast, the literature suggests that a relationship does exist between motor ability and lesion volume in the acute phase (summarized in Mark et al., 2008b). It was suggested that while the extent of lesion damage to the brain may be important for determining the severity of hemiparesis in the acute phase, the extent of the lesion damage might lose its influence on motor ability over time due to adaptation of the brain in response to chronic motor impairment. This same hypothesis could apply to white matter integrity. Several studies have identified a relationship between white matter integrity and motor ability in the acute phase of hemiparesis (Cho et al., 2007a; Cho et al., 2007b; Higano et al., 2001; Konishi et al., 2005; Kunimatsu et al., 2003; Kusano et al., 2009; Thomalla, Glauche, Weiller, & Rother, 2005; Yoshioka et al., 2008); however very few have studied this question in the chronic patient population (Schaechter et al., 2009; Yu et al., 2009) and those that have differ in their conclusions. We can speculate that perhaps in the acute stage of hemiparesis, damage to the brain paired with non-use of the affected extremity leads to a decrease in the integrity of the white matter. Over time
the brain compensates for the decreased integrity through neuroplastic changes, eventually leaving the decreased white matter integrity unrelated to the amount of motor ability.

There was also no relationship found between the integrity of the white matter or CST at pre-treatment and the amount of motor improvement due to CI therapy. Previous studies from this laboratory found no relationship between the lesion location (Gauthier et al., 2009) or lesion volume (Mark et al., 2008b) at pre-treatment and the amount of motor recovery due to CI therapy. In both studies it was hypothesized that the ability of CI therapy to produce neuroplastic change could possibly produce improvements in motor ability could be due to circumventing the effects of lesion damage by engaging neuroplastic processes. This therefore would have the effect of producing a lack of relationship between lesion volume or lesion location and motor recovery. The results of this study may indicate that the amount of recovery due to CI therapy is not limited by the integrity of the white matter in much the same way that it is also not limited by lesion volume or lesion location. While previous studies have analyzed the relationship between white matter integrity and spontaneous recovery (Lai et al., 2007; Parmar et al., 2006), this is the first study to investigate white matter integrity and its relation to the benefits of an efficacious rehabilitation therapy, specifically CI therapy.

Even though there was an improvement in the motor ability of patients in the CI therapy group, we found no changes in the integrity of the white matter or the CST. Previous studies have identified changes in the function of the brain (Kopp et al., 1999; Liepert et al., 2000; summarized in Mark, Taub, & Morris, 2006; summarized in Mark & Taub, 2003; Schaechter et al., 2002; Wittenberg et al., 2003) and more recently structural
changes were seen in the gray matter segment of the brain after CI therapy (Gauthier et al., 2008). However, similar changes in white matter were not identified. There are several possible explanations for this finding. First, DTI, while providing information on both integrity and location of axon tracks, is limited to information dealing with water diffusion. It is possible that changes are occurring in the white matter segment of the brain that are either not large enough to be detected by diffusion images or are not associated with water diffusion. Another possibility is that there were changes in the water diffusion in the white matter but current DTI techniques are not sufficient to detect them. A third possibility is that the increased use of the affected extremity resulting from CI therapy lead to changes in the extrapyramidal tracts associated with motor ability, such as the corticopontocerebellar, reticulospinal, rubrospinal, tectospinal, and vestibulospinal tract. There would be no indication of neuroplastic change if one analyzed just the CST, though this may have occurred elsewhere in the white matter. Finally due to the small number of patients receiving a post-treatment scan, the power to detect significant differences was extremely diminished.

Although no relationship between white matter integrity and motor ability was found, we did identify a difference in motor ability between patients with a displaced/disrupted CST and patients with an unaltered CST, regardless of the integrity of the fibers; however, this finding does not take into account possible damage to the subcortical nuclei. The basal ganglia, which consist of the caudate, putamen, globus pallidus, subthalamic nuclei, and substantia nigra, along with the thalamus are subcortical gray matter nuclei that are positioned close to the CST and are integral to motor control (Wichmann & DeLong, 1996). In this study these structures were not analyzed; however,
a lesion or hydrocephalus *ex vacuo* that changes the path of the CST would also most likely affect these nuclei as well. Similar to other movement disorders such as Huntington’s and Parkinson’s disease, alterations in the functioning of these structures could result in motor ability impairment. The results of this study could thus be pointing to an overall disruption in the motor circuits and not specifically an alteration in the CST. This might also indicate why we did not find a strong relationship between the integrity of the CST and motor ability. The more important factor might be the integrity of the entire motor circuit in which the CST is only one participant.

There were several limitations in this study including the small sample size, especially in the CI therapy group. This not only decreased our overall power to detect significant results, but also limited the types of analysis that were possible. We also combined data from stroke and MS patients with the understanding that, while the diseases had different cellular mechanisms, the clinical presentation of hemiparesis was extremely similar. Finally the scanning parameters for the diffusion imaging were not optimal, specifically in regard to the size of the voxels; they also changed during the experiment due to equipment upgrades.

Future studies should aim at correcting these limitations by first increasing the sample size and improving scanning sequences. With a larger sample size, a study could analyze differences in treatment outcome due to CI therapy between patients with a distorted/disrupted CST and patients with an unaltered CST. The potential differences in white matter integrity between stroke and MS patients could be analyzed to determine if the cellular mechanism of CNS damage affects the potential for neuroplasticity and motor improvement in response to CI therapy. Finally there are several studies which have
identified bilateral changes in the brain due to CI therapy (Gauthier et al., 2008; Kopp et al., 1999). Analyzing the corpus callosum might identify changes in the brain due to a shift in motor control from the affected hemisphere to the unaffected hemisphere.

There are several points that distinguish this project from previous studies. First, as mentioned previously, most studies in this area focus on patients in the acute to sub-acute phase of hemiparesis (ending 6 months to 1 year post-incident). It was previously assumed that chronic patients plateaued in their motor recovery and as a result it was not of great importance to study this population. CI therapy research has prompted revision of this view. Through the use of CI therapy large improvements in motor function can be produced years after stroke onset. This laboratory has worked with many chronic patients and has the unique opportunity to study the brains of patients’ years, sometimes decades, after stroke. Second, the use of an efficacious therapy in conjunction with DTI analysis techniques is novel and to our knowledge the first time diffusion imaging has been used to analyze brain plasticity due to CI therapy. Third, motor performance was evaluated by two different measures: MAL and WMFT. While timed, on-command motor tests such as the WMFT are common in hemiparesis research, the use of the MAL, which measures the amount and quality of spontaneous use in the life situation has not been analyzed in regard to its relationship with white matter integrity.
REFERENCES


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 23, 2012. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines.

Principal Investigator: PERKINS, CHRISTI
Co-Investigator(s): 
Protocol Number: X070914001
Protocol Title: Neurorehabilitation in the Stroke Affected Brain: A DTI Study (A Treatment for Excess Motor Disability in the Aged)

The IRB reviewed and approved the above named project on 8-10-09. 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: 8-10-09
Date IRB Approval Issued: 8-10-09

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.
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.

☐ 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.

☐ 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.

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

Date

Date of Expedited Review
Signature of Chair, Vice-Chair or Designee

Date