University of Alberta

Indications of neuroplasticity using diffusion tensor imaging of children with spastic cerebral palsy before and after intensive voice treatment

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

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Edmonton, Alberta
Fall 2009

Your file Votre référence
ISBN: 978-0-494-55722-8
Our file Notre référence
ISBN: 978-0-494-55722-8

ABSTRACT

The purpose of this study was to find evidence of treatment-dependent neuroplasticity as a result of Lee Silverman Voice Treatment (LSVT) implemented with children who have spastic quadriplegia cerebral palsy (SQCP). A small between-group longitudinal design on five children with SQCP and matched controls was used. Diffusion tensor images (DTI) were acquired at pre-treatment, immediately post-treatment, and at twelve weeks following treatment. Findings from this study included a significant difference in fractional anisotropy (FA) and mean diffusivity (MD) for the white matter tracts analysed through DTI in the treatment group and not in the control group when examined at follow-up. These findings support the neuroplastic impact of the intensive treatment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The current thesis research examined whether structural white matter changes in the brain could be detected after undergoing intensive voice therapy in a group of children with spastic quadriplegia cerebral palsy. The following is an overview of the thesis.

A brief review of cerebral palsy including its current definition, characteristic symptoms, related speech deficits, and aetiology are first described to familiarise the reader with the study population. Then an introduction to the theory behind and practise of the intensive voice therapy (Lee Silverman Voice Therapy) used in this study follows.

A summary of the neuroplasticity and neurorehabilitation literature provides the theoretical basis for this study. First, a current definition of neuroplasticity is presented with a brief look at some accepted mechanisms of neuroplasticity in both the typical and the lesioned brain. Second, a short review of literature citing white matter changes in developing brains is provided to demonstrate that structural change in the brain is possible. Concluding the discussion on neuroplasticity is an examination of factors considered integral to perturbation of a system as they relate to the intensive therapy used in this study. Finally, a basic overview of magnetic resonance imaging and diffusion tensor imaging is provided. Incorporated in this overview are the measures taken from the images including mean diffusivity, fractional anisotropy, and their component eigenvalues. Definitions and examples of each measure's significance are described.

Implications pertaining to clinical outcomes resulting from this intensive intervention may have profound clinical relevance. Anatomical changes that correlate with therapeutic functional improvements following intensive therapy would support a global picture of therapy influence and would expand our knowledge of how to optimise natural neuroplasticity associated with the developing brains of children with cerebral palsy.

Cerebral Palsy

Cerebral Palsy (CP) is a term used to describe a group of nonprogressive, motor disorders of movement and posture (Bax, Goldstein, Rosenbaum, Leviton, & Paneth, 2005). This group of disorders results from damage to the developing brain before, during, or shortly after birth. It is the most common movement disorder in children affecting 2 to 2.5 in 1000 births in the industrialised countries of the world (Bax, Tydeman, & Flodmark, 2006; Gupta, 2001; Krigger, 2006; Stiller, Marcous, & Olson, 2003).

Within this category of disorders, spastic CP is the most common type accounting for more than 50% of cases (Brunstrom, 2001; Krigger, 2006). Spastic CP can be further classified based on the number of limbs that are affected: monoplegia - one limb; diplegia – all four limbs with only mild involvement of the upper limbs; hemiplegia – both upper and lower limbs on one side of the body; quadriplegia – both upper and both lower limbs; paraplegia – both lower limbs; triplegia – three limbs (Workinger, 2005). The current research will focus on children with spastic quadriplegia CP (SQCP); all four limbs, trunk, and speech are affected in this group.

Characteristic symptoms of spastic CP include hypertonicity, hyper-reflexivity, muscle weakness, excessive co-activation of muscular activity, limited range of motion, and problems with posture, balance, walking, speech, and swallowing (Goldstein, 2001; Workinger, 2005). As a result, these children require early rehabilitative treatment from a multi-disciplinary team of professionals including but not limited to a paediatric physiatrist, paediatric neurologist, orthopaedic surgeon, physical therapist, occupational therapist, and speech-language pathologist (Brunstrom, 2001; Krigger, 2006; Workinger, 2005).

Over 25% of children with CP have difficulty with their speech. Severity and type of CP combine to increase this number substantially (Fedrizzi, Botteon, Carpanelli, Dal Brun, & Inverno, 1992; Pirila et al., 2007; Stiller et al., 2003). Children with CP undergo speech therapy that targets the specific deficits present in their speech production, namely those associated with dysarthria (Clement & Twitchell, 1959; Neilson & O'Dwyer, 1981; Workinger, 2005), and affecting all their speech subsystems (Clement & Twitchell, 1959; Hixon & Hardy, 1964; Keesee, 1976; Solomon & Charron, 1998; Workinger, 2005). The disordered respiratory subsystem includes deficits such as shallow inspirations with forced expirations and monoloudness. The laryngeal subsystem involves deficits such as monopitch or involuntary pitch variability and breathy voice quality. The main deficit in the velopharyngeal subsystem is hypernasality. Finally, the disordered articulatory subsystem involves difficulty articulating lingual/dental sounds, raising the velum for plosives, vowels, and fricatives, pursing the lips, and articulation of sounds requiring back tongue movements.

Although CP is considered a nonprogressive disorder, it changes as the children grow and interact with their environment. As these children mature, their speech often deteriorates as a result of abnormally increasing muscle tone and abnormal patterns of flexor and extensor spasticity (Keesee, 1976). Unfortunately, there is limited therapy available to this population, especially after the children have reached school age. In addition, much of the literature available on communication interventions with this population comes from the augmentative stream applied with children for whom speech motor control is severely impaired. Very little is known about efficacious treatments for children with spastic CP who are capable of oral communication (Garvey, Giannetti, Alter & Lum, 2007; Pennington, Goldbart, & Marshall, 2005; Yorkston, 1996).

The physical effects of spastic CP on function of the speech mechanism in children result in speech deficits that have profound negative social consequences for communication related to decreased intelligibility and deficient compensatory strategies. Additional deficits related to this disorder that are more common in SQCP include hearing and visual impairments, learning disabilities, mental retardation, and seizure disorders (Brunstrom, 2001; Scherzer, 2001). Beyond the physical impairments, functional consequences of CP also affect academic progress, social and emotional development, independent living, and employment opportunities (Brunstrom, 2001; Michelsen, Uldall, Kejs, & Madsen, 2005).

The neural aetiology of CP is quite varied; however, the causes can be broadly classified as congenital or acquired CP. The aetiology of SQCP for all

subjects in this study is classified as congenital. Congenital CP is the most common classification accounting for more than 80% of all CP cases. This aetiology is a result of damage or dysfunction during pre-, peri-, or post-natal birth such as in utero stroke or periventricular haemorrhage and consequent low birth weight, birth asphyxia, maternal infections such as rubella, toxoplasmosis, Rh incompatibility, and central nervous system malformations (Gupta, 2001). Acquired CP contributes to the remainder of CP cases. This latter etiology is a result of factors such as brain infections (e.g., bacterial meningitis or viral encephalitis) and head injury occurring in the first few months or years of life (Gupta, 2001).

Studies investigating the neuroanatomical lesions within the SQCP group have found a wide range of lesion sites. Generally, children with SQCP may have one or more lesions anywhere throughout the pyramidal system. Either the corticospinal or the corticobulbar tract may be involved, from the upper motor neurons located in the primary motor region through the corona radiata and internal capsule to the cranial nerves that innervate the face and neck and the spinal cord. More specifically, lesions have been found as bilateral periventricular leukomalacia lesions, subcortical lesions, or polymicrogyria with associated extensive bilateral diffuse involvement (Bax, Tydeman, & Flodmark, 2006; Gupta, 2001; Yin, Reddihough, Ditchfield, & Collins, 2000). The large range of sites and diffuse nature of these centrally located lesions reflect the variety and extent of peripheral motor signs of SQCP in particular.

Both normal development and therapeutic effects can alter the symptomology of CP. The developing impaired nervous system changes neurologically and physically through both maturation and compensation for varying deficits. These children acquire both adaptive and maladaptive behaviours associated with oral communication that parallel other physical adaptations associated with SQCP such as posture and movement (Keesee, 1976).

Voice Therapy Background

Theories of motor development complimentary to theories of motor learning have provided the basis for Lee Silverman Voice Treatment (LSVT), which is the intensive voice treatment program used in this study. Dynamic systems theory in combination with neuronal group selection theory (NGST) provides a strong theoretical foundation on which to base LSVT as a treatment strategy for impaired motor development. Dynamic systems theory reflects the coordination of neural, muscular, internal states, and external factors in motor development. This theory describes motor development as an emergent property of the self-organisation of mutually interdependent components (Thelen, 1995). The theory describes moments of instability, during which time exploration and selection of new behaviours occurs. The system also can intermittently fall into moments of stability which occur in between changes in physical growth and maturation across a developmental sequence. The times of instability are described as *trial and error* experiences that are integral to the process of development which is the change that moves the system from one moment of stability to another (Thelen, 1995). General beliefs and clinical consequences of this theory include:

1) treating the system early while it is unstable to take advantage of neural plasticity; 2) intervening when the system is in transition between stable moments; and 3) introducing instability into the system to facilitate new experiences, exploration, and consequent realisation of personal limits (Kamm, Thelen, & Jensen, 1990).

Dynamic systems theory does not acknowledge specific neuronal mechanisms of developing, mature, or atypical motor systems (Hadders-Algra, 2000; Sporns & Edelman, 1993). In contrast, NGST addresses these neural mechanisms based on principles of neuroanatomy and neurophysiology and their variability. NGST incorporates: 1) neural diversity that allows for experience-driven selection and change in the brain; and 2) the dense overlapping pattern of connectivity in the brain that allows for coordination and integration of sensory and motor areas of the brain (Thelen, 1995). However, NGST also shares many concepts with dynamic systems theory such as recognising the emergence of motor development from multiple systems.

LSVT as a therapy approach also demonstrates the underlying principles of motor learning in the context of voice treatment. The following paragraphs elaborate on these motor learning strategies LSVT uses including intensity of treatment, effortful practice, increased number of trials, and saliency of treatment incorporated through simplicity and sensory awareness.

LSVT is intensive. It involves four one-hour sessions every week for four weeks, which means LSVT is more intensive than any other standardised speech therapy intervention program currently practised. Intensive treatments, such as

constraint induced therapy (CIT), are at the forefront in physical therapy research and clinical practice. Significant improvement in motor function has been documented in populations such as stroke, traumatic brain injury, and CP (Grotta et al., 2004; Taub & Uwasatte, 2005). However, despite research-based reports of successful intensive treatments of this type in physical therapy practice, the area of speech-language pathology has few intensive treatment approaches.

LSVT also involves effortful practice. The client is coached to produce each phonation task with maximum effort for both loudness and length of phonation. This therapy approach promotes *physical exercise* for each subsystem of the speech mechanism including the respiratory, laryngeal, velopharyngeal, and oromotor aspects.

LSVT requires increased and repeated practice during each of the therapy sessions as well as outside of the sessions. Practice involves maximum effort with multiple repetitions and constant phonatory practice throughout the entire hour of therapy. Moreover, the varying contexts in which the trials are practised help to increase attainment of the skills needed for a good quality, loud voice and provide an adequate amount of practice for generalising these skills outside of the treatment room. To accomplish these practice tasks, the patient follows a strict practice schedule, both in and out of the therapy room. The repeated practice also contributes to automatic cognitive processing, which enables the individual's cognitive resources to be free for higher level functioning instead of focusing on vocal effort, loudness, and good quality for every phonation.

Instructions for LSVT are kept simple to minimise cognitive demands. The task is modeled and minimal verbal instructions to, "Do what I do." are used. As well, LSVT is simplistic in its treatment focus: vocal loudness. The clinician and client focus on improving voice and all involved subsystems including respiratory, articulatory, and velopharyngeal subsystems. All these subsystems improve with this one focus and one cue of "loud" (Fox, Ramig, Ciucci, Sapir, McFarland, & Farley, 2006). Indirect respiratory training includes strategies such as modeling posture, producing words that are released at the top of the breath cycle, and increasing frequency of breathing. Modeling a loud voice with an exaggerated open mouth, dropped jaw, and depressed tongue function to indirectly target vocal tract training.

Finally, sensory feedback and awareness are important to changing a patient's internal perception of his or her vocal loudness, speaking effort, and good voice quality. LSVT terms this motor learning principle as "calibration." The patient repeats the desired correct productions of a trial many times while maintaining good voice quality. Specific feedback is provided by the therapist immediately after each trial during initial sessions. The clinician reinforces the patient's attention to how that "good voice" feels, where it is coming from, and how it sounds. During the last few sessions, the patient is asked to provide analytical feedback on his or her productions. This strategy helps the patient internalise the desired vocal effort and loudness. The patient eventually learns to self-cue the required vocal effort and loudness for phonation.

In addition to its strong theoretical basis for therapeutic intervention with children having CP, LSVT previously has been demonstrated to have clinical efficacy for use with the Parkinson population (Countryman & Ramig, 1993; Countryman, Ramig, & Pawlas, 1994; Ramig, 1995; Ramig, Bonitati, Lemke, & Horii, 1994; Ramig, Countryman, Thompson, & Horii, 1995; Smith, Ramig, Dromey, Perez, & Samandari, 1995). Individuals who received this treatment demonstrated increased effort across the speech mechanism, which resulted in a spread of effects (El Sharkawi et al., 2002; Spielman, Borod, & Ramig, 2003; Sapir et al., 2003; Sapir, Spielman, Ramig, Story, & Fox, 2007). Findings from those previous studies demonstrated associated changes in speech and voice measures, including articulation (Baumgartner, Sapir, & Ramig, 2001; Dromey, Ramig, & Johnson, 1995; Ramig & Dromey, 1996; Sapir et al., 2007) and intelligibility (Ramig, 1992). In addition, Spielman, Ramig, & Borod (2001) documented changes in facial expression. Additional effects included facilitation of velopharyngeal closure and reduction of velopharyngeal orifice size as a function of loudness (Ramig, Fox, & Sapir, 2004). The patient builds strength and endurance of the speech mechanism and all muscles involved in respiration and phonation. Training vocal loudness may serve as a global variable that affects multiple levels of speech production increasing motor output for all of them (Fox et al., 2006).

Individuals are considered appropriate candidates to receive LSVT based on a speech assessment and their stimulability for loudness. The format for each session involves three tasks: 1) maximum duration of sustained phonation; 2)

maximum fundamental frequency range; and 3) maximum functional speech loudness with functional phrases. The first task maximises efficiency of phonation. It attempts to improve vocal fold adduction, loudness, and duration of phonation by training respiratory and laryngeal coordination. In addition, this task helps rescale amplitude of phonatory output for generalisation to speech. The second task improves intonation through improved range of motion of the cricothyroid, which creates longitudinal tension and elongation of the vocal folds. Through practise of maximum fundamental frequency range vertical laryngeal movement is increased, which also improves swallowing function (El Sharkawi et al., 2002). Similar to the first task, it helps rescale amplitude of phonatory output for generalisation to speech. The third task assists the patient with carry-over. It trains, cues, and calibrates the patient to the increased phonatory effort required for normal voice production.

This last task allows for distributed practice which is required for maintenance, whereas the first two tasks are blocked repeated trials that are required for initial learning. Arranging the tasks in this way allows a voice warm-up period followed by ample processing time during each block of tasks, which increases accuracy within each trial.

In summary, LSVT is based on principles of dynamic systems theory specific to a single motor organising theme (i.e., to increase vocal loudness). LSVT maximally impacts other aspects of speech production including respiration, articulation, velopharyngeal and oromotor function. Because of the intensity of

the treatment, the simplicity of the model, and the single behavioural focus (loudness), LSVT affects a maximum change with minimum cognitive effort.

Speech Therapy and Cerebral Palsy

Although conservative estimates suggest that over 25% of CP cases have difficulty with speech (Pennington et al., 2005; Pirila et al., 2007; Stiller et al., 2003), individuals with CP largely have been disregarded as candidates for speech therapy. This neglect may be due to issues such as the nature of the disorder having been classified as nonprogressive or discordance between effective treatment options especially when considering the physical nature of the disorder (i.e., easy fatigue and energy inefficiency).

As stated earlier, CP is classified as a nonprogressive disorder. However, children with CP change through maturational development and experiential growth. In addition, their brains adapt to the damaged cortex early in life when the insult occurs (Carr, Harrison, Evans, & Stephens, 1993; Kulak, Sobaniec, Kuzia, & Bockowski, 2006; Maegaki et al., 1999), similar to the manner in which stroke patients demonstrate compensatory changes in neuroanatomical structure and improvements in cortical and peripheral function immediately after the insult (Carmichael, 2003; Keyvani & Schallert, 2002). Due to the malleability of the developing brain and the structural neural adjustments made as a result of ischemic damage, the CP brain experiences many instances of growth and change despite CP being considered a nonprogressive disorder.

Treatment practices used for speech and gross motor deficits in children with CP have typically avoided intensive therapy. Due to the nature of the disorder,

issues such as fatigue, energy inefficiency, and reduced functional capacity mitigate against providing therapy to this population. For example, in a study examining energy expenditure when walking, Rose, Gamble, Burgos, Medeiros, & Haskell (1990) discussed quicker fatigue and energy inefficiency of children with CP compared to normal developing children. Another study looking at effects of aquatic exercise on respiratory function of children with CP confirmed reduced lung function compared to normative data on non-affected children of the same age (Hutzler, Chacham, Bergman, & Szeinberg, 1998).

Despite concern surrounding the use of intensive therapy with this population, research also has shown that fatigue decreases as the child builds strength and endurance through an intensive treatment strategy. Positive short- and long-term effects of intensive therapy have been found for children with CP (Blundell, Shepherd, Dean, Adams, & Cahill, 2003; Goldstein, 2001; Krigger, 2006; Stiller et al., 2003). As well, new approaches incorporating aspects of constraint-induced therapy are being proposed that capitalise on the intensive nature of that type of therapy (Charles & Gordon, 2006).

LSVT, the intensive voice therapy proven efficacious for individuals with Parkinson disease (Countryman et al., 1994; Ramig et al., 2001; Ramig et al., 1995; Smith et al., 1995), is currently being researched with other neuromotor-impaired populations. In fact, LSVT has already been successfully implemented with individuals suffering from Parkinson Plus syndromes (Countryman et al., 1994), multiple sclerosis (Sapir, Pawlas, Ramig, Seeley, Fox, & Corboy, 2001), stroke (Will, Fox, & Ramig, 2002), ataxic dysarthria (Sapir et al., 2003), aging

voice (Ramig, L., Gray, S., et al., 2001), cerebellar ataxia (Sapir, Spielman, Countryman, et al., 2003), and Down syndrome (Petska, Halpern, Ramig, & Robinson, 2006). Beyond the documented behavioural changes associated with LSVT, one study with the Parkinson population examined functional neural changes correlated with treatment effects using positron emission tomography (Liotti et al., 2003). After analysis, the investigators suggested that this adjustment of neuronal function represented a shift in the central nervous system from effortful speech to more automatic execution of speech-motor tasks within the individuals who received the treatment.

Its implementation in the juvenile CP population also has been documented and effects have been reported (Fox & Boliek, submitted). Some of these effects included increased respiratory support and capacity as well as increased sensory proprioception as a result of incorporating movement in the therapy session. In addition, integration of games and conduct of treatment in the context of play allowed active involvement of the child in the therapy tasks. That active involvement was thought to further solidify the treatment experience for the child, thus producing more positive therapeutic results.

Neuroplasticity

Neuroplasticity can be defined as "...a change in structure over time resulting in a change in function [or, from the perspective of neuroimaging,] a reorganization of distributed patterns of normal task-associated brain activity that accompany action, perception, and cognition and that compensate impaired function resulting from disease or brain injury" (Ward & Frackowiak, 2004, p.

105). Neuroplasticity occurs throughout life during normal learning and development but also can occur after an insult to the brain. Research examining the effects of brain injury on the central nervous system questions whether functional and/or structural change is possible. The current study examined the structural changes influenced by perturbation of a stable system. The following paragraphs provide a review of the neural mechanisms thought to be involved in neuroplasticity and compare normal-developing structures with chronic-lesioned structures.

Understanding and manipulating neural mechanisms is a primary focus of current neurorehabilitation research. Some possible mechanisms for neuroplasticity of a normal brain include: 1) strengthening or weakening of connections between cells accomplished through increased excitation or inhibition respectively, referred to as Hebbian learning theory; 2) altered effectiveness of synaptic transmission, commonly known as long-term potentiation or long-term depression; and 3) anatomical changes such as dendritic arborisation and axonal sprouting.

Mechanisms of early compensatory neuroplasticity of a lesioned brain can be different than the mechanisms of a typical brain listed above. For instance, a change in balance of excitation and inhibition, by a process termed unmasking, may strengthen synapses from secondary connections (Bach-y-Rita, 1992; Hallett, 2005). In addition, dendritic arborisation from surviving cells may lead to new synapses and receptor development (Bach-y-Rita, 1992; Schallert, Leasure, & Kolb, 2000). Imaging studies are used as evidence of neuroplasticity in the

brain and note displacement and expansion of functional cortical maps (Keyvani & Schallert, 2002). A more detailed review of neuroplasticity and current literature examining the white matter in a typical developing brain will be summarised followed by a brief examination of how a lesioned brain develops through experience and compensation for the injury.

Developmental Neuroplasticity

There are different structural imaging methods used to detect changes in the brain. Previous brain MRI studies have examined changes in white matter (WM) with diffusion tensor images (DTI) that reflect normal structural development. For example, Snook, Paulson, Roy, Phillips, & Beaulieu (2005) compared regional changes of WM in the brain between childhood (8-12 years) and young adulthood (21-27 years). They found increases in fractional anisotropy, which is the degree of directionality of diffusion, in the corpus callosum, corona radiata, and basal ganglia pathways within the child group as well as between the two groups (Snook et al., 2005). The increase in fractional anisotropy may indicate an increase in barriers to diffusion as the brain develops, such as higher density, more coherent organisation, or a greater degree of myelination of the fibres (Snook et al., 2005). They also found reductions in mean diffusivity, which is the average amount of diffusion, in the child group and into young adulthood (Snook et al., 2005). The decrease in mean diffusivity may indicate decreases in magnitude of diffusion related to maturational growth. These researchers concluded that normal brain microstructural development continues though adolescence (Snook et al., 2005).

Another study using quantitative T1-weighted MRI conducted a cross-sectional look at the brain's WM development through childhood and adolescence with participants ranging in age from 4 to 17 years (Paus et al., 1999). Those researchers found increases in WM density of the corpus callosum, internal capsule, corticospinal tract, and frontotemporal pathways, supporting the idea that there is a gradual maturation of pathways responsible for motor and speech functions during late childhood and adolescence (Paus et al., 1999).

Congruent with the previously mentioned studies, a DTI study by Barnea-Goraly et al. (2005) looked at normally developing individuals between the ages of 6 and 19 years and found an increase in fractional anisotropy values in the corpus callosum, internal capsule, basal ganglia and thalamic pathways, prefrontal regions, arcuate fasciculus, and ventral visual pathways that correlated with increases in age. Importantly, no WM regions were found to have significant decreases in fractional anisotropy values with age (Barnea-Goraly et al., 2005). The researchers inferred that during childhood and adolescence anisotropic changes in WM in the brain reflect important growth in attention, motor skills, cognitive ability, and memory skills (Barnea-Goraly et al., 2005). The researchers also concluded that these changes may reflect regional increases in each or a combination of axonal myelination, axonal diameter, and fibre tract density (Barnea-Goraly et al., 2005).

Generally these studies and others in this area reflect trends associated with increases in WM density and fractional anisotropy and decreases in mean diffusivity during brain maturation throughout childhood and young adulthood.

Understanding diffusion tensor imaging values in typically developing brains can serve as a standard from which atypical brain development can be compared.

Developmental Neuroplasticity Specific to Cerebral Palsy

Individuals with CP experience different WM growth and maturational patterns in the brain than normal developing individuals. The cause of this discrepancy is related to two interdependent factors: the structural reorganisation of the brain resulting from the insult early in life and the compensatory organisation resulting from experience and developmental processes.

Structural reorganisation resulting from brain insult has been noted throughout the stroke literature. Specifically, a period of time referred to as spontaneous recovery occurs shortly after the stroke, when a possible significant return of function takes place. This recovery is highly dependent on location and extent of injury as well as the functional consequences of the damage (Chugani, Muller & Chugani, 1996; Kulak & Sobaniec, 2004; Staudt, Grodd, Gerloff, Erb, Stitz, & Krageloh-Mann, 2002). Through mechanisms discussed earlier, the injured brain may stabilise transient projections, enhance normally occurring connections, or develop new projections (Carr et al., 1993; Maegaki et al., 1999). For instance, Johansen-berg (2006) lesioned monkeys and found that novel connections were made following the damage and observed changes in fibre direction around the lesion site and growth of new connections. However, many researchers have found that neuroplasticity also occurs long past the period in which maximum spontaneous recovery takes place (Bach-y-Rita, 1992; Bach-y-

Rita & Bach-y-Rita, 1990; Hodics, Cohen, & Cramer, 2006; Mateer & Kerns, 2000; Taub & Uwasatte, 2005).

Evidence of this reorganisation also is seen in individuals with CP. For instance, a noticeable difference exists between the sensory and motor pathways in CP (Kulak & Sobaniec, 2004; Thickbroom, Byrnes, Archer, Nagarajan, & Mastaglia, 2001). Using transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) techniques, Thickbroom et al. (2001) found evidence of an interhemispheric dissociation between sensory input and motor output in a group with hemiplegic CP. The researchers suggested that differences between the organisation of sensory and motor pathways are due to an impairment of sensorimotor integration as a result of reorganisation of the motor system in the CP brain (Thickbroom et al., 2001).

Researchers look towards studies showing effects of learning through experience on normally developing brain structure as possible evidence for plasticity within the injured brain (Cramer & Chopp, 2000). Preliminary evidence of effects of learning on a normal brain comes from animal studies. Dobkin (1993) and Johansen-berg (2006) reviewed research demonstrating that motor learning can produce arborisation of dendrites and growth of synapses in the cortex. More specifically, a study of adult monkeys found that learning a challenging new skill leads to the generation of novel and more extensive connections in the brain (Johansen-berg, 2006).

Motor learning research has established that neuroanatomical changes occur in humans as well. According to a study by Bengtsson, Nagy, Skare, Forsman,

Forssberg, & Ullen (2005), WM microstructure correlates with years of piano training revealing extensive white matter development in specific brain regions. Neuroplasticity also has been documented in the motor cortex during acquisition and practise of motor skills (Ungerleider, Doyon & Karni, 2002) and in interhemispheric connections after early-onset lesion of the primary visual cortex (Kiper, Zesiger, Maeder, Deonna, & Innocenti, 2002; Knyazeva, Maeder, Kiper, Deonna, & Innocenti, 2002). An important conclusion for chronic brain injury research is that experience stimulates measurable structural changes in brain pathways.

Further to compensating for the initial insult, an injured brain compensates structurally as the individual develops and learns through experience. Differences between the normal developing brain and the CP brain are evident due to these compensatory changes within the CP brain. In many cases of CP, the non-injured hemisphere contributes both structurally and functionally to reorganisation that is dependent on experience (Keyvani & Schallert, 2002). Studies also have found evidence of involvement of ipsilateral pathways of the affected cortex in structural reorganisation (Carr et al., 1993; Kulak & Sobaniec, 2004). In summary, the CP brain re-establishes some of its function after injury by compensating for resulting deficits, and further develops through experience and learning.

Therapeutic Neuroplasticity

As described above, much of the premise for therapeutic neuroplasticity is based on evidence of change after spontaneous recovery and the effect of growth and development within the system that occurs without intervention.

Specific peripheral perturbations of the motor system have been explored in studies designed to examine what effect, if any, therapeutic intervention has on the brain.

One program was developed to train children with CP who were unable to control their eye movements and therefore could not read (Gauthier & Hofferer, 1983). The children went through intensive 1-hour training sessions daily for up to 10 weeks. With their heads restrained, the children were forced to move their eyes to follow the image, were highly motivated to do so, and experienced a successful outcome in both diagnostic and therapeutic results for the abnormal oculomotor system (Bach-y-Rita & Bach-y-Rita, 1990). The basic principles underlying that study are intensity of treatment, motivation, and forced use. These factors also have been successful strategies in therapies such as constraint-induced therapy (CIT) (Taub & Uwasatte, 2005), hand–arm bimanual intensive training (HABIT) (Charles & Gordon, 2006), virtual reality therapy (VRT) (You, Jang, Kim, Kwon, Barrow, & Hallett, 2005), and LSVT (Fox et al., 2006; Ramig et al., 2001).

Constraint-induced therapy has been shown to be effective in certain physical therapy trials. Positive treatment effects after chronic damage and changes in brain organisation and function were found after CIT use (Kopp, Kunkel, Muhlnickel, Villringer, Taub & Flor, 1999; Landers, 2004; Taub & Uwasatte, 2005). Constraint-induced therapy incorporates intensive, concentrated, repetitive training during the treatment period. In addition, constraining the less-affected limb occurs during the entire period. In the context of treating young

children with CP, Taub & Uwasatte (2005) described performing the therapy during play and keeping the children motivated and attentive. Taub & Uwasatte (2005) also described studies demonstrating treatment-dependent cortical reorganisation in patients with chronic upper limb hemiparesis pre- and post-therapy.

Hand–arm bimanual intensive training was developed from principles of CIT (Charles & Gordon, 2006). The researchers recognised a need for bimanual training due to impairments in bimanual coordination beyond the unilateral impairments in hemiplegic CP. According to Charles & Gordon (2006), HABIT emphasises intense, structured practice, forced bimanual hand use in functional activities, and a motivating, child-focused protocol.

Virtual reality therapies are currently being systematically examined for efficacy as a form of physical therapy. A recent case report by You et al. (2005) examined effects of VRT implemented for a child with hemiparetic CP and demonstrated positive treatment effects. That line of therapy incorporates an intensive treatment plan, enjoyable, interactive games motivating to the child, and increasing resistive force in therapy practice as the bases for therapy.

As described above, LSVT incorporates these same principles. Intensity of treatment in LSVT is achieved through an intense session schedule with intense practice within each session. Motivation on the part of the client, if not evident at the outset of therapy, appears as the client experiences increasing success with communication. Forced use in the previous treatments is analogous to the structured homework outlined in LSVT. Without following homework practice, the

client does not achieve the same success. LSVT is an efficacious therapy for which research has provided evidence of treatment-dependent functional changes (Liotti et al., 2003).

Imaging Measures

Magnetic resonance imaging (MRI) is a non-invasive brain imaging technique that does not use radiation to produce the images. Rather it uses a magnetic field and energy impact on hydrogen atoms. MRI also provides excellent resolution and tissue contrast for research purposes. Noted disadvantages associated with MRI include high costs as well as magnetic concerns such as patients with cardiac pacemakers, aneurysm clips, and cochlear, otologic, or ear implants. For a full list of contraindications for MRI, please refer to Appendix A.

MRI uses basic properties of the hydrogen atom. The hydrogen proton absorbs and releases energy as it transitions between energy levels imposed on it by the magnet. The process of MR signal generation can be broken down into two general stages: a) stimulation to resonance and b) relaxation from resonance. Stimulation involves aligning the hydrogen protons with the static magnetic field from their normally random arrangement. A second magnetic field from the radio-frequency coil is placed perpendicular to the static field. If this second field matches the frequency of the protons, the protons are able to jump to a higher energy level. Relaxation occurs when the second field is turned off. This change releases energy from the protons which is recorded as an MR signal by a receiver and then computed through Fourier transform. Each signal is

represented by a different colour on the grey scale where a brighter colour is a stronger signal.

Diffusion tensor imaging (DTI) is a unique MR imaging technique used to differentiate and measure the integrity of individual WM tracts of the brain. The technology is based on the Brownian motion of water molecules (i.e., the random distribution of molecules in a liquid or a gas) (Basser, 2006). DTI provides information about tissue microstructure as an indirect measure of myelination and axonal density (Beaulieu, 2002). Beaulieu and colleagues maintain caution concerning inferences made from the diffusion tensor signals. These researchers specify that signals measured using this imaging process are not direct measures of myelin, but of the contribution of interactions between water molecules and cellular structures incorporating factors such as the density of axons (Basser, 2006; Beaulieu, 2006; Beaulieu & Allen, 1994). Therefore, interpretations from experiments incorporating this process should forego broad approximations in their conclusions.

The term tractography refers to the process used to reconstruct WM tracts from DTI data. When viewing these images, 2D colour maps most often are used where red, green, and blue colours represent left - right, anterior - posterior, and superior - inferior directions the tracts follow respectively.

The MR image is divided into smaller areas termed voxels. To measure diffusion, moving particles are examined in each voxel. Voxels with particles that do not move are refocused in a white colour, whereas voxels with a large amount of movement give a decreased signal and are refocused as a darker colour in the

grey scale. A diffusion tensor is measured in each voxel. This tensor is a 3 x 3 symmetrical matrix calculated with six or more gradient directions and requires seven different images per slice for the DT image; it provides a 3D image for analysis (Jones, 2006).

Two main parameters are derived from DT-MRI. These are mean diffusivity (MD) and anisotropy. Mean diffusivity represents the average magnitude of diffusion. It is calculated as the average of three eigenvalues (λ), or diagonal elements of the diffusion tensor. The following equation is used to calculate MD:

$$MD = \frac{(\lambda 1 + \lambda 2 + \lambda 3)}{3}$$

As stated earlier, a decrease in MD may indicate decreases in magnitude of diffusion related to maturational growth. In other words, a decrease in this parameter means a decrease in the average amount of diffusion within a tract (see Figure 3). Anisotropy represents directional movement versus random movement of molecules. A more specific element of anisotropy, fractional anisotropy (FA), is described below. By examining elements of the FA parameter, i.e., the eigenvalues, further information can be deduced.

Three eigenvalues are used in calculating the FA value: $\lambda 1$, $\lambda 2$, and $\lambda 3$. The following equation is used to calculate FA:

$$FA = [\sqrt{(3/2)}]\ \frac{\sqrt{[(\lambda_1-\lambda)^2 + (\lambda_2-\lambda)^2\ (\lambda_3-\lambda)^2]}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

$$\text{Where } \lambda = MD = \frac{(\lambda 1 + \lambda 2 + \lambda 3)}{3}$$

The largest eigenvalue, λ1, represents the measurement of diffusivity parallel to the tract and is referred to as axial/parallel diffusivity (Song et al., 2005). A change in parallel diffusivity can represent axonal integrity. For example, a decrease in λ1 can relate to axonal degradation (Song et al., 2005). The average of λ2 and λ3 represents the measurement of diffusivity perpendicular to the tract and is referred to as radial/perpendicular diffusivity (Song et al., 2005). A change in perpendicular diffusivity can represent a change in axonal packing or myelination. For example, a decrease in perpendicular diffusivity can relate to increased packing of axons or an increase in myelination (Song et al., 2005). It is important to note that the conclusions drawn from a change in the perpendicular measure are more accepted in the literature than conclusions about change in the parallel measure.

Breaking down FA into its eigenvalue components is useful to analyse how and why the FA parameter changes. If FA increases, diffusion is assumed to be more directional. However, this change may be due to an increase in parallel diffusivity (λ1) or a decrease in perpendicular diffusivity (the average of λ2 and λ3). If the FA value does not change, the eigenvalues may indicate no change for both parallel and perpendicular diffusivity or may indicate an equal change of both parallel and perpendicular diffusivity. Hence, these eigenvalues offer more information than the FA value alone.

Fractional anisotropy relates to the degree of directionality (i.e., how directional the tensor is, where 0 is isotropic and 1 is highly anisotropic). It is a ratio of the magnitude of anisotropic diffusion to the magnitude of the whole

tensor. The term *isotropic* is used when diffusion is equal in all directions ($\lambda 1 = \lambda 2 = \lambda 3$), for example, when the diffusion shape is spherical as in cerebrospinal fluid (Figure 1).

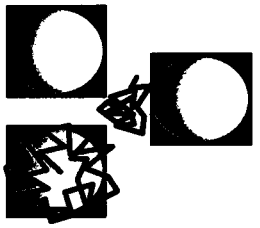


Figure 1. Isotropic diffusion represented as spherical particle movement. Used with permission from Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR in Biomedicine, 15*, 435-455.

The term *anisotropic* is used when diffusion is directional ($\lambda 1 > \lambda 2 = \lambda 3$), for example, when the diffusion shape is ellipsoidal (Figure 2).

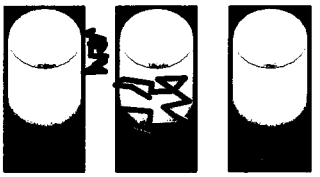


Figure 2. Anisotropic diffusion represented as cylindrical particle movement. Used with permission from Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR in Biomedicine, 15*, 435-455.

This measure offers information about the amount of asymmetry but not the direction of movement (see Figure 3).

Tractography was performed for all DTI analyses using a 3D region of interest. For each tract, seeding, target, and exclusion regions were selected

manually on the 2D FA colour map (see Figure 3). All voxels within the seeding region were used as seed points for fibre tracking for each subject, and the target and exclusion regions served to include or exclude fibres passing through specific areas.

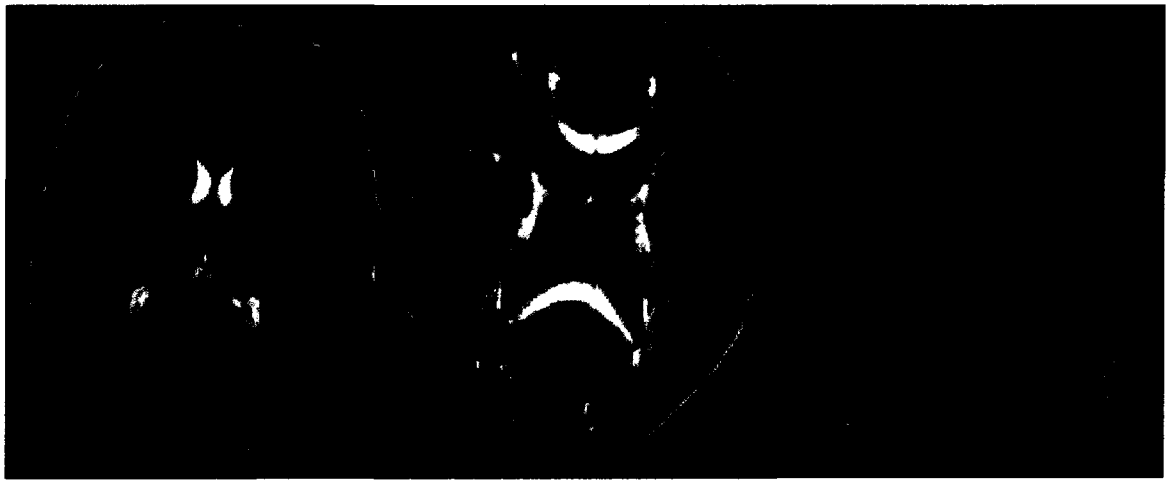


Figure 3. Images from subject M1001C. From left to right: MD map, FA map, FA colour map. MD map is a map of average diffusion: bright regions reflect high diffusion, darker regions reflect low diffusion. FA map is a map of anisotropy: bright regions reflect high anisotropy, darker regions reflect high isotropy. FA colour map is a map depicting preferred direction of diffusion, where red reflects left – right, blue reflects superior – inferior, and green reflects anterior – posterior.

A final measurement gleaned from DTI analysis is that of tract volume. The volume measurement is calculated from multiplying the number of voxels the WM tract runs through by the voxel volume (in this study, number of voxels x 0.8592 x 0.8592 x 3 mm). This volume measurement does not necessarily represent actual tract volume. It offers the possibility of different causes for an FA change. For example, a decrease in volume may indicate a decrease in myelination of that tract, influence of a lesion blocking the tract, or influence of crossing fibres.

Some controversy exists in reporting this value as its applicability in DTI analysis is in question (Huang, Zhang, van Zijl, & Mori, 2004; Reich et al., 2006). However the volume parameter was included in the current study to offer a complete picture of change in the brain.

Previous research using DTI and fibre tracking technology consists mainly of group comparison studies between typical and patient populations or analysis within a patient population. The outlined project applied an analysis of the DT images to a longitudinal study to examine potential changes in WM over time.

DTI is especially advantageous for this application as there is an established correlation between the CP diagnosis and lesions in the motor cortex and throughout its descending WM tracts (Korzeniewski, Birbeck, DeLano, Potchen & Paneth, 2008; Nagae et al., 2007; Kulak et al., 2006). For example, researchers have found evidence of abnormal branching and bilateral projections of the corticospinal tract through EMG studies involving subjects with CP (Farmer, Harrison, Ingram & Stephens, 1991; Carr et al., 1993). Follow-up analyses of aberrant WM tracts, only able to be provided by DTI *in vivo*, would help establish these findings and perhaps further change opinions of WM variability in CP. In addition, emerging evidence from exploration of structural neuroplasticity in chronic-lesioned patients suggests that the CP population is ideal for the current study (Carey et al., 2002; Ludlow et al., 2008; Trivedi et al. 2008; Wang et al., 2006). Finally, DTI provides information not found on conventional MR images. In fact, Son et al. (2007) found focal lesions of the corticospinal tract in a group of subjects with hemiplegic CP using DTI with fibre tractography that were

unidentifiable in conventional MRI. DTI can increase our understanding of pathogenesis in CP as well as other developmental disorders involving WM abnormalities. From the information available describing WM injury in the CP population, as well as the building knowledge involving neural plasticity, utilising DTI in a study of this nature is a logical next step.

Therapeutic Changes

Peripheral treatment-dependent changes were measured at each stage of this project. Indices of peripheral change included chest wall EMG, respiratory kinematics and articulatory acoustics associated with speech and speech production post intervention. These peripheral measures will be reported in detail elsewhere. However, when appropriate, general links between measures of peripheral change and measures of central structural change were presented and interpreted in the context of habilitation and neuroplasticity.

Hypotheses of central changes due to perturbation through intensive treatment have developed from evidence of change at the periphery. For example, increased vocal loudness developed from increased effort in respiratory and laryngeal subsystems can be documented from SPL instrumentation and EMG and respiratory patterns. From these data, corticospinal tract (CST) involvement can be inferred as changes in communication between motor cortex and cranial and spinal nerves innervating the laryngeal complex, oromotor, velopharyngeal, and respiratory subsystems.

Treatment driving change in the central nervous system also can be documented with functional imaging techniques, such as positron emission

tomography and fMRI. For instance, Dai, Liu, Sahgal, Brown, & Yue (2001) recorded muscle output online with fMRI data to determine a relationship between central and peripheral activity. Those researchers discovered a direct relationship between handgrip force and fMRI signal as well as EMG and fMRI signal suggesting a correlated, integrated set of communicating systems. Through a review of the current literature, Nielsen (2002) examined inhibition of the CST through transcranial magnetic stimulation and explained that the CST contributes to muscle activity as recorded through EMG of the active muscle in human subjects. In addition, Norton & Gorassini (2006) revealed that increases in CST innervation in part facilitate improvements in movement function of subjects with incomplete spinal injury. Another study by Thomas & Gorassini (2005) found that intensive training had effects on increased activity of the CST as noted through MEPs in subjects with incomplete spinal cord injury. Following these findings, documenting structural central nervous system change through methods such as DTI, which allows examination of white matter structures in the brain, is a logical next step.

Hypotheses

The purpose of the current study was to find evidence of treatment-dependent neuroplasticity as a result of LSVT implemented with children who have SQCP. Image analysis of upper motor neuron (UMN) WM tracts was compared among normal developing controls, children with SQCP, and children with SQCP undergoing intensive voice treatment. Analyses focused on average amount of

diffusion and anisotropy changes seen in DT images taken over time. The following questions will be answered:

1) Does Treatment having 2 levels (LSVT and Control) affect UMN WM tracts analysed through DTI?

2) Does Time having 3 levels (pre-treatment, post-treatment and 12 weeks post-treatment follow-up) affect UMN WM tracts analysed through DTI?

3) Do Treatment and Time interact to affect UMN WM tracts analysed through DTI?

Design

The current study is a small group design with repeated measures and multiple dependent variables. This design allowed for heterogeneity within the CP classification, including differences in neuropathology contributing to developmental and therapeutic neuroplasticity changes and pre-therapy function of speech (i.e., severity of the speech disorder prior to delivering therapy). Each subject was yoked to a control, further increasing strength in the study's results. Whereas behavioural and physiological data were collected across multiple baselines, brain images were collected once for each of pre, post, and follow-up time points.

Challenges in scheduling treatment sessions and data collection made concurrent participation of subjects difficult. To account for these difficulties, a non-concurrent design was used.

The study proper was the second phase of five under a larger umbrella. This project replicated phase one in which case study designs, small group

experiments, and single-subject designs were used (Fox & Boliek, submitted). There was only one active treatment in the phase one design, sample sizes were small, there was a lack of strict external controls, and Type I and Type II errors were tolerated (Fox & Boliek, submitted; Robey & Schultz, 1998). Thus, phase two replicated phase one with the addition of EMG, respiratory kinematics, speech intelligibility, and DTI analyses.

In addition to documenting WM plasticity, information pertaining to lesions of SQCP found with the MRI-DTI data were documented to contribute to our understanding of this disorder. Effectiveness of LSVT with this population also was discussed.

It was hypothesised that intensive voice therapy would produce significant changes in the primary UMN WM tracts only with the children who have SQCP who underwent intensive voice therapy. These changes were expected to be observable in post-treatment DTI analyses.

METHODS

Participants

Five children with a diagnosis of SQCP were recruited through the Glenrose Rehabilitation Hospital, Physical Medicine section. None of these children had previous experience or knowledge of the first phase of the larger study. Written informed consent and assent was obtained from all subjects (see Appendix B). Two of these children, one girl and one boy, initially served as controls and then received treatment as outlined below. The three remaining children received treatment as outlined below. The three girls and two boys with SQCP ranged in age from 7;8 to 11;2 with a mean age of 9;10 at the time of enrolment in the

study. One female was walking independently; one female and one male used assistive walking devices; one female and one male were wheelchair dependent.

Each child with CP was paired with a yoked control without CP and tested through the same time-frame as the subjects with CP. The yoked controls were recruited through word of mouth. Written and informed assent were obtained from all controls.

The methods used in this study were approved by the Health Research Ethics Board – Biomedical Panel of the University of Alberta on October 6, 2006 (see Appendix C).

Inclusion & Exclusion Criteria

Inclusion criteria for participants consisted of: 1) a minimum age of 6 years and a maximum age of 12 years; 2) a perceptible speech or voice disorder, such as dysarthria; 3) hearing within normal limits, or aided to be within normal limits; 4) the cognitive ability to follow directions and perform the tasks associated with the study protocol; 5) average or near average cognition (with some learning deficits); 6) medically stable; and 7) clinically diagnosed with SQCP by a paediatrician.

Exclusion criteria included: 1) severe velopharyngeal incompetence; 2) vocal fold pathology; and 3) severe structural disorders of the speech mechanism, for example, un-repaired cleft lip or palate.

Procedures

Two subjects with SQCP served as clinical-group controls. These children completed two MRIs one month apart. The MRIs were examined for changes in

white matter tracts that may be related to normal development in the CP group. These two subjects then received treatment and were included in the SQCP treatment group (refer to Figure 4 for a chart of the experimental timeline).

The subjects with SQCP in the treatment group completed one MRI at baseline one week prior to beginning therapy. The therapy was conducted for one hour each day for four consecutive days, over four consecutive weeks (i.e., 16 one-hour therapy sessions) in the subject's home. Within one week after completing therapy, each subject completed a post-treatment MRI scan. Three follow-up LSVT therapy sessions were conducted over the subsequent 12 weeks, and all subjects with SQCP had a final MRI scan at the end of this time.

For this thesis four of the five children with SQCP were each paired with a yoked control without CP. A fifth yoked control without CP will be included in later analyses. These control children completed two MRIs one month apart and one additional scan 12 weeks after the second to match the same time-frame as scans acquired from the experimental group. These scans were used to document any changes in white matter tracts related to normal development.

	MRI #1 (5 weeks before tx)	MRI #2 (1 week before tx)	Tx (4 weeks)	MRI #3 (1 week after tx)	MRI #4 (12 weeks after tx)
CP-Control (2 subjects)	✓	✓			
CP (3 subjects +2 CP-controls)		✓	✓	✓	✓
Control (4 subjects)	✓	✓			✓

Figure 4. Chart of experimental timeline. CP-control group consisted of 2 subjects with SQCP that were given 2 MRIs 1 month apart (no therapy during that period of time). After confirming no significant change in DVs over the 1 month time frame, the first MRIs from these 2 subjects were then included in the pre-treatment time point of the CP group. The control CP group did receive treatment as shown in the figure. The final CP group results (N = 5) were compared with the control group results (N = 4).

Treatment compliance of all subjects is outlined in Table 1.

Table 1

Therapeutic Subject Compliance between Weeks 9 – 12 of Study

Subject	Practice Reported
F0802E	One practice daily with mother, 7 days per week/4 weeks
F1001E	Total of 5 practices with LSVT DVD
F1201E	One practice at school 5 days per week/4 weeks
M0901E	One practice daily with LSVT DVD/7 days per week/4 weeks
M1001E	Two practices daily with mother/7 days per week/4 weeks

Pre-therapy DTI

All MRI scans were performed on a 1.5T Siemens Sonata MRI scanner in the NMR Research Centre at the University of Alberta Hospital. DTI used single-shot, diffusion-weighted, twice-refocused spin-echo echo planar imaging with a repetition time of 6400 ms, an echo time of 88ms, and 8 averages (Beaulieu et al., 2005). Forty 3-mm-thick contiguous axial slices with a matrix of 128 x 128 zero-filled to 256 x 256, 75% phase partial Fourier, and a 22-cm field-of-view was acquired in 6:06 minutes and yielded an effective in-plane resolution of 0.85 x 0.85 mm^2 after zero filling. The diffusion tensor was acquired for each slice with six sets involving diffusion gradients placed along non-collinear directions (diffusion sensitivity, b = 1000 s/mm^2) and an individual set without diffusion weighting (b = 0 s/mm^2). Isotropic 3D 1 x 1 x 1 mm^3 resolution anatomical MP-RAGE (magnetization prepared rapid acquisition with gradient echo) scans were also obtained of the entire brain. Total acquisition time averaged 25 minutes.

The MRI protocol used in this study was composed of eight different scans. The first images were from a localiser scan, which provided three rough pictures in the coronal, transverse, and sagittal planes in order to position the remainder of the scans. A sagittal T1 scan and a DTI scan provided research images for analysis. Following these scans a Fluid Attenuated Inversion Recovery (FLAIR) DTI scan was performed, which minimised partial volume effects of diffusion measurements on tracts near cerebrospinal fluid. An MP-RAGE scan was added to the protocol to provide the 3D volumetric images used to identify the neuroanatomical pathologies. To view lesions and any other abnormalities, an Axial DWI (diffusion–weighted image) followed the protocol sequence. Finally, to view chronic lesions, Axial T2 and Axial FLAIR images completed the protocol.

Two aspects of DTI must be accounted for to attain representative images: 1) SNR and 2) movement artefacts. SNR is comprised of field strength, voxel size, and number of averages. This study used a field strength of 1.5T, an acquired voxel size of 1.7 x 1.7 x 3mm^3 (approximately 8.7mm^3), and 8 averages. These numbers equate to a calculated SNR range between 50 and 60, which is considered adequate for these analyses. Movement artefacts did not undergo post-processing. However, FA and colour maps were visually inspected for good image quality.

Therapy

Two clinicians delivered the intensive voice treatment to all subjects with supervision from an LSVT instructor in order to maintain consistency in treatment delivery. Treatment sessions occurred one hour per day, four days per week,

over four consecutive weeks. Every session occurred in the subject's home, and no sessions were missed. Each session consisted of repetitions of specific tasks: 1) maximum duration sustained phonation, 2) maximum fundamental frequency range, and 3) maximum functional speech loudness with functional phrases. Increasing loudness was implemented through a hierarchy of speech tasks outlined over the four weeks of treatment and included words/phrases (week 1), sentences (week 2), reading (week 3), and conversation (week 4). In order to follow this hierarchy with the children in the study, progression involved naming flashcards, describing pictures, reading stories, and participating in conversation to elicit loud speech.

Gross movements were incorporated into the maximum duration sustained phonation and maximum fundamental frequency range tasks when implementing LSVT with the children in the study. For example, forced movement of the arms up for highs and down for lows were used to exaggerate the concept. In addition, the children practised the tasks in various positions including sitting, standing, supine, and through jumping and rolling activities.

Post-therapy DTI

The procedure for all subject post-therapy scans replicated the procedure for pre-therapy scans. The same 1.5T Siemens Sonata MRI scanner in the NMR research centre at the University of Alberta Hospital was used to obtain the images. These scans followed the same protocol as the pre-therapy MRI scans outlined above. A total of two separate post-therapy scans were taken. One was

completed within 1 week following therapy, and the other was completed 12 weeks post-therapy.

DATA ANALYSIS

Variables

Two independent variables (IVs) were analysed: 1) time and 2) treatment. Time was a within-subjects variable and consisted of three levels: 1) pre-treatment, 2) immediately post-treatment, and 3) 12 weeks post-treatment follow-up. Treatment was a between-subjects variable and consisted of two levels: 1) children with SQCP who received LSVT and 2) normal developing children who did not receive treatment.

Two dependent variables (DVs) were analysed through DTI tractography of the structural white matter in each brain. The first DV was fractional anisotropy (FA), expressed as a percent of the tensor attributed to anisotropic diffusion. The other DV was mean diffusivity (MD), expressed as an average of diffusion for a particular region of interest.

DT Imaging Analysis

All DT imaging analyses were completed using DtiStudio version 2.4 software (H. Jiang, S. Mori; Department of Radiology, Johns Hopkins University, Baltimore, MD; refer to Jiang, van Zijl, Kim, Pearlson, & Mori, 2006, for more information on this program). Fibre tracking was performed using a continuous tractography method (FACT), where every voxel in the brain is used as a seed point for fibre tracking. A vector is generated in the direction of the principal eigenvector of the diffusion tensor for each voxel, and the process is repeated for

every voxel following. Tracking stops at a pre-specified FA threshold and turning angle to limit the detection of fibres that are not part of the tract of interest. In this study, the FA threshold was set at 0.25 and the turning angle threshold was set at 70°. The DtiStudio software used in these analyses required specification of a noise threshold as well as an option for automatic outlier rejection. These values were set at 25 and 2.3 respectively and were maintained throughout the analyses. Because this study was designed to be exploratory in nature, all WM tracts reliably identified in the images were recorded and analysed. Hence, a total of 10 tracts were analysed from each subject and chosen according to previous studies and recommendations using DT imaging analysis methods (Fan, Yu, Quan, Sun, & Guo, 2006; Mori et al., 2002; Nagae et al., 2007; Stieltjes et al., 2001; Wakana, Jlang, Nagae-Poetscher, van Zljl, & Morl, 2004). Researchers performing the DTI analyses were blinded to subject identity and testing session.

All tracts reported in this study were acquired using an ROI method that applies existing anatomic knowledge of tract location and manually-defined ROIs (Catani, Howard, Pajevic, & Jones 2002; Jiang et al., 2006; Mori et al., 2002; Mori & Mori, 1999; Wakana et al., 2004). Multiple ROIs were used to extract a tract from the DT image with any combination of three types of operations: 1) *AND*, which defines maintaining only fibres found through both first and second regions identified (intersection); 2) *OR*, which defines including all fibres found in the region identified (union); and 3) *NOT*, which defines eliminating all fibres found in a second region identified that are included in the first region identified

(exclusion) (Jiang et al., 2006). Figure 5 illustrates the isolation of the corticospinal tract using this method:

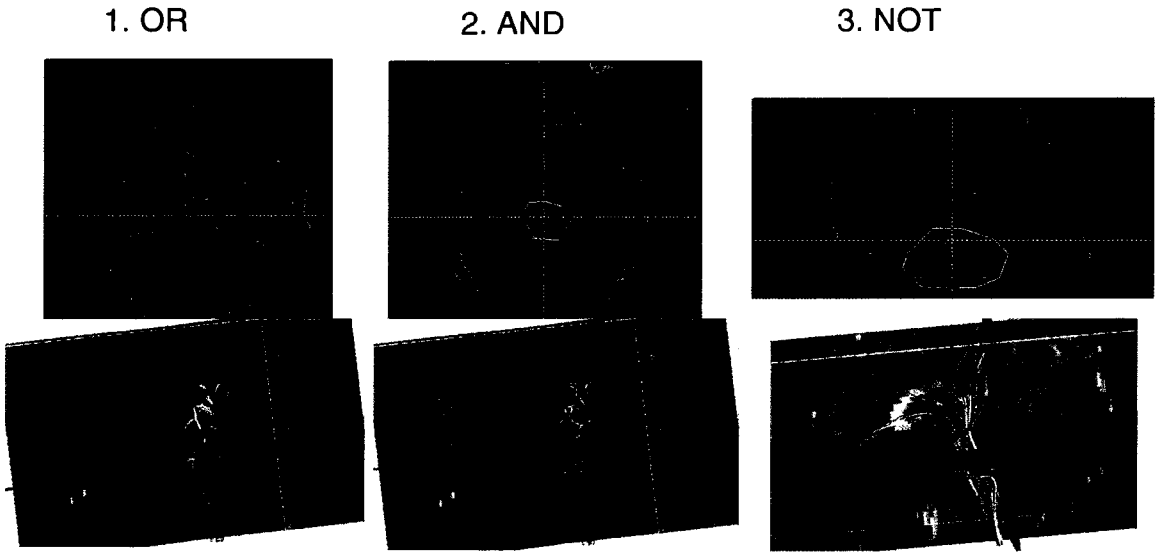


Figure 5. 3D ROI protocol for CST using tractography. Steps include OR, AND, then NOT operations shown on FA colour map with each resulting 3D image.

An ROI protocol outlining the specific ROIs used to isolate each tract in this study as well as referenced visuals to a DTI Atlas (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005) are given in Table 2. Every tract isolated using this method was analysed noting specifically FA, MD, eigenvalues, and volume from the fibre statistics. Each parameter was averaged across subjects for statistical analyses.

Table 2

DTI ROI Protocol

Tract	Operations
Corpus Callosum (CC)	• OR include all red CC on sagittal • NOT fornix on axial

Cingulum (CG)	• NOT cingulum on coronal • p. 28 in atlas[a] • OR circle green dots just superior to CC on both LH and RH on coronal • NOT fibres from CC • p. 27 in atlas[a]
Posterior Thalamic Radiation (PTR) Separately analysed left and right hemispheres	• OR ~½ hemisphere of occipital lobe on coronal on posterior half of thalamus • AND posterior thalamus on coronal • p. 20 in atlas[a]
Anterior Thalamic Radiation (ATR) Separately analysed left and right hemispheres	• OR ~½ hemisphere mid-anterior on coronal on anterior half of thalamus • AND anterior thalamus on coronal • p. 20 in atlas[a]
Middle Cerebellar Peduncle (MCP)	• OR circle red above and below purple dots/CST on inferior axial • AND red inferior region on mid-sagittal • NOT superior cerebellar peduncle on axial • p. 18 & 51 in atlas[a]
Inferior Longitudinal Fasciculus (ILF) Separately analysed left and right hemispheres	• OR green lateral area below CC on axial (p. 63 in atlas[a]) • AND inferior green on mid-anterior coronal

	(p. 135 in atlas[a]) • If UNC included, take AND further back • p. 24 in atlas[a]
Superior Longitudinal Fasciculus (SLF) Separately analysed left and right hemispheres	• OR green lateral triangle protrusion from CC on mid-posterior coronal • AND just posterior to OR on coronal • NOT CST • p. 23 in atlas[a]
Inferior Fronto-occipital tract (IFO) Separately analysed left and right hemispheres	• OR green spot below CC on mid-anterior coronal • AND just posterior to OR on coronal • NOT green line/UNC just below on coronal • p. 25 in atlas[a]
Uncinate Fasciculus (UNC) Separately analysed left and right hemispheres	• OR purple spot anterior to IFO on axial • AND inferior portion of hemisphere on coronal – only superior bunch (p. 139 in atlas[a]) • p. 25 in atlas[a]
Corticospinal tract (CST)	• OR anterior blue spots on inferior axial – just before they join to inferior blue dots as the axial slices move superiorly (p. 39 in atlas[a]) • AND just superior to OR on axial to get both hemispheres of fibres and exclude the MCP

	(p. 61 in atlas[a])
	• NOT MCP on coronal
	• Keep communication fibres at base of tract
	• p. 18 in atlas[a]

[a] From Mori, S., Wakana, S., Nagae-Poetscher, L.M., & van Zijl, P.C.M. (2005) MRI Atlas of Human White Matter. Elsevier B.V. Amsterdam, The Netherlands

Tracts of Interest in the Brain

Tracts were analysed separately. The following describes an *a priori* organisation of the tracts of interest.

A primary tract of interest was chosen based on expected peripheral changes dependent on treatment and factors of neuroplasticity mentioned previously. The projection tracts, the corticospinal tract (CST) and the corticobulbar tract (CBT), were identified as primary tracts. The CST was expected to correlate with EMG chest wall and respiratory pattern changes, where involvement was inferred as changes in communication between motor cortex and cranial and spinal nerves innervating the laryngeal complex, oromotor, velopharyngeal, and respiratory subsystems. The CBT was expected to correlate with acoustic changes including articulatory and intelligibility changes post-treatment.

Choice of secondary tracts was founded on tractographic sensitivity to tract identification (i.e., tracts that are considered reproducible in both 2D and 3D images) (Wakana et al., 2004). These secondary tracts of interest were grouped according to function and therefore, as tracts that were either expected or not expected to change due to treatment.

Tracts where treatment-dependent changes were expected included the thalamic radiations (i.e., the posterior thalamic radiation [PTR] and the anterior thalamic radiation [ATR]), which are involved in emotional, behavioural, cognitive, and motor functions, attention, learning and memory (Barnea-Goraly et al., 2005) and the association tracts, which may demonstrate neuroplasticity through changes in intrahemispheric connectivity. Association tracts that were examined included the inferior longitudinal fasciculus (ILF), the superior longitudinal fasciculus (SLF), the inferior fronto-occipital tract (IFO), the uncinate fasciculus (UNC), and the cingulum (CG). The ILF is believed to play a role in visual memory, which may be linked to the key features of LSVT, including the simple, "Do what I do." instruction as the subject gleans important information from simply watching the therapist's example. The SLF is noted to play a role in focusing spatial information and regulating motor behaviour. In addition, the SLF is integrally tied to the language areas of the brain. The IFO is thought to play a role in cognition (Taoka et al., 2006) and associative learning. The UNC also is thought to play a role in cognitive and memory functions (Taoka et al., 2006). The CG was chosen as it links the thalamic radiations and the limbic system. The limbic system is an important system to consider in this study because heightened emotions and increases in facial animation have been observed in patients with Parkinson disease following LSVT (Spielman et al., 2003). The corpus callosum (CC) is integral to interhemispheric communication, motor and sensory integration, and general cognitive function; therefore, FA and MD values were expected to change as a result of treatment.

Tracts where treatment-dependent changes were not expected included the cerebellar tracts, specifically the middle cerebellar peduncle (MCP). The MCP was the most reliable tract in the cerebellum to isolate so it was chosen as the only tract from the cerebellum in the analysis. Ungerleider (2002) suggested the cerebellum may be involved functionally when a task is initially learned; however, it is not integral to functioning after that task has been learned. In addition, Fan et al. (2006) found no visual differences or significant difference in FA values for the MCP between control subjects and those with CP. Therefore this tract was examined in the study and used as a control measure within subjects across time points.

An analysis of FA and MD values between the control and the CP group was run for each time point through the study to identify differences between the two groups and respective tract changes over time. Additionally, a within-groups comparison for the CP group was performed to look at asymmetries between FA values for each tract in each hemisphere. Then an examination of asymmetrical differences between the two groups was completed.

This study was exploratory and there were minimal data available describing how sensitive DTI would be to detecting changes after an intensive behavioural intervention; therefore, it was important to include several control paradigms so that if change was detected post treatment it could be attributed to change related to that treatment and not to other factors. As a result, three control analyses were used. First, a control tract (the middle cerebellar peduncle) was isolated as a tract where treatment-dependent changes were not expected to

occur based on knowledge of functions assumed by this tract, as stated previously. This tract was used to identify stability across time in the CP group using the DTI tractography method. Second, a control group was used that consisted of children without CP who did not undergo treatment. The control group allowed for direct comparisons between the CP group and the control group both prior to and after treatment. Third, a CP-control group was used that consisted of children with CP who did not undergo treatment. This CP-control group demonstrated no change detected by DTI across two time points and provided evidence of stability in the WM tracts prior to undergoing treatment. Thus, any changes identified in the CP group after treatment could be attributed to treatment-dependent effects.

MR Imaging Analysis

The scans from all five subjects with SQCP were analysed using MPRAGE images acquired during the MRI scans. A neurophysiologist from the University of Alberta Hospital used these MPRAGE images to identify neuroanatomical pathology for each subject. A neuroradiologist will confirm the reading of the scans prior to publication. (T2 images from each of the five SQCP subjects are given in Appendix D.) The conventional MRI findings and demographic data for all subjects were compiled in Table 3.

Table 3

Clinical Identifying Characteristics and MRI Observations of CP Subjects

Subject	Age	Gender	Diagnosis	CP Characteristics	MRI MPRAGE Observations
F0802E	7;8	F	SQCP	• Mild severity • Mild articulation • Poor respiratory support	• Mild R hydrocephalus d/t excess choroid plexus • L cysts inferior to lateral ventricles, L lateral to CC • Thin CC
F1001E	10;1	F	SQCP	• Severe severity • Mild-moderate dysarthria • Poor respiratory support • VP incompetence	• Poor image quality • R hydrocephalus • Pathological ventricle • Lesion R parietal • Thin CC
F1201E	9;9	F	SQCP	• Moderate severity • Mild articulation	• PCA stroke

				• Mild dysarthria • Strained-strangled voice	
M0901E	11;2	M	SQCP	• Moderate severity • Moderate dysarthria • Poor respiratory support	• L lack of gyri
M1001E	11;1	M	SQCP	• Severe severity • Severe dysarthria • Poor respiratory support	• Obstructive hydrocephalus → lack of WM • Thin CC

F = female, M = male, SQCP = spastic quadriplegia cerebral palsy, CP = cerebral palsy, VP = velopharyngeal, R = right, L = left, CC = corpus callosum, WM = white matter.

RESULTS

All analyses were conducted by two investigators who were blind to subject group and time points. Reports in the literature suggested the successful isolation of the corticobulbar tract in both a typical population and a population with CP (Mori et al., 2005; Thomas et al., 2005). However, crossing fibres may have impeded the ability to isolate the corticobulbar tract using the tractographic techniques applied. Therefore, the corticobulbar tract was not included in the current study.

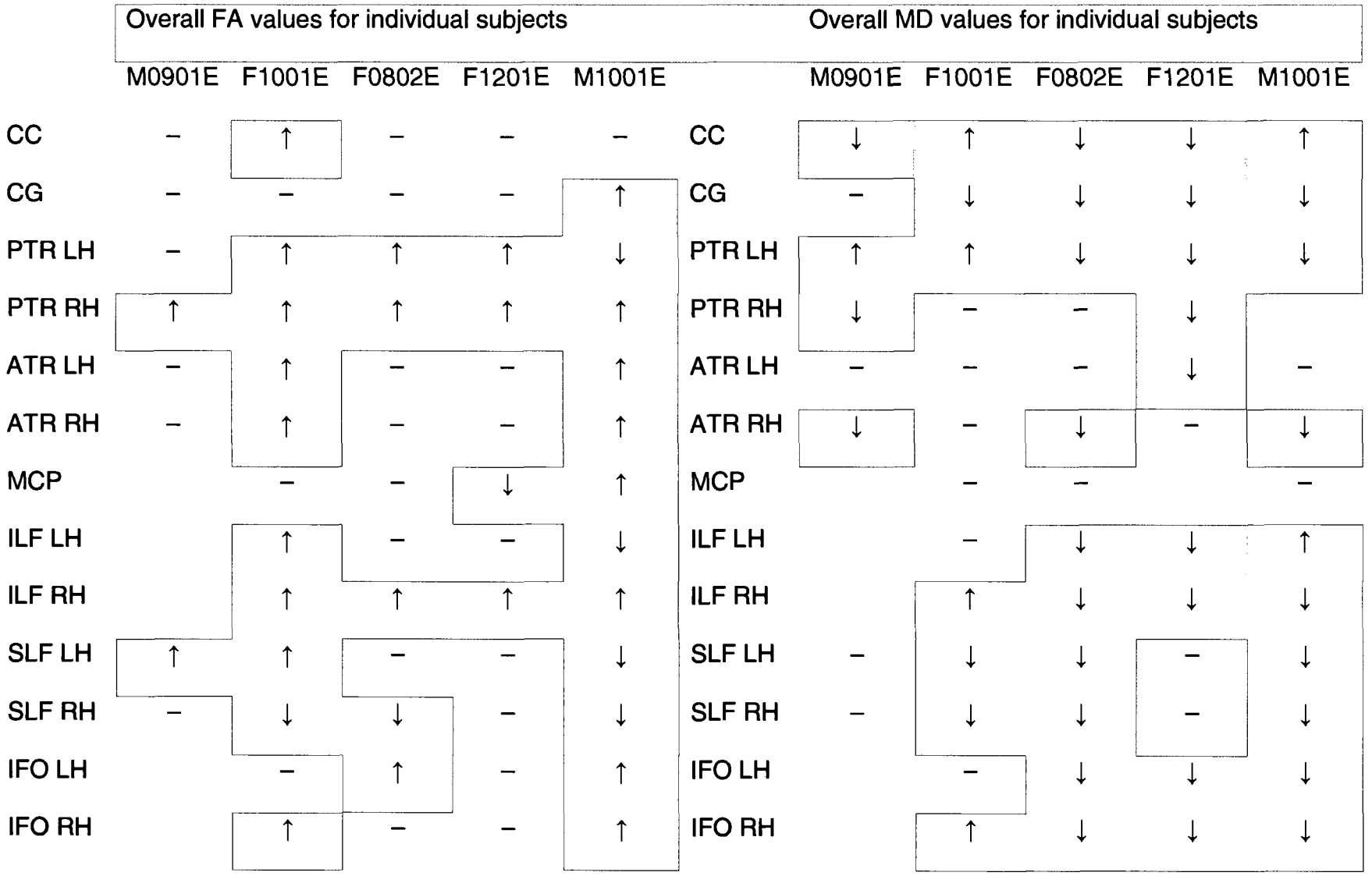
Reliability

A tractographic analysis of all diffusion tensor scans from the group with CP was completed, where FA and MD values were recorded for every tract analysed. Intra-rater reliability measures were performed on a random selection of 20% of all the CP tracts analysed. These selected tracts then were measured a second time. All FA and MD values from the CP tracts were compared between the first analysis and the second analysis. A Spearman rho statistic resulted in a strong correlation [$r(105) = 0.927$, $p < 0.01$] suggesting excellent intra-rater reliability. The same intra-rater reliability procedure was performed on 20% of the control tracts for FA and MD values resulting in an r value of $r(90) = 0.943$, $p < 0.01$. Intra-rater reliability of each tract then was examined. The intra-rater reliability range of Spearman rho for all 16 CP tracts was $r(6) = 0.905$ to 0.999, $p < 0.001$. The intra-rater reliability range of Spearman rho for all 16 control tracts was equally as strong, $r(4) = 0.943$ to 0.999, $p < 0.01$.

The procedure used to measure intra-rater reliability was duplicated for an inter-rater reliability analysis. A second researcher performed reliability measures after being trained to use the DTI analysis software program. The inter-rater reliability Spearman rho obtained for CP and control tracts was $r(108) = 0.974$, $p < 0.01$ and $r(91) = 0.912$, $p < 0.01$; respectively.

Visual Analyses

Each tract for each subject and control was examined visually to note trends in change of FA and MD values over time. Figures 6 and 7 show in which direction these trends for FA and MD values changed over time and if these changes were in the expected direction (indicated by the colour green). The total number of tracts that changed for each DV in the CP group (i.e., 70) was much larger in comparison to the total number of tracts that changed in the control group (i.e., 22). The tracts that showed the highest frequency of change in the CP group included the PTR and the ILF in the right hemisphere and the CST for FA, and the CG for MD. No tracts demonstrated the same frequency of change in the control group. As well, the right hemisphere showed more changes across subjects than the left hemisphere. Finally, more changes occurred in the expected direction for MD than for FA. In addition, these changes for MD were larger than the changes for FA.


Overall FA values for individual subjects
M0901E F1001E F0802E F1201E M1001E
CC – ↑ – – –
CG – – – – ↑
PTR LH – ↑ ↑ ↑ ↓
PTR RH ↑ ↑ ↑ ↑ ↑
ATR LH – ↑ – – ↑
ATR RH – ↑ – – ↑
MCP – – ↓ ↑
ILF LH ↑ – – ↓
ILF RH ↑ ↑ ↑ ↑
SLF LH ↑ ↑ – – ↓
SLF RH – ↓ ↓ – ↓
IFO LH – ↑ – ↑
IFO RH ↑ – – ↑
Overall MD values for individual subjects
M0901E F1001E F0802E F1201E M1001E
CC ↓ ↑ ↓ ↓ ↑
CG – ↓ ↓ ↓ ↓
PTR LH ↑ ↑ ↓ ↓ ↓
PTR RH ↓ – – ↓
ATR LH – – – ↓ –
ATR RH ↓ – ↓ – ↓
MCP – – –
ILF LH – ↓ ↓ ↑
ILF RH ↑ ↓ ↓ ↓
SLF LH – ↓ ↓ – ↓
SLF RH – ↓ ↓ – ↓
IFO LH – ↓ ↓ ↓
IFO RH ↑ ↓ ↓ ↓

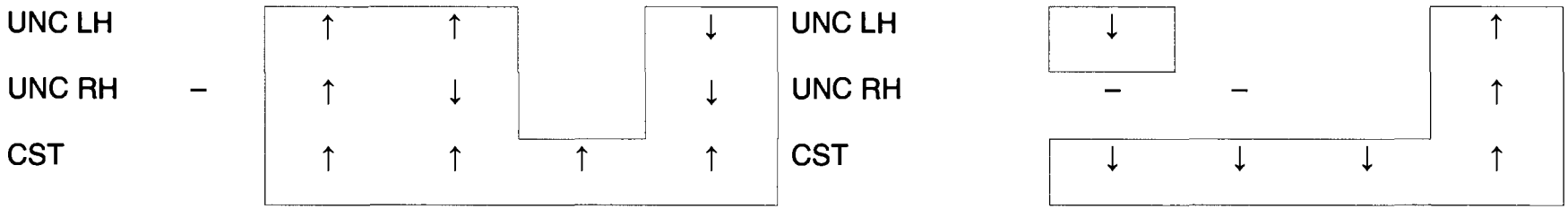
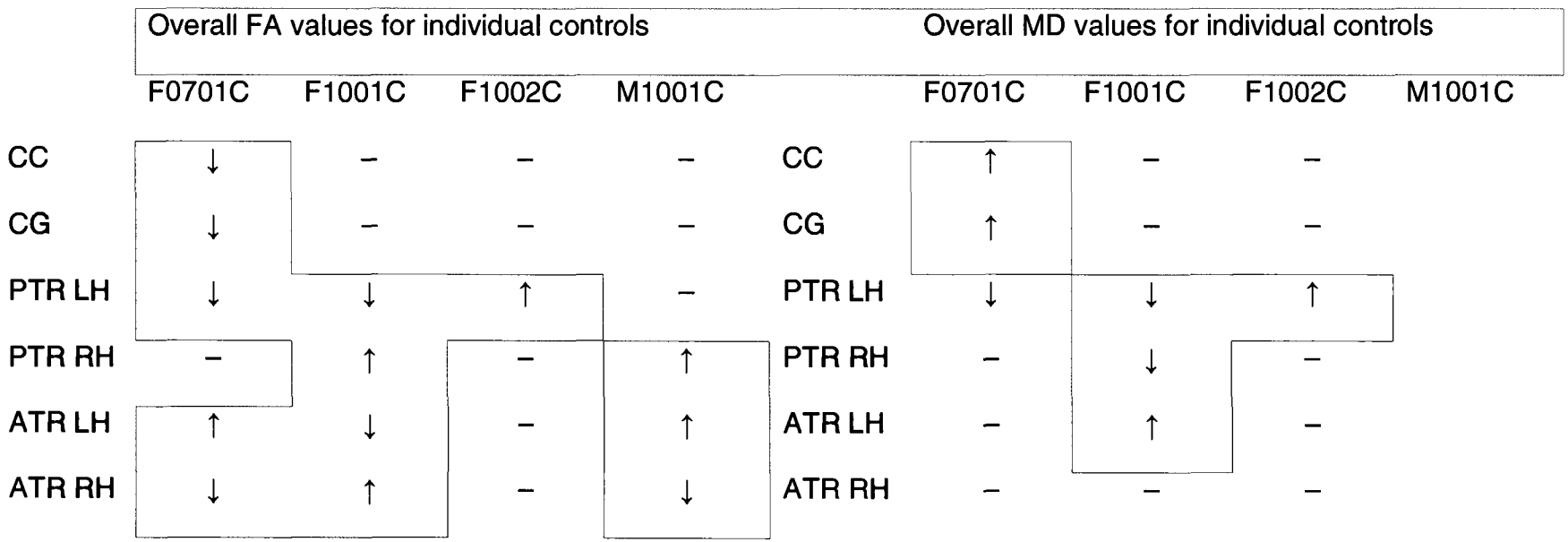


Figure 6. CP group visual trend data from pre-treatment to follow-up timepoints. ↑ = increase in value over time. ↓ = decrease in value over time. – = no change in value over time. An empty cell = no data available for analysis. A green cell indicates the increase or decrease of that value over time was in the expected direction. A red cell indicates the increase or decrease of that value over time was not in the expected direction. Subjects are listed across top of chart. CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.



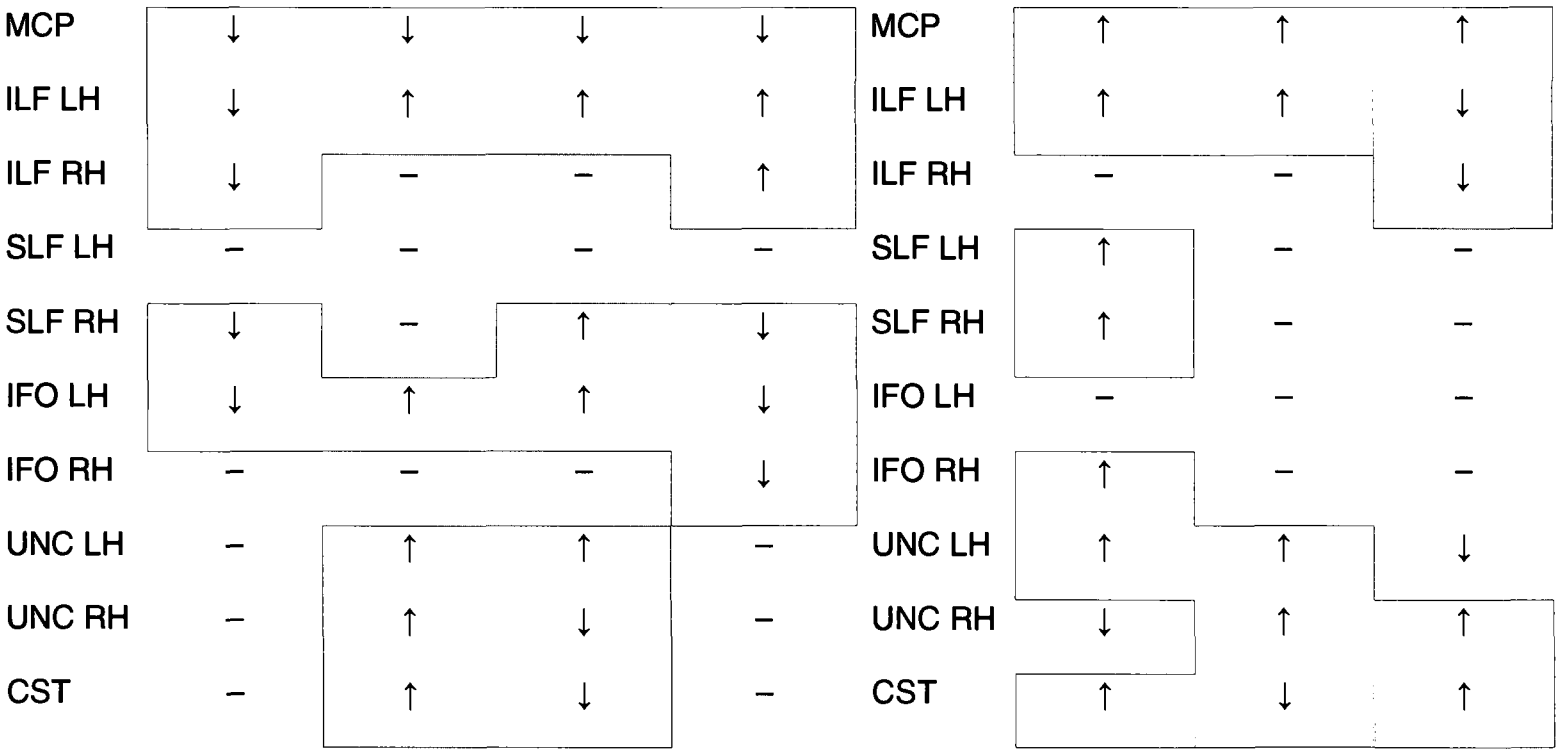


Figure 7. Control group visual trend data from time 1 to time 3. ↑ = increase in value over time. ↓ = decrease in value over time. – = no change in value over time. An empty cell = no data available for analysis. A green cell indicates the increase or decrease of that value over time was in the expected direction of change when detected. A red cell indicates the increase or decrease of that value over time was not in the expected direction of change when detected. Controls are listed across top of chart. CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

A visual analysis of boxplots created for each value (FA and MD) for each tract and across the three time points was completed to assess the distribution of the group data and examine individual outliers relative to the group in the FA and MD values. Outlier data points were present in the CP-group boxplots but no outliers were observed in the control dataset. Out of 58 outliers, 18 pairs were symmetrically spread across the three plotted time points, 16 were present against the median trend line, and 6 were present in the same direction of the trend. When outliers were removed from the dataset, no change in central tendency was observed in the boxplot graphs; therefore, all data points were included in the statistical analyses.

Statistical Analyses

The means, standard deviations, and medians for FA and MD for subjects, tracts, and time are reported in Table 4. All statistical analyses were completed using SPSS version 15.0. Descriptive statistics for group-averaged FA and MD values for each of the tracts confirmed that distributions were either positively or negatively skewed. Therefore, the median FA and MD values were a better indicator of central tendency and used for all tests of statistical difference using appropriate nonparametric statistics for repeated measures: 1) Between-group analyses for each tract were completed using a Mann Whitney U test of independent samples, and 2) Follow-up pair-wise comparisons using a Wilcoxon signed-ranks test for two related samples were conducted when Friedman tests were significant. The threshold for statistical significance was set *a priori* at $p \leq 0.05$. Only a 2-tailed option for each nonparametric statistic was provided;

however, change for each DV was expected in one direction, so each resulting *p*-value was divided by 2 for comparison to the threshold.

Table 4

Median and Mean ± SD FA & MD Values for CP (N = 5) and Control (N = 4) Groups

	Fractional Anisotropy (Median) (Mean ± SD)						Mean Diffusivity (x $10^{-3}mm^2/s$) (Median) (Mean ± SD)					
	Control			CP			Control			CP		
Tracts	Pre	Post	Follow-up	Pre	Post	Follow-up	Pre	Post	Follow-up	Pre	Post	Follow-up
CC	0.62	0.61	0.60	0.55	0.56	0.56	0.82	0.82	0.84	0.99	0.96	0.90
	0.62	0.62	0.60	0.54	0.56	0.55	0.82	0.83	0.86	0.98	0.95	0.93
	± 0.01	± 0.02	±0.01	± 0.05	± 0.03	± 0.05	± 0.02	± 0.04	± 0.05	± 0.05	± 0.05	± 0.07
CG	0.54	0.52	0.52	0.47	0.47	0.47	0.82	0.82	0.83	0.87	0.83	0.84
	0.53	0.52	0.51	0.47	0.47	0.47	0.82	0.82	0.83	0.89	0.87	0.85
	± 0.02	± 0.03	± 0.03	± 0.05	± 0.04	± 0.04	± 0.02	± 0.03	± 0.02	± 0.05	± 0.07	± 0.05
PTR	0.50	0.51	0.49	0.50	0.52	0.55	0.83	0.85	0.82	0.89	0.91	0.85

LH	0.50	0.52	0.50	0.48	0.50	0.51	0.84	0.84	0.82	0.93	0.94	0.90
	± 0.01	± 0.03	± 0.03	± 0.06	± 0.06	± 0.09	± 0.03	± 0.04	± 0.01	± 0.10	± 0.13	± 0.09
PTR	0.48	0.52	0.50	0.52	0.51	0.54	0.84	0.85	0.83	0.93	0.89	0.86
RH	0.49	0.53	0.49	0.49	0.51	0.55	0.85	0.84	0.85	0.96	0.89	0.87
	± 0.01	± 0.06	± 0.02	± 0.08	± 0.06	± 0.01	± 0.03	± 0.03	± 0.04	± 0.08	± 0.07	± 0.03
ATR	0.49	0.48	0.49	0.48	0.49	0.49	0.77	0.77	0.78	0.83	0.80	0.80
LH	0.48	0.48	0.50	0.47	0.46	0.49	0.78	0.78	0.78	0.86	0.82	0.81
	± 0.03	± 0.01	± 0.01	± 0.05	± 0.05	± 0.03	± 0.02	± 0.02	± 0.01	± 0.07	± 0.04	± 0.04
ATR	0.49	0.48	0.49	0.46	0.46	0.48	0.77	0.77	0.77	0.83	0.82	0.79
RH	0.49	0.48	0.48	0.46	0.45	0.47	0.77	0.78	0.77	0.86	0.81	0.80
	± 0.02	± 0.03	± 0.03	± 0.05	± 0.06	± 0.03	± 0.01	± 0.04	± 0.01	± 0.05	± 0.03	± 0.02
MCP	0.56	0.56	0.51	0.50	0.51	0.52	0.84	0.86	0.91	0.90	0.89	0.86
	0.55	0.54	0.52	0.50	0.51	0.52	0.84	0.87	0.92	0.91	0.89	0.86
	± 0.03	± 0.05	± 0.03	± 0.02	± 0.03	± 0.01	± 0.02	± 0.04	± 0.05	± 0.04	± 0.06	± 0.01
ILF	0.53	0.54	0.52	0.50	0.51	0.49	0.86	0.84	0.86	0.89	0.89	0.88

LH	0.53	0.55	0.52	0.49	0.51	0.49	0.85	0.85	0.87	0.92	0.89	0.88
	± 0.02	± 0.03	± 0.05	± 0.06	± 0.05	± 0.06	± 0.03	± 0.05	± 0.02	± 0.06	± 0.03	± 0.02
ILF	0.54	0.55	0.53	0.46	0.50	0.51	0.89	0.86	0.87	0.90	0.88	0.85
RH	0.53	0.55	0.53	0.45	0.50	0.51	0.87	0.86	0.88	0.90	0.88	0.85
	± 0.01	± 0.02	± 0.01	± 0.03	± 0.04	± 0.05	± 0.04	± 0.03	± 0.03	± 0.08	± 0.03	± 0.02
SLF	0.51	0.51	0.50	0.45	0.45	0.46	0.82	0.82	0.83	0.87	0.83	0.82
LH	0.50	0.50	0.49	0.44	0.45	0.44	0.81	0.82	0.83	0.88	0.83	0.83
	± 0.02	± 0.02	± 0.02	± 0.03	± 0.03	± 0.05	± 0.03	± 0.04	± 0.02	± 0.05	± 0.02	± 0.03
SLF	0.51	0.50	0.52	0.45	0.45	0.46	0.80	0.81	0.81	0.88	0.83	0.83
RH	0.51	0.51	0.51	0.45	0.45	0.44	0.80	0.81	0.81	0.90	0.82	0.83
	± 0.02	± 0.02	± 0.03	± 0.03	± 0.04	± 0.04	± 0.02	± 0.03	± 0.03	± 0.06	± 0.03	± 0.04
IFO	0.52	0.52	0.52	0.47	0.50	0.48	0.82	0.81	0.83	0.89	0.86	0.88
LH	0.52	0.52	0.51	0.47	0.50	0.47	0.82	0.81	0.83	0.90	0.86	0.88
	± 0.04	± 0.03	±0.04	± 0.06	± 0.02	± 0.04	± 0.01	± 0.02	± 0.001	±0.03	± 0.04	± 0.01
IFO	0.53	0.53	0.53	0.47	0.48	0.50	0.82	0.82	0.84	0.87	0.84	0.84

RH	0.53	0.52	0.53	0.48	0.48	0.50	0.82	0.82	0.84	0.87	0.84	0.84
	± 0.03	± 0.03	± 0.02	± 0.05	± 0.07	± 0.05	± 0.01	± 0.01	± 0.03	± 0.04	± 0.04	± 0.01
UNC	0.48	0.48	0.48	0.40	0.42	0.45	0.84	0.83	0.86	0.85	0.89	0.83
LH	0.47	0.47	0.47	0.40	0.43	0.45	0.84	0.84	0.86	0.85	0.89	0.83
	± 0.04	± 0.03	± 0.03	± 0.02	± 0.04	± 0.01	± 0.03	± 0.03	± 0.02	±0.03	± 0.07	± 0.01
UNC	0.47	0.47	0.46	0.45	0.41	0.43	0.83	0.83	0.85	0.84	0.86	0.86
RH	0.47	0.47	0.47	0.44	0.43	0.43	0.84	0.83	0.85	0.86	0.86	0.86
	± 0.02	± 0.02	± 0.02	± 0.02	± 0.04	± 0.04	± 0.04	± 0.01	± 0.02	± 0.05	± 0.06	± 0.03
CST	0.58	0.57	0.56	0.54	0.54	0.55	0.81	0.83	0.86	0.92	0.90	0.88
	0.58	0.57	0.56	0.51	0.54	0.55	0.81	0.82	0.85	0.96	0.91	0.88
	± 0.01	± 0.02	± 0.01	± 0.05	± 0.03	± 0.02	± 0.02	± 0.02	± 0.02	± 0.10	± 0.04	± 0.04

CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Between-group analyses for each tract were completed using a Mann Whitney U test of independent samples. The comparisons between the CP group and the control group were done for each DV, for each tract, at each time point.

Consistent with the use of nonparametric analyses, a Friedman one-way analysis of variance for tract and time by ranks with repeated measure for time was completed for each DV, for each tract, for both CP and control groups separately. Follow-up pairwise comparisons using a Wilcoxon signed-ranks test for two related samples were conducted when Friedman tests were significant. A Bonferroni correction on p-value ≤ 0.05 was not used for the CST analyses because the CST served as the primary tract of interest. Analyses of the secondary tracts were considered exploratory and any changes in the values of interest were important to the investigative nature of this study. Hence a more conservative p-value may have led to missed changes in these values.

CP-control group

Two of the five subjects with CP served as experimental controls for this study. These subjects had two MRI scans taken one month apart and prior to beginning treatment. The time between scans simulated the one month duration within which therapy occurred for the remaining three subjects. All of the tracts from these two pre-treatment scans for each CP-control were analysed for changes over this one-month time period without treatment.

A Wilcoxon signed ranks test for two related samples was used to test for differences between the DVs across the two time points. All results were not significant with a Z-score range of 0.45 to 1.34 and a probability range of 0.18 to

0.66, indicating no significant change between time-1 and time-2 DTI scans for the CP-controls. Based on these results, data from the first of the two scans was chosen to represent pre-treatment data from these two subjects when subsequently analysed as part of the treatment group. This time point also was selected because it best represented all subjects entering the study (e.g., no external or internal experimental influence).

CP and control groups

CP and the control group tract comparisons

A Mann Whitney U test of independent samples was used to examine between group (CP vs controls) X tracts (16) X time (pre, post, and treatment follow up) with repeated measures on time for each DV. At time 1, only the IFO and the UNC, both in the right hemisphere, did not show a significant difference between the two groups for either FA or MD. However, eight tracts were significantly different between the CP and control groups for FA and 11 showed a significant difference for MD (see Table 5). At time 2, seven tracts were significantly different from the control group for FA and five were significantly different for MD (see Table 6). At time 3, four tracts showed a significant difference between the groups for FA and six were significantly different for MD (see Table 7). Overall, the number of significantly different tracts between the two groups decreased from time 1 to time 3. By time 3 the tracts that remained significantly different between the CP group and the control group for the FA value were the CC, the PTR in the right hemisphere, and the SLF in both left and right hemispheres. The remaining significantly different tracts between the two groups for the MD value at time 3 were the PTR in the left hemisphere, ATR in

both hemispheres, the interhemispheric MCP, the IFO in the left hemisphere, and the UNC in the left hemisphere.

Table 5

Results of Mann Whitney U Test Comparison of FA & MD Values between CP and Control Groups at T1

Tract	U-statistic		Z-standard score		*P*-significance	
	FA	MD	FA	MD	FA	MD
CC	0.00	0.000	2.449	2.449	0.014	0.014
CG	2.000	0.000	1.960	2.449	0.050	0.014
PTR LH	6.000	3.000	0.980	1.715	0.327	0.086
PTR RH	5.000	1.000	1.225	2.205	0.221	0.027
ATR LH	10.000	1.000	0.000	2.205	1.000	0.027
ATR RH	7.000	0.000	0.735	2.449	0.462	0.014
MCP	1.000	0.000	2.205	2.449	0.027	0.014
ILF LH	5.000	2.000	1.225	1.960	0.221	0.050
ILF RH	0.000	7.000	2.449	0.735	0.014	0.462
SLF LH	1.000	2.000	2.205	1.960	0.027	0.050
SLF RH	1.000	0.000	2.205	2.449	0.027	0.014
IFO LH	3.000	0.000	1.715	2.449	0.086	0.014
IFO RH	4.000	4.000	1.470	1.470	0.142	0.142
UNC LH	1.000	8.000	2.021	0.000	0.043	1.000
UNC RH	4.000	6.000	1.470	0.980	0.142	0.327
CST	1.000	0.000	2.205	2.449	0.027	0.014

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. FA = fractional anisotropy, MD = mean diffusivity, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Table 6

Results of Mann Whitney U Test Comparison of FA & MD Values between CP and Control Groups at T2

Tract	U-statistic		Z-standard score		*P*-significance	
	FA	MD	FA	MD	FA	MD
CC	0.000	0.000	2.449	2.449	0.014	0.014
CG	3.000	6.000	1.715	0.980	0.086	0.327
PTR LH	10.000	2.000	0.000	1.960	1.000	0.050
PTR RH	8.000	6.000	0.490	0.980	0.624	0.327
ATR LH	10.000	0.000	0.000	2.449	1.000	0.014
ATR RH	7.000	6.000	0.735	0.980	0.462	0.327
MCP	4.000	8.000	1.470	0.490	0.142	0.624
ILF LH	4.000	5.000	1.470	1.225	0.142	0.221
ILF RH	3.000	5.000	1.715	1.225	0.086	0.221
SLF LH	1.000	8.000	2.205	0.490	0.027	0.524
SLF RH	1.000	7.000	2.205	0.735	0.027	0.462
IFO LH	6.000	2.000	0.980	1.960	0.327	0.050
IFO RH	6.000	7.000	0.980	0.735	0.327	0.462

UNC LH	5.000	5.000	1.225	1.225	0.221	0.221
UNC RH	3.000	5.500	1.715	1.107	0.086	0.268
CST	2.000	0.000	1.960	2.449	0.050	0.014

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. FA = fractional anisotropy, MD = mean diffusivity, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Table 7

Results of Mann Whitney U Test Comparison of FA Values between CP and Control Groups at T3

Tract	U-statistic		Z-standard score		*P*-significance	
	FA	MD	FA	MD	FA	MD
CC	3.000	4.000	1.715	1.470	0.086	0.142
CG	4.000	6.000	1.470	0.980	0.142	0.327
PTR LH	5.000	1.000	1.225	2.205	0.221	0.027
PTR RH	0.000	4.000	2.449	1.470	0.014	0.142
ATR LH	9.000	2.000	0.245	1.960	0.806	0.050
ATR RH	7.000	1.000	0.735	2.205	0.462	0.027
MCP	9.000	3.000	0.245	1.715	0.806	0.086
ILF LH	7.000	6.000	0.735	0.980	0.462	0.327
ILF RH	8.000	4.000	0.490	1.470	0.624	0.142
SLF LH	2.000	8.000	1.960	0.490	0.050	0.624

SLF RH	1.000	6.000	2.205	0.980	0.027	0.327
IFO LH	4.000	0.000	1.470	2.449	0.142	0.014
IFO RH	4.000	8.000	1.470	0.490	0.142	0.624
UNC LH	5.000	1.000	1.246	2.242	0.213	0.025
UNC RH	4.000	5.000	1.476	1.230	0.140	0.218
CST	7.000	5.000	0.735	1.225	0.462	0.221

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. FA = fractional anisotropy, MD = mean diffusivity, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Analysis of tracts across time

Friedman one-way analysis of ranks tests followed by pairwise comparisons on significant results were completed on the FA and MD values for all tracts in the control group and all tracts in the CP group (see Tables 8, 9, 10, and 11).

Table 8

Results of Friedman Analysis for Control Group for FA Values

Tract	X^2 (df)	Significance	Pairwise Comparisons [X^2(1)]		
			T1 – T2	T2 – T3	T1 – T3
CC	6.5 (2)	0.039	--	4.00	4.00
CG	1.5 (2)	0.472	--	--	--
PTR LH	3.5 (2)	0.174	--	--	--
PTR RH	0.5 (2)	0.779	--	--	--
ATR LH	3.5 (2)	0.174	--	--	--
ATR RH	2.0 (2)	0.368	--	--	--
MCP	3.5 (2)	0.174	--	--	--
ILF LH	1.5 (2)	0.472	--	--	--
ILF RH	3.5 (2)	0.174	--	--	--
SLF LH	0.5 (2)	0.779	--	--	--
SLF RH	1.5 (2)	0.472	--	--	--
IFO LH	0.0 (2)	1.000	--	--	--
IFO RH	0.5 (2)	0.779	--	--	--
UNC LH	1.5 (2)	0.472	--	--	--
UNC RH	1.5 (2)	0.472	--	--	--
CST	2.0 (2)	0.368	--	--	--

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. FA = fractional anisotropy, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior

longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract; -- = no significant post hoc Wilcoxon result.

Table 9

Results of Friedman Analysis for Control Group for MD Values

Tract	X^2 (df)	Significance	Pairwise Comparisons [X^2(1)]		
			T1 – T2	T2 – T3	T1 – T3
CC	4.5 (2)	0.105	--	--	--
CG	0.5(2)	0.779	--	--	--
PTR LH	0.5 (2)	0.779	--	--	--
PTR RH	0.0 (2)	1.000	--	--	--
ATR LH	0.5 (2)	0.779	--	--	--
ATR RH	0.0 (2)	1.000	--	--	--
MCP	4.5 (2)	0.105	--	--	--
ILF LH	1.5 (2)	0.472	--	--	--
ILF RH	1.5 (2)	0.472	--	--	--
SLF LH	0.5 (2)	0.779	--	--	--
SLF RH	0.5 (2)	0.779	--	--	--
IFO LH	1.5 (2)	0.472	--	--	--
IFO RH	1.5 (2)	0.472	--	--	--
UNC LH	1.5 (2)	0.472	--	--	--
UNC RH	2.0 (2)	0.368	--	--	--
CST	2.0 (2)	0.368	--	--	--

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. MD = mean diffusivity, CC = corpus

callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract; -- = no significant post hoc Wilcoxon result.

Table 10

Results of Friedman Analysis for CP Group for FA Values

Tract	X^2 (df)	Significance	Pairwise Comparisons [X^2(1)]		
			T1 – T2	T2 – T3	T1 – T3
CC	2.8 (2)	0.247	--	--	--
CG	1.6 (2)	0.449	--	--	--
PTR LH	2.8 (2)	0.247	--	--	--
PTR RH	5.2 (2)	0.074	--	--	5.00
ATR LH	2.8 (2)	0.247	--	--	--
ATR RH	1.6 (2)	0.449	--	--	--
MCP	0.0 (2)	1.000	--	--	--
ILF LH	1.6 (2)	0.449	--	--	--
ILF RH	7.6 (2)	0.022	5.00	--	5.00
SLF LH	3.6 (2)	0.165	--	--	--
SLF RH	0.0 (2)	1.000	--	--	--
IFO LH	2.8 (2)	0.247	--	--	--
IFO RH	4.8 (2)	0.091	--	--	5.00
UNC LH	6.5 (2)	0.039	--	--	4.00
UNC RH	2.8 (2)	0.247	--	--	--
CST	6.4 (2)	0.041	--	--	5.00

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori p* = 0.05 threshold. FA = fractional anisotropy, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract; -- = no significant post hoc Wilcoxon result.

Table 11

Results of Friedman Analysis for CP Group for MD Values

Tract	X^2 (df)	Significance	Pairwise Comparisons [X^2(1)]		
			T1 – T2	T2 – T3	T1 – T3
CC	1.6 (2)	0.449	--	--	--
CG	5.2 (2)	0.074	--	--	5.00
PTR LH	0.4 (2)	0.819	--	--	--
PTR RH	5.2 (2)	0.074	--	--	5.00
ATR LH	2.8 (2)	0.247	--	--	--
ATR RH	4.8 (2)	0.091	--	--	5.00
MCP	1.2 (2)	0.549	--	--	--
ILF LH	2.8 (2)	0.247	--	--	--
ILF RH	4.8 (2)	0.091	--	5.00	--
SLF LH	5.2 (2)	0.074	--	--	5.00
SLF RH	3.6 (2)	0.165	--	--	--
IFO LH	2.8 (2)	0.247	--	--	--
IFO RH	0.0 (2)	1.000	--	--	--
UNC LH	1.5 (2)	0.472	--	--	--

UNC RH	1.2 (2)	0.549	--	--	--
CST	5.2 (2)	0.074	--	--	5.00

Note. Significance is 2-tailed. As change in the DV was expected in one direction, the 2-tailed *p*-value shown here was divided by 2 in later analyses for statistical comparison to the *a priori* $p = 0.05$ threshold. MD = mean diffusivity, CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract; -- = no significant post hoc Wilcoxon result.

The results of the Friedman tests revealed no significant change for the primary tract of interest, the CST, in the control group across any of the time points. However, the CST in the CP group was significantly different from time 1 to time 3. Specifically, FA values increased [X^2 (2) = 6.4, $p = 0.02$, 1-tailed] and MD values decreased [X^2 (2) = 5.2, $p = 0.04$, 1-tailed] from pre- to follow up treatment time point [both FA and MD: $X^2(1) = 5.00$, $p < 0.05$].

Next, FD and MD values derived from secondary tracts of interest across the three time points were analysed using the Friedman tests followed by appropriate *post hoc* pairwise comparisons. As can be seen in Table 8, the control-group tests resulted in only one significant change found in the FA value for the CC. FA values significantly decreased for this tract between time 1 and time 3 as well as between time 2 and time 3. In comparison, data from the CP group revealed several significant differences across time for FA and MD. The FA values in four tracts (the UNC in the left hemisphere, and the PTR, the ILF, and the IFO in the right hemisphere) increased from time 1 to time 3. There also was a significant increase in FA for the ILF in the right hemisphere from time 1 to time 2. Significant changes in MD values were found in five tracts. Four of these five

tracts (the CG, the SLF in the left hemisphere, and the PTR and the ATR in the right hemisphere) showed a significant decrease in MD from time 1 to time 3. The fifth tract, the ILF in the right hemisphere, had a significant decrease in MD from time 2 to time 3 (see Figures 6 and 7 for overall visual trends in each tract for each CP subject and each control).

Eigenvalues

Parallel and perpendicular eigenvalues were examined only in the tracts that showed significant results from the Friedman one-way analysis of ranks test (see Tables 12 and 13). This analysis was performed to identify a possible explanation for the significant change in either the FA or the MD value due to increases or decreases in their component parallel or perpendicular eigenvalues. The CC in the control group showed an increase in both parallel and perpendicular eigenvalues. The primary tract of interest in the CP group, the CST, revealed a decrease in both the parallel and the perpendicular eigenvalues (mean ± SD for $\lambda_{\parallel}$ pre: 1.54 ± 0.07, post: 1.52 ± 0.05, follow-up: 1.48 ± 0.04; mean ± SD for $\lambda_{\perp}$ pre: 0.66 ± 0.18, post: 0.60 ± 0.16, follow-up: 0.58 ± 0.17). Of the seven secondary tracts in the CP group exhibiting significant change across time, the perpendicular eigenvalue decreased in 6 tracts (the CG, the PTR, ATR, and ILF in the right hemisphere, and the SLF and UNC in the left hemisphere) and increased in one tract (the IFO in the right hemisphere). Parallel eigenvalues decreased in 4 tracts (the CG, the SLF in the left hemisphere, and the IFO and PTR in the right hemisphere), increased in 2 tracts (the ATR in the right

hemisphere and the UNC in the left hemisphere), and showed no change in one tract (the ILF in the right hemisphere).

Table 12

Mean ± SD Parallel ($\lambda_{\parallel}$) and Perpendicular ($\lambda_{\perp}$) Eigenvalue Measurements for Control Group

Tract	$\lambda_{\parallel}$ (mean ± SD) ($10^{-3}mm^2/s$)			$\lambda_{\perp}$ (mean ± SD) ($10^{-3}mm^2/s$)		
	Pre	Post	Follow-up	Pre	Post	Follow-up
CC	1.50 ± 0.19	1.50 ± 0.03	1.53 ± 0.04	0.48 ± 0.18	0.49 ± 0.19	0.52 ± 0.17
CG	1.34 ± 0.06	1.34 ± 0.03	1.35 ± 0.02	0.55 ± 0.22	0.56 ± 0.22	0.57 ± 0.22
PTR LH	1.34 ± 0.09	1.37 ± 0.04	1.33 ± 0.04	0.58 ± 0.18	0.58 ± 0.19	0.57 ± 0.15
PTR RH	1.35 ± 0.09	1.39 ± 0.05	1.36 ± 0.01	0.60 ± 0.18	0.57 ± 0.19	0.59 ± 0.17
ATR LH	1.22 ± 0.10	1.23 ± 0.01	1.25 ± 0.05	0.55 ± 0.16	0.55 ± 0.17	0.54 ± 0.15
ATR RH	1.22 ± 0.06	1.22 ± 0.01	1.22 ± 0.05	0.54 ± 0.17	0.56 ± 0.17	0.54 ± 0.15
MCP	1.42 ± 0.09	1.44 ± 0.04	1.50 ± 0.06	0.55 ± 0.15	0.58 ± 0.17	0.63 ± 0.17
ILF LH	1.41 ± 0.17	1.43 ± 0.02	1.43 ± 0.07	0.57 ± 0.20	0.56 ± 0.21	0.59 ± 0.19

ILF RH	1.44 ± 0.17	1.45 ± 0.07	1.45 ± 0.05	0.58 ± 0.21	0.56 ± 0.21	0.59 ± 0.21
SLF LH	1.27 ± 0.01	1.28 ± 0.02	1.30 ± 0.05	0.58 ± 0.26	0.58 ± 0.28	0.60 ± 0.26
SLF RH	1.27 ± 0.02	1.28 ± 0.04	1.28 ± 0.04	0.56 ± 0.25	0.54 ± 0.22	0.58 ± 0.28
IFO LH	1.36 ± 0.07	1.33 ± 0.04	1.35 ± 0.04	0.55 ± 0.17	0.55 ± 0.17	0.57 ± 0.16
IFO RH	1.36 ± 0.05	1.35 ± 0.05	1.41 ± 0.06	0.55 ± 0.18	0.55 ± 0.18	0.56 ± 0.18
UNC LH	1.32 ± 0.11	1.31 ± 0.05	1.35 ± 0.05	0.61 ± 0.16	0.61 ± 0.17	0.61 ± 0.16
UNC RH	1.31 ± 0.01	1.31 ± 0.04	1.32 ± 0.02	0.60 ± 0.15	0.59 ± 0.15	0.61 ± 0.13
CST	1.42 ± 0.03	1.43 ± 0.03	1.46 ± 0.04	0.50 ± 0.15	0.52 ± 0.17	0.55 ± 0.15

CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Table 13

Mean ± SD Parallel ($\lambda_{\parallel}$) and Perpendicular ($\lambda_{\perp}$) Eigenvalue Measurements for CP Group

Tract	$\lambda_{\parallel}$ (mean ± SD) ($10^{-3}mm^2/s$)			$\lambda_{\perp}$ (mean ± SD) ($10^{-3}mm^2/s$)		
	Pre	Post	Follow-up	Pre	Post	Follow-up
CC	1.63 ± 0.09	1.62 ± 0.06	1.57 ± 0.05	0.65 ± 0.18	0.62 ± 0.17	0.60 ± 0.16
CG	1.38 ± 0.03	1.34 ± 0.07	1.32 ± 0.03	0.65 ± 0.19	0.63 ± 0.19	0.62 ± 0.19
PTR LH	1.44 ± 0.10	1.50 ± 0.11	1.44 ± 0.19	0.67 ± 0.20	0.66 ± 0.19	0.63 ± 0.21
PTR RH	1.51 ± 0.12	1.46 ± 0.16	1.46 ± 0.06	0.68 ± 0.21	0.61 ± 0.16	0.57 ± 0.18
ATR LH	1.33 ± 0.05	1.28 ± 0.10	1.30 ± 0.05	0.62 ± 0.19	0.59 ± 0.17	0.57 ± 0.16
ATR RH	1.11 ± 0.46	1.25 ± 0.09	1.25 ± 0.04	0.63 ± 0.20	0.60 ± 0.16	0.57 ± 0.15
MCP	1.45 ± 0.02	1.43 ± 0.06	1.05 ± 0.01	0.64 ± 0.22	0.62 ± 0.20	0.44 ± 0.18
ILF LH	1.45 ± 0.06	1.43 ± 0.06	1.39 ± 0.07	0.65 ± 0.21	0.62 ± 0.19	0.63 ± 0.21
ILF RH	1.37 ± 0.08	1.41 ± 0.02	1.37 ± 0.08	0.67 ± 0.22	0.62 ± 0.19	0.58 ± 0.18

SLF LH	1.33 ± 0.07	1.27 ± 0.06	1.25 ± 0.07	0.65 ± 0.20	0.62 ± 0.20	0.62 ± 0.20
SLF RH	1.37 ± 0.08	1.24 ± 0.10	1.24 ± 0.10	0.67 ± 0.20	0.62 ± 0.21	0.63 ± 0.22
IFO LH	1.40 ± 0.05	1.38 ± 0.06	1.37 ± 0.04	0.65 ± 0.17	0.59 ± 0.18	0.63 ± 0.18
IFO RH	1.37 ± 0.04	1.33 ± 0.12	1.36 ± 0.06	0.58 ± 0.13	0.60 ± 0.17	0.59 ± 0.17
UNC LH	1.24 ± 0.02	1.34 ± 0.09	1.28 ± 0.03	0.65 ± 0.16	0.67 ± 0.18	0.61 ± 0.16
UNC RH	1.32 ± 0.07	1.29 ± 0.07	1.30 ± 0.03	0.64 ± 0.16	0.65 ± 0.16	0.63 ± 0.17
CST	1.54 ± 0.07	1.52 ± 0.05	1.48 ± 0.04	0.66 ± 0.18	0.60 ± 0.16	0.58 ± 0.17

CC = corpus callosum, CG = cingulum, PTR = posterior thalamic radiation, LH = left hemisphere, RH = right hemisphere, ATR = anterior thalamic radiation, MCP = middle cerebellar peduncle, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus, CST = corticospinal tract.

Volume

The volume measurements derived from the current dataset were extremely variable. Due to the high variability in the data, correlations between FA and volume at each time point did not yield statistically detectable patterns of change by tract or time. However, a visual inspection of the volume data did show that 12

of the 16 tracts in the CP group showed increases in volume across time, whereas none of the tracts in the control group revealed an increase across time.

Hemisphere asymmetry

A lateralisation index ($A = (p_R - p_L) / (p_R + p_L)$) was used in the current study to examine asymmetry in both the CP and control groups, where *p* is a parameter of choice whether FA, volume, or another value of interest. The FA value was chosen for these analyses. The index values can range from -1 to +1, where a negative lateralisation index reflects a larger value in the left hemisphere and a positive lateralisation index reflects a larger value in the right hemisphere.

The lateralisation index was derived for six tracts which were originally analysed as separate tracts in each hemisphere. These tracts included the PTR, ATR, ILF, SLF, IFO, and UNC (see Table 14 and 15). The CC, CG, MCP, and CST were examined as interhemispheric tracts only and could not be submitted to the lateralisation index measure. There was no identifiable visual pattern in the control group lateralisation index values for these six tracts across time. The CP group showed a change in the SLF, IFO, and UNC from a larger left hemisphere index value to a larger right hemisphere index value from time 1 to time 2. The PTR index value was larger in the left hemisphere across time, and the ATR index value was larger in the right hemisphere across time. These patterns were subtle and not tested statistically.

Table14

Lateralisation Index Results for Control Group

Tract	T1	T2	T3
PTR	0.014	-0.010	0.004
ATR	-0.008	0.006	0.013
ILF	0.001	0.001	-0.007
SLF	-0.007	-0.006	-0.014
IFO	-0.003	-0.006	-0.024
UNC	-0.001	-0.009	0.009

Note. Results range from -1 to +1, where -1 represents a larger value in left hemisphere and +1 a larger value in right hemisphere. PTR = posterior thalamic radiation, ATR = anterior thalamic radiation, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus.

Table 15

Lateralisation Index Results for CP Group

Tract	T1	T2	T3
PTR	-0.011	-0.012	-0.038
ATR	0.019	0.017	0.018
ILF	0.038	0.009	-0.024
SLF	-0.002	0.010	0.006
IFO	-0.016	0.026	-0.026
UNC	-0.054	0.009	0.024

Note. Results range from -1 to +1, where -1 represents a larger value in left hemisphere and +1 a larger value in right hemisphere. PTR = posterior thalamic radiation, ATR = anterior thalamic radiation, ILF = inferior longitudinal fasciculus,

SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus.

Next, comparisons between the FA values for left and right hemispheres in each group were performed using a Wilcoxon signed ranks test for two related samples for both the control and the CP groups. The control group showed a significant difference for FA between left and right hemispheres only for the PTR at time 1, $Z = 1.826$, $p < 0.05$, 1-tailed. The CP group showed significant differences in FA between the two hemispheres for ATR, ILF, IFO, and UNC (see Table 16). The PTR and SLF were the only two tracts that did not show significant differences for FA at any time point between hemispheres in the CP group.

Table 16

Hemisphere Asymmetry Comparisons of FA for CP and Control groups Using Wilcoxon Signed Ranks Test

	Control Group						CP Group					
Tract	T1		T2		T3		T1		T2		T3	
	Z	sig	Z	sig	Z	sig	Z	sig	Z	sig	Z	sig
PTR	1.826	0.068	0.365	0.715	0.000	1.000	0.405	0.686	0.674	0.500	0.674	0.500
ATR	1.461	0.144	0.730	0.465	0.000	1.000	2.023	0.043	1.214	0.225	2.023	0.043
ILF	0.000	1.000	0.365	0.715	0.535	0.593	1.753	0.080	0.944	0.345	2.023	0.043
SLF	1.095	0.273	0.365	0.715	1.604	0.109	0.405	0.686	0.944	0.345	0.135	0.893
IFO	0.365	0.715	0.730	0.465	1.069	0.285	2.023	0.043	0.944	0.345	1.753	0.080
UNC	0.365	0.715	0.365	0.715	1.069	0.285	1.826	0.068	1.753	0.080	1.219	0.223

Note. Significance is 2-tailed. PTR = posterior thalamic radiation, ATR = anterior thalamic radiation, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFO = inferior fronto-occipital tract, UNC = uncinate fasciculus

DISCUSSION

Cerebral palsy is a motor disorder that can affect all, or part, of the speech mechanism. It is considered a nonprogressive disorder; however, people with CP exhibit many features associated with central neuroplasticity beginning from immediately post-insult before or at birth throughout development. Data from limb studies show possible activity-dependent neuroplasticity that can have a potentially large impact on the CP brain (Charles & Gordon, 2006; Martin et al., 2007; Taub & Uwasatte, 2005). The principles of neuroplasticity and motor learning outlined in these limb studies also apply to speech when using LSVT. There are many reports of spreading effects across the entire speech system in the literature examining LSVT effects in the Parkinson population (El Sharkawi et al., 2002; Spielman et al., 2003; Sapir et al., 2003; Sapir et al., 2007). These changes are detectable at all behavioural levels and infer a change in the central nervous system. White matter is largely affected in the brains of CP children, and thus, DTI technology presented the opportunity to detect changes in the central nervous system associated with expected therapeutic changes in this population post-intensive voice treatment.

The purpose of this study was to find evidence of treatment-dependent neuroplasticity as a result of LSVT implemented with children who have SQCP. General findings of this study include a significant difference in the values analysed, specifically FA and MD, for the WM tracts analysed through DTI in the treatment group and not in the control group when examined at follow-up. These findings support the neuroplastic impact of this intensive treatment.

The following discussion will present an interpretation of the results from this study relative to: (a) reliability of the findings; (b) FA, MD, and their component eigenvalues as indicators of central neural change post treatment; and (c) associated potential mechanisms underlying the observed changes post treatment. First, a summary of the measurement fidelity including reliability derived in the current study will be reported. Next, the tract comparisons between the control and CP groups will be examined more closely, followed by a thorough look at how and why each tract may or may not have changed across time in each group. Volume measurements and the hemisphere asymmetry analysis will be examined next, both within the CP group as well as between the CP and control groups. Finally, possible mechanisms for changes observed in this study will be reasoned along with study limitations and future research directions.

Reliability

Previous studies have raised issues about measurement reliability associated with fibre tractography. For example, Ozturk, et al. (2008) suggested that caution be used when analysing tracts such as the internal capsule and centrum semivale because their derived values for these tracts had the largest range of variability of those studied. Consequently, only those tracts with relatively good intra- and inter-rater reliability were selected for analysis in the current study. As well, Nagae et al. (2007) suggested that establishing strict ROI placement could aid in differences related to subjective ROI placement and tract editing. To maximize the stability of ROI placement, a detailed procedure for isolating each tract was used in the current study. These procedures included a step-by-step

process with reference to images presented in a DTI Atlas (Mori et al., 2005). Pfefferbaum et al. (2003) discussed cross-scanner bias versus within-scanner bias in the context of reproducibility of FA and trace values. They found that within-scanner values of FA and trace were highly reproducible whereas a large cross-scanner bias existed for both of these values. In the present study the same scanner was used for every scan, which increased reproducibility of the results. Finally, inter- as well as intra-rater reliability analyses were performed in the current study. The results of these reliability measures were significant and suggested excellent agreement within and between both researchers using the DtiStudio software and extracting tracts from the DTI scans while being blinded to group and scan session.

CP and control group tract comparisons

The comparison of each tract between CP and control groups was performed to establish differences at the onset of the study and to show change between the two groups after treatment. The FA and MD values for both the control and the CP groups at time 1 were consistent with previous reports of these values in a typical population and a population with CP; respectively (Lebel et al., 2008; Trivedi et al., 2008). At the pre-treatment time point, only the right hemisphere IFO and UNC were similar in both FA and MD values between control and CP groups. This large difference in derived FA and MD values for the tracts between the two groups was expected. A summary of all retrieved published DTI studies focusing on periventricular leukomalacia (PVL) CP is provided for comparison in Table 17. As discussed earlier, the CP brain experiences neuroplastic changes

from the initial neurological insult as well as neurological changes due to development that also may be affected by the insult. Interestingly, data from the current study indicated that from immediately post-treatment to 12 weeks follow-up, the number of tracts in the CP group showing a significant difference from the control tracts actually decreased. These between-group comparisons indicated that perhaps a global change in WM in the CP brain occurred following treatment whereas healthy controls exhibited a more stable trajectory over the same period of time.

Table 17

DTI Studies Reporting on the CP Population

Authors (Year of Publication)	Details of Study
Fan, Yu, Quan, Sun, & Guo, (2006)	• Study aim: Investigate MR-DTI and fibre tractography in the assessment of altered major WM tracts in periventricular leukomalacia (PVL) • Number (Age Range in Years) of Subjects: 12 (3 – 10) • Measure Used for Analysis: Visual investigation of WM fibre tracts, FA • Tracts Analysed: CST in brainstem, MCP, medial lemniscus, anterior/posterior limb of internal capsule, arcuate fasciculus, PTR, genu of CC, splenium of CC, corona radiata, CG, SLF • Results: Posterior limb of internal capsule, arcuate fasciculus, PTR, corona radiata, CG, SLF, CC all attenuated in size; posterior limb internal capsule, arcuate fasciculus, PTR, corona radiata, CG, SLF, CC significantly reduced FA
Hoon et al. (2002)	• Study aim: Use DTI to examine central WM pathways • Number (Age Range in Years) of Subjects: 2 (6)

	• Measure Used for Analysis: Visual investigation of WM fibre tracts • Tracts Analysed: Corona radiata, CC, internal capsule, PTR, brainstem CST • Results: Motor impairments in PVL may reflect disruption of sensory connections
Lee, Byun, Jang, Ahn, Moon, & Chang, (2003)	• Study aim: Comparison of DTI and conventional MR imaging in CP • Number (Age Range in Years) of Subjects: 2 (4) • Measure Used for Analysis: Visual investigation of WM fibre tracts, FA • Tracts Analysed: Internal capsule, motor pathways, cerebral peduncles • Results: DTI more efficient at revealing microstructural abnormalities of the brain than conventional MRI
Lee et al. (2005)	• Study aim: Review examining developmental WM CNS anomalies including CP with DTI and fibre tractography • Number (Age Range in Years) of Subjects: Reviewed Hoon et al. (2002); showed figures from 2 subjects (1;8 – 6) • Measure Used for Analysis: Visual investigation of WM fibre tracts • Tracts Analysed: sensory fibres, CST, periventricular fibres, PTR, CC, MCP, medial

	lemniscus, transverse pontine fibres • Results: CP may be due to inhibitory stimuli from the thalamus, thinning of CC, both normal and abnormal CST found, sensory fibres decreased in size
Nagae et al. (2007)	• Study aim: Examine whether DTI is a suitable technique to provide in vivo characterisation of specific WM tract lesion in children with CP associated with PVL • Number (Age Range in Years) of Subjects: 24 (1 – 15) • Measure Used for Analysis: Visual investigation of WM fibre tracts using an ordinal grading system for severity of abnormality • Tracts Analysed: inferior cerebellar peduncles, ascending sensory tract, corticopontine, CST, MCP, superior cerebellar peduncles, anterior comissure, UNC, IFO, decussation of the superior cerebellar peduncles, inferior CG, inferior fornix, cerebral peduncle, ILF, external capsule, anterior limb of internal capsule, SFO, ATR, thalamus, posterior limb of internal capsule, retrolenticular part of internal capsule, PTR, tapetum, CC, superior corona radiata, SLF, superior CG, superior fornix • Results: Marked variability in WM injury pattern in patients with PVL, most frequent

	injury to retrolenticular part of internal capsule, PTR, superior corona radiata, and commissural fibres; DTI is a suitable technique for in vivo assessment of WM lesions in patients with PVL
Nagy et al. (2005)	• Study aim: Examination of adolescents born at term, diagnosed with moderate hypoxic-ischemic encephalopathy (HIE), but had not developed CP using DTI • Number (Age Range in Years) of Subjects: 8 (unknown) • Measure Used for Analysis: FA • Tracts Analysed: unspecified • Results: Posterior limb of internal capsule bilaterally, right hemisphere anterior limb of internal capsule, anterior and posterior CC had decreased FA
Son et al. (2007)	• Study aim: Use DTI with fibre tractography to demonstrate focal lesions of the CST in hemiparetic patients with CP who showed no specific focal lesion on conventional brain MRI • Number (Age Range in Years) of Subjects: 4 (0;9 – 7) • Measure Used for Analysis: FA, ADC, asymmetric anisotropy index (AA), asymmetric

	mean diffusivity index (AD) • Tracts Analysed: CST • Results: All patients showed interrupted fibre tractography at the periventricular WM level (PVWM) compared to the opposite side not detected on conventional MRI and significant AA and AD only at the PVWM level; DTI with fibre tractography may be a useful modality for investigating focal lesions in this group
Thomas et al. (2005)	• Study aim: Determine usefulness of DTI and fibre tractography in delineating the primary and secondary degenerative changes in cerebral WM and deep grey matter in patient with spastic CP due to PVWM injury and to look for any possible reorganisation of the axonal architecture • Number (Age Range in Years) of Subjects: 5 (12 – 16) • Measure Used for Analysis: DTI fibre count, FA, MD • Tracts Analysed: CST, CBT, ATR, superior thalamic radiation, PTR, CG, SLF, MCP, CC • Results: degeneration of various motor and sensory pathways as well as deep grey

	matter structures appears to be important in determining the pathophysiological mechanisms in patients with congenital periventricular WM injury; evidence noted of reorganisation of sensorimotor tracts in the unaffected side of hemiparetic patients
Trivedi et al. (2008)	• Study aim: Examine whether botulinum injection followed by a physiotherapy regimen induces plastic changes in the CST that can be assessed using DTI • Number (Age Range in Years) of Subjects: 8 (3 – 12) • Measure Used for Analysis: FA, MD • Tracts Analysed: CST at various levels • Results: A significant increase in FA was evident in CST at the level of the posterior limb of the internal capsule and PVWM of the temporal lobe; improved clinical motor scores; all suggesting plasticity of the central motor pathway after combined therapy

Control group tract analysis

It was hypothesised that control participants would maintain stable values for FA and MD for all tracts across all three time points. However, the results indicated that FA values for the CC were significantly lower from time 1 to time 3 and from time 2 to time 3. The change in FA for this particular region could be due to neural maturation but this is unlikely for the following reasons. First, no other tracts demonstrated a significant difference through the same time interval of 16 weeks. It is unlikely that only FA values from the CC tract would change in isolation of other tracts studied. Lebel et al. (2008) studied the development of numerous WM tracts as well as deep grey matter and subcortical WM in a group of 202 subjects. Evidence from that study suggested that for children between the ages of approximately 5 and 15 years, FA values associated with the CC may be changing but FA values for other tracts such as the SLF and the IFO also would change. Second, Lebel et al. (2008) showed that by 12 years of age children exhibit a developmental plateau for FA in the region of the CC but a decrease in MD in the same region. The current findings did not indicate a decrease in MD over the 16-week time period. Third, a decrease across time in the perpendicular eigenvalue (the average of $\lambda 1$ and $\lambda 2$) would support an increase in myelination for that tract (Giorgio et al., 2008; Lebel et al., 2008; Snook et al., 2005; Song et al., 2005). An examination of the perpendicular eigenvalue of the CC over the three time points in the current study revealed an increase rather than a decrease in the perpendicular value, which cannot be explained in the developmental context established in previous studies. Taken

together, the FA change noted for the CC in the present control group is likely due to chance rather than reflective of a true developmental effect.

CP group tract analysis

Primary tract of interest

The hypothesis for this study was that DT imaging would detect an increase in the FA values and a decrease in the MD values following treatment indicating changes in WM structure in the brains of children with CP. Interpretation of the findings for the primary tract of interest will be presented first, followed by secondary tracts of interest.

The primary tract of interest in the current study was the CST. It connects the motor regions of the brain to the peripheral motor pathways and continually adjusts to the activity occurring in the sensory and motor cortex, cognitive regions of the brain, and peripheral physical movement. The group of children with CP in the current study exhibited a significant change in FA and MD values (in the predicted direction) between pre-treatment and follow-up for the CST. Martin (2005) suggests changes in the CST may occur further into development than other neural systems. The ostensibly longer developmental trajectory for maturation of the CST may allow for more windows of opportunity to (re)habilitate this pathway through motor learning.

Martin, Friel, Salimi & Chakrabarty (2007) reported their success in using activity-dependent processes to re-establish normal CST connections and limb use in cats after experiencing a neural insult. These investigators linked their findings to possible restoration of CST pathways in disordered systems like those

associated with CP. Their data also support CNS plasticity and related potential for learning new motor skills regardless of age.

The observed decrease in the perpendicular eigenvalue for the CST across the three time points in the current study suggests an increase in myelination or other changes in cellular structures including axonal packing. This finding infers improvement in tract integrity that may be the result of intensive practice, increased motivation, and forced use, which were the primary components of treatment used in the present study.

The significant change in the CST corresponded to changes in behavioural outcomes observed in each subject. For example, a louder, clearer voice with improved vocal quality, better posture, and improved respiratory support were noted in the CP subjects after treatment. The observed behavioural changes were especially significant in conjunction with DTI findings, which strengthen the DTI evidence of central change in the CP group. Additional evidence of global central nervous system change is indicated by observed differences in FA, or MD, or both, in 7 of 15 secondary tracts analyzed before and after treatment.

Secondary tracts of interest

Since the study was exploratory, secondary tracts of interest also were analysed. These tracts were chosen based on their function in the brain and their potential link to treatment effects. In addition, the tracts selected in the current study reflected tracts that are known to be reliably produced and measured using DTI procedures. Tracts such as the reticulospinal tract and the fornix, which would be expected to change due to LSVT in this population, were not included

for analysis because they did not meet the criteria for isolation reliability. The DTI Atlas (Mori et al., 2005) and numerous published reports of specific brainstem tracts, association tracts, and other groups of tracts were considered prior to secondary tract selection (Fan et al., 2006; Mori et al., 2002; Nagae et al., 2007; Stieltjes et al., 2001; Wakana et al., 2004).

To begin, the thalamic radiations, both PTR and ATR, were examined as secondary tracts of interest. These tracts are believed to be involved in emotional, behavioural, cognitive, and motor functions as well as in attention, learning and memory (Barnea-Goraly et al., 2005). From pre-treatment to follow-up there was a significant increase in FA values for the PTR in the right hemisphere and a significant decrease in MD values for both the PTR and ATR of the right hemisphere. These results reflect the changes of each value in the expected direction (e.g., increase in FA and decrease in MD) that are indicative of improvement in tract integrity such as increased myelination (Lebel et al. 2008). The effected change seen in the right hemisphere for the thalamic radiations also supports a study conducted by Liotti et al. (2003). Using positron emission tomography (PET) these investigators found increases in right hemisphere activation post LSVT in a group of people with Parkinson disease. Despite the lack of significant change in either FA or MD values in the left hemisphere for PTR and ATR tracts in the current study, the perpendicular eigenvalue decreased in both the PTR and ATR in both hemispheres. This finding further supports evidence of a positive change in integrity of the thalamic radiations following treatment.

Next, the association tracts were studied for effects of treatment in changing FA and MD values. The association tracts were hypothesised to demonstrate neuroplasticity through changes in intrahemispheric connectivity.

The ILF is believed to play a role in visual memory, which may be linked to the key features of LSVT, including the simple, "Do what I do." instruction as the subject gleans important information from simply watching the therapist's example. The ILF showed significant change of FA and MD values across time only in the right hemisphere, which also supports the increase in right hemisphere activation post LSVT found using PET (Liotti et al. 2003). However, the perpendicular eigenvalue decreased for this tract in both hemispheres across time, representing an interhemispheric change of increased myelination in both right and left hemispheres following treatment.

The SLF is involved in focusing spatial information and regulating motor behaviour, and is integrally tied to the language areas of the brain. This tract showed significant change across time only for the MD value in the left hemisphere. Interestingly, the left hemisphere is where language is thought to be lateralised. In addition, Lebel and Beaulieu (in press) report this tract as lateralised to the left hemisphere and correlate their finding to language test scores. This tract also demonstrated a decrease across time for the perpendicular eigenvalue suggesting increased myelination of this tract following treatment.

The IFO is poorly understood. However, it is believed to play a role in cognition (Taoka et al., 2006) and associative learning. This tract showed a

significant difference across time for FA in the right hemisphere; however, unlike other tracts analysed the IFO did not exhibit a decrease in its perpendicular eigenvalue for this hemisphere. The resulting right hemisphere significance across time further supports right hemisphere activation following LSVT (Liotti et al., 2003).

The UNC also is thought to play a role in cognitive and memory functions (Taoka et al., 2006). In the current study, the FA value for the left hemisphere tract showed a significant change across time. The UNC also showed both increases and decreases in its perpendicular eigenvalue in both hemispheres. The variable change in the UNC over the three time points reflects the effect of the intense voice treatment on this tract. The UNC connects the frontal lobe with the anterior gyri of the temporal lobe reflecting connections between areas of attentional memory and speech and language functions (Niogi et al., 2008). Both attentional memory and speech function may be secondarily affected through the intensive voice treatment applied in the current study. The UNC also is considered part of the paralimbic system, contributing to emotional processing (Fujie et al., 2008). As described in the following paragraph for the CG, the intensive treatment delivered to the CP group resulted in emotional lability, which supports changes observed in the UNC as well.

The CG was chosen as it links the thalamic radiations and the limbic system. The limbic system is an important system to consider in this study as emotional changes have been observed with the Parkinson population post LSVT (Spielman et al., 2003). These same changes in affect also were noted in the CP

group for this study. The children became more animated and demonstrated emotional lability as treatment sessions progressed. The CG showed a significant change of the MD value in this group as expected. As well, the perpendicular eigenvalue decreased across time for this tract further supporting evidence of change through increased myelination. Change observed in this tract potentially links the effects of voice treatment with other neural centres for voice production (Ludlow, 2004; Ludlow, 2005).

Finally, the subjects of this study who exhibited decreased density of the CC were hypothesised to demonstrate treatment-dependent changes in this tract. The CC is integral for interhemispheric communication, motor and sensory integration, and general cognitive function; therefore, it was expected to show changes in DVs post treatment. However, no significant change was revealed across the time points for either FA or MD value. Yet when examining the perpendicular eigenvalue for this tract, a decrease was observed from pre-treatment through to follow-up. Consequently evidence of improved integrity of this tract also is available. An enhanced connection between hemispheres may be occurring since positive changes in FA and MD were seen in many other tracts in the CP group. In addition, the CC is the largest WM structure of the brain so may serve as a primary target for detecting increases in myelin and axonal packing.

In addition to the tracts where FA and MD changes were expected, a control tract was measured throughout the course of the study to provide additional evidence of change due to a therapeutic effect. As reported earlier in this

document, Ungerleider (2002) suggested the cerebellum may be involved functionally when a task is initially learned; however, it is not integral to functioning after that task has been learned. In addition, Fan et al. (2006) found no visual difference of this tract and no significant difference of FA values between a control group and a subject group with CP for the MCP. In compliance with these reports, the MCP did not demonstrate a significant change across time for the CP group. However, it is important to note that a decrease in this tract's perpendicular eigenvalue was revealed. This finding suggests that an underlying effect of treatment did take place to increase myelination of the MCP. In addition, a possible increase in myelination of the control tract in the study provides evidence of treatment-dependent change for the entire brain. The inherent interconnectivity of the brain may have an impact on proximal or distal cortical and subcortical regions that may not be directly affected by the treatment. When further exploring the literature concerning possible functions of the MCP, the role of the cerebellum in relation to cognition, learning, attention, language, and behavioural-affective regulation became more evident (Baillieux, De Smet, Paquier, De Deyn, & Marien, 2008; Lekue et al., 2002). Overall, the central changes observed post-treatment in the CP group were more global than expected.

Interestingly, pairwise comparisons completed for the significant Friedman results revealed that the vast majority of tract changes occurred between pre-treatment and follow-up for the CP group. Changes detected at 12 weeks post intervention could indicate: 1) a longer passage of time was required before

treatment-dependent changes physically occurred in the CP group (e.g., synaptogenesis, cortical map reorganisation); 2) a longer passage of time was required before treatment-dependent changes could be detected with the DTI tractography used in this study; 3) the importance of continued practice to maintain the new skill (see Table 1); or 4) a combination of all three. Based on the data from controls, changes due to development are unlikely in the treated group with CP.

Volume

Volume measurements in both the control and CP groups were highly variable so no statistical analysis was applied. However, a visual analysis of the data revealed an increase in volume for 75% of the CP tracts and none of the control tracts across the three time points. The number of CP tracts showing a trend for increased volume may yield additional evidence for treatment-dependent change. An increase in volume suggests that a change is occurring for these tracts in the following manner: 1) the treatment-dependent increase in FA for a particular tract now meets the pre-determined threshold so it can be tracked; 2) the increase in FA for the particular tract of interest now exceeds that of a crossing tract, consequently the crossing tract is ignored instead of the tract of interest; or 3) the treatment-dependent changes affected the integrity of cellular structures surrounding an obstructive lesion that now has less impact on the tract of interest. Caution should be used when interpreting the subtle trend observed in the volumetric data because of its significant variability.

Hemisphere asymmetry

Asymmetry analyses were completed to identify differences between hemispheres in the CP brains and then compare these differences to asymmetry profiles found in the control brains. Six tracts in this study were isolated separately in each hemisphere for each group: PTR, ATR, ILF, SLF, IFO, and UNC. A lateralisation index was calculated for each of these tracts and time points. The lateralisation index derived from controls did not change in any systematic way from one time point to the next. However, indices from the CP group indicated a slight shift from the left to right hemisphere in the SLF, IFO, and UNC immediately following treatment. This trend is commensurate with other findings indicating functional activation of the right hemisphere immediately following LSVT in people with Parkinson disease (Liotti et al., 2003).

Next, Wilcoxon signed ranks tests were performed to statistically compare hemispheric differences in each group. These results support the qualitative findings showing a larger asymmetry in the CP brains than in the control brains. Interestingly the PTR was the only asymmetrical tract in the control brain but one of two that did not show a significant difference between hemispheres in the CP brain. This tract has been reported as severely affected in subjects with CP (Hoon et al., 2002; Fan et al., 2006; Nagae et al., 2007). Consequently, differences associated between the CP and control groups may be attributed to this essential difference in the CP brain.

Possible mechanisms of change

The brain is a large distributed network constantly adjusting to its immediate neural environment and the effects of peripheral change in the body. It is

extremely dynamic and adaptive. Evidence of rapid and long-lasting changes found by using such technology as TMS, fMRI, and PET assumes the changes of neural-map distributions are dependent on improved motor skill and periods of motor learning. Inextricably related to these same changes are cellular modifications such as activity-driven synaptic changes, dendritic sprouting, and neurogenesis. Some of the possible mechanisms for changes reported in DTI variables in the current study will be discussed in more detail. Changes in the WM tracts of children with CP noted in this study were considered treatment-dependent. Therefore, the treatment parameters of LSVT need to be examined in the context of potential neural mechanisms underlying the changes observed.

LSVT incorporates strength, endurance, and precision training through the intensive treatment protocol. First, strength training of all muscles of the speech system including postural, respiratory, laryngeal, and articulatory muscles occurs over the intensive 4-week treatment period. In their review of neuroplasticity evidence from animal models, Adkins, Boychuk, Remple, & Kleim (2006) discussed possible mechanisms of strength training as altered motoneuron excitability and induced synaptogenesis. However these changes were reported to occur in the spinal cord but not in the motor cortex.

Endurance training also occurs in LSVT and can be measured by peripheral changes such as increased respiratory support that results in increased duration of phonation. The main neural outcome associated with increased endurance is angiogenesis in the brain (Adkins et al., 2006). Similar to strength training, endurance training does not directly alter the motor map representations in the

cortex (Adkins et al., 2006). However, exercise is reported to increase neurotrophic factors such as BDNF and to help create a neural environment conducive to neural plasticity (Adkins et al., 2006; Kleim, Jones, Schallert, 2003). It is also hypothesised that endurance training helps activate dormant neuroplasticity mechanisms (Kleim et al., 2003). These mechanisms may include the process of unmasking that strengthens synapses from secondary connections (Bach-y-Rita, 1992; Hallett, 2005) or dendritic arborisation from surviving cells leading to new synapses and receptor development (Bach-y-Rita, 1992; Schallert, Leasure, & Kolb, 2000). These neuroplastic processes, all induced through endurance training, may be the advantage required for the central neurological changes detected with DTI.

Finally, precision training occurs with LSVT as revealed through increased articulatory precision and improved coordination of respiratory and laryngeal subsystems. This type of training is reported to induce synaptogenesis, synaptic potentiation, and reorganisation of the motor map in the cortex (Adkins et al., 2006). For example, teaching rats to perform skilled tasks such as reaching through a narrow opening to grasp small food pellets or execute acrobatic movements can drive use-dependent dendritic plasticity and synaptogenesis (Kleim et al., 2003). In addition, motor activity and skilled motor learning may encourage neuroplastic molecular events in the peri-injury area, as well as in remote brain regions (Kleim et al., 2003). In a study by Stroemer et al. (1995), the protein GAP-43, useful in the identification of axonal sprouting, increased in expression quickly post injury whereas the protein synaptophysin, an indicator of

number of synaptic terminals, increased in later stages of recovery which included use-dependent function. These data supported the occurrence of neurogenesis followed by synaptogenesis ipsilateral and contralateral to the infarct, which correlated with behavioural recovery from the infarct in the study (Stroemer et al., 1995). Horner & Gage (2000) reviewed mechanisms responsible for axonal growth and regeneration of the damaged central nervous system at the cellular level. They discussed the importance of progenitor cells, capable of proliferation and differentiation into mature myelinating oligodendrocytes, and neurotrophic molecules, which contribute to cell survival and axon growth-promoting effects after injury (Horner & Gage, 2000). However, they also provided alternative explanations of regeneration including axonal sprouting of non-injured axons, activation of redundant pathways and alterations in the receptor number or excitability of surviving neurons or glia (Horner & Gage, 2000). They listed several growth-promoting molecules having a developmental role in axon guidance, fasciculation, synapse formation and regeneration, and activity dependent plasticity (see Horner & Gage, 2000, for a complete list of molecules involved in axon growth and guidance). Keyvani & Schallert (2002) also presented a list of molecules with a recognised role in post-lesional and experience-induced plasticity including immediate early genes (IEGs)/transcription factors, kinase network molecules, neurotransmitter receptors, growth factors/receptors, neuronal growth-associated molecules, cytoskeletal molecules, synapse-related molecules, and adhesion molecules (refer to Keyvani & Schallert, 2002, for a complete list). These researchers

described displacement and expansion of cortical maps, recruitment of parallel and subcomponent pathways, altered efficacy of synaptic activity, and neosynaptogenesis as part of the brain's adaptive strategies (Keyvani & Schallert, 2002).

Important to note is the interconnectedness of the brain. Any change occurring in one area of the brain has the potential for change structurally and/or functionally in another area. Adkins et al. (2006) termed this event as "reactive plasticity." Changes in the anatomy of the brain reflect changes in the neural connections which further relates to behavioural changes. For example, all pyramidal neurons connected by the CST axons have a large distribution of dendrites, which communicate with other neurons and other axons. This expansive interconnected communication potentially increases the effect of stimulation in one place of the brain to many others (Sanes & Donoghue, 2000).

It is possible that changes detected by DTI methods following intensive voice treatment reflect one or more of the suggested neuroplasticity mechanisms including synaptogenesis, angeogenesis, protein synthesis, synaptic potentiation, axonal sprouting of non-injured axons, and activation of redundant pathways as indicated in comparable activity-dependent studies of neuroplasticity in animals. This study found a significant difference in both FA and MD values across time for the CP group in the CST, which was the primary tract of interest. Significant changes also were found in 7 of the 15 secondary tracts of interest in the CP group following treatment. Further analyses of the component eigenvalues for CP tracts suggested global changes in the central nervous system following

treatment. These changes were not mirrored in the control group, suggesting that any changes detected in the CP group were due to the intensive treatment employed in the study. In conclusion, this study revealed DTI as a sensitive measure for detecting change after a significant perturbation to the CP system.

Limitations

The limitations concerning DTI-based fibre tractography need to be addressed. First, the imaging resolution of DTI is limited typically to 1 – 5 mm. This low resolution only allows the study of large bundles of axons with the same orientation (Huang et al., 2004; Jiang et al., 2006; Thomas et al., 2005). Second, DTI reflects the averaged water diffusion within a voxel. Consequently, DTI results are biased by the dominant axonal component (Huang et al., 2004; Jiang et al., 2006; Thomas et al., 2005; Wakana et al., 2004). This issue is relevant also when dominant fibre bundles "cross" or "kiss" a fibre bundle with a lower FA value. In these cases, the dominant tract will be represented at the cost of ignoring the less dominant resulting in either a misrepresentation or an abrupt stop of the less dominant tract (Holodny et al., 2005). Third, the ideal way to have completed the analyses would be to co-register the images at time 2 and time 3 to the image at time1, and place the ROIs for each tract on the time 1 image only thereby decreasing variability between ROI placements across timepoints. Fourth, the ROI protocol used for control group may not have been appropriate for use in the CP group. Finally, the reconstruction results are sensitive to noise, partial volume effects, and image artefacts (Huang et al., 2004; Thomas et al., 2005). Generally speaking, even with these detection and measurement

limitations, similar results can be reported across studies, across different analysis software, and across individuals conducting measurement procedures. The use of DTI is not only becoming a popular research tool but also shows potential as a clinical tool (Mori et al. 2002; Catani et al. 2002).

The design of the current study also had inherent limitations. First, this study consisted of a small sample size, which decreased the power of statistical analysis; however, the majority of DTI studies involving the CP population report results on small subject group sizes. Increases in statistical power were realised in the study's longitudinal feature and the ability to produce group averages across repeated measures. Second, there were only two time points (4 weeks apart) between the two CP-control scans instead of a third time point representing follow up at 12 weeks. However due to time, subject compliance, and cost restraints, these two scans for the CP-control group were expected to appropriately demonstrate any changes that may be related to development. Third, whereas treatment research such as that conducted in the present study is extremely time-intensive, the inclusion of another comparison group receiving an alternative treatment with the same intensity may have helped substantiate the current findings. Fourth, practice may also have played a role in the changes detected from immediately post-treatment to follow-up in the CP group. Each subject in the CP group had variable practice between these two time points in the study due to differences in compliance with maintenance tasks (see Table 1). As previously discussed, practice is recognised as an important principle of neuroplasticity. Additionally, practice is required to maintain skills attained

through LSVT as reported in studies with patients with Parkinson disease (Ramig et al., 2001). Fifth, asymmetry between the left and right hemispheres in the subjects with SQCP may have depended on what hemisphere was initially injured. Allowing this variable, i.e., injured hemisphere, to be included in the asymmetry analyses would be advantageous to understanding the effects of lesions on WM tract asymmetry in these brains. Sixth, the volume of grey matter, WM, and cerebrospinal fluid on the 3D MPRAGE scans could have been measured to further examine differences between the subjects with SQCP and the controls. Seventh, the CST and the CG could have been separated as right and left hemispheric tracts in the analysis to more accurately depict the structure of these tracts in the brain. Further, the CST could have been analysed at different levels inferiorly from the brainstem to its superior fibres. Breaking up the CST this way may have offered a more accurate depiction of change within the CP group as well as a greater understanding of the tract's differences between the CP and the control group. Finally, corroborating evidence from fMRI during phonation tasks would have been ideal.

Future directions

One analysis that was not performed in the current study was the use of the DTI AxialFlair scan to examine treatment-dependent change around periventricular lesions in this group. An examination of structural change surrounding a lesion is possible with this scan, which compensates for CSF signal contamination and hence increases ventricular clarity and enhances

analysis of the areas surrounding lesion sites. Studying the structural effects of treatment-dependent change on a chronic lesion also has not been investigated.

Other neuroimaging techniques could be another step to take in analyses of this nature. For example, TMS could be used to map the motor areas of the brains of children with CP to observe how treatment may or may not alter cortical mapping. One study used TMS with a group of subjects with a median age of 14 with bilateral lesions that had CP and found evidence of neural plasticity (Maegaki et al 1999). This group offered possible explanations of the plasticity they found: 1) a more extensive and enhanced connections system of the ipsilateral projections of the CST and cortico-reticulospinal tracts; 2) an abnormal branching of the contralateral CST axons; and 3) a persistence of transient fetal connections that typically regress in the developing brain (Maegaki et al 1999). Further to this study, response of the CP brain in a longitudinal study pre- to post-treatment could be performed using TMS as an appropriate tool of analysis.

As part of the efficacy studies for LSVT, an examination of this treatment's effects with different populations could be employed. For example, children with Down syndrome are currently being studied for detectable physiological changes due to LSVT. These types of studies will expand understanding and improve the efficacy and effectiveness of this treatment. Examining changes in WM with DTI in these different populations would also increase understanding of UMN WM changes related to intensive voice treatment.

Further research in the areas of CP and DTI, specifically examining central change due to treatment, is required. Great variability existed on various levels

between the eight DTI studies on CP reviewed in the current literature (Fan et al., 2006; Hoon et al., 2002; Lee, Byun, Jang, Ahn, Moon, & Chang, 2003; Nagae et al., 2007; Nagy et al., 2005; Son et al., 2007; Thomas et al., 2005; Trivedi et al., 2008). For example, the regions of interest in each study varied from whole-brain analyses (Hoon et al., 2002; Nagy et al., 2005) to isolation of as few as one WM tract (Trivedi et al., 2008) and as many as 26 WM tracts (Nagae et al., 2007). As well, the values of interest in each study varied. Only three of the eight studies reported both FA and MD values, three reported only FA, and two discussed only visual findings. In addition, only one study was longitudinal (Trivedi et al., 2008). Finally, the number of subjects in each study greatly varied. The average number of subjects in the eight articles reviewed was 8, the median was 6.5, and the range was 2 to 24. There is also significant variability within this population, which has been considered the reason for the amount of inconsistency in treatment outcomes studied. Consequently, there exists a need for further studies on intensive interventions with this population.

As stated earlier, using DTI analyses may provide further understanding of the pathogenesis of CP and could lead to improvements in clinical classification and treatment for children with CP and other neurologic disorders by providing specific treatment options based on the pattern of WM injury and response to treatment. The analyses in the current study do show treatment-dependent change detectable in the WM of the CP brain. However, further findings could result from future studies scanning across a greater length of time and on a larger number of individuals. The importance of small feasibility studies especially

those using neuroimaging such as the one used in the current study can lead to larger, long-term control studies and stronger hypotheses that allow for a continuation of exploration and translation into practice (Ludlow et al. 2008).

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APPENDICES

Appendix A

MRI screening forms

Capital Health

Patient History and MRI Screening (Female)

CARITAS HEALTH GROUP

Name: _____ Hospital #: _____

The following items may interfere with your Magnetic Resonance Imaging examination, and some can be potentially hazardous. **Please indicate if you have the following:**

Section 1

Yes	No	
☐	☐	Cardiac Pacemaker / Automatic Defibrillator
☐	☐	Aneurysm Clip(s)
☐	☐	Implanted Insulin Pump
☐	☐	Implanted Drug Infusion Device
☐	☐	Bone Growth or Bio Stimulator
☐	☐	Neurostimulator
☐	☐	Epicardial Leads
☐	☐	Cochlear Implant
☐	☐	Intra-vascular Coils
☐	☐	Swan-Ganz Catheter

Section 2

Yes	No	
☐	☐	Stents
☐	☐	Any type of surgical clip or staple(s)
☐	☐	Heart Valve Prosthesis
☐	☐	Vena Cava Filter
☐	☐	Middle Ear Implant
☐	☐	Eye Prosthesis
☐	☐	Shrapnel or Bullet
☐	☐	Magnetically operated devices
☐	☐	Wire Sutures
☐	☐	Silver impregnated dressing (Acticoat, Actisorb Plus, Aquacel)

Section 3

Yes	No	
☐	☐	Diaphragm or IUD
☐	☐	Intraventricular Shunt
☐	☐	Intracranial Pressure Monitor
☐	☐	Wire Mesh
☐	☐	Artificial Limb or Joint
☐	☐	Any orthopedic item(s) (i.e. pins, rods, screws, nails, clips, plates, wire, etc.)
☐	☐	Dentures or any type of removable dental item
☐	☐	Hearing Aid
☐	☐	Tattoos
☐	☐	Body Piercings
☐	☐	Transdermal Patches (i.e. nicotine, nitroglycerine, etc.)

Have you ever had any surgical procedure or operation? ☐ Yes ☐ No

Type: _____ Year: _____

Type: _____ Year: _____

Type: _____ Year: _____

Have you **EVER** had any metal fragments in your eyes, or had an injury to your eyes with metal? ☐ Yes ☐ No

Are you pregnant or do you suspect that you are pregnant? ☐ Yes ☐ No LMP: _____

Patient Weight: _____ lb / kg Patient Height: _____ in / cm

I have answered the above questions to the best of my ability.
The MRI examination has been explained to me and I have had my questions answered to my satisfaction.

_____ _____

Signature of Patient or Guardian Date

_____

Witness / Technologist

CH-0185 Jun 2005

Appendix B

Consent and assent forms

PARENT CONSENT FORM

Title of Project: *Intensive Voice Treatment for Children with Cerebral Palsy: Sensorimotor Neuroplasticity and Functional Outcomes*

Principal Investigator: ***Carol A. Boliek, PhD*** **Phone Number:** ***492-0841***
Co-Investigators: *Jonathan Norton, PhD and Christian Beaulieu, PhD*

	Yes	No
Do you understand that your child has been asked to participate in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw your child from the study at any time, without having to give a reason and without affecting your child's future medical care or therapeutic treatment?	☐	☐
Do you understand who will have access to your child's records, including personally identifiable health information?	☐	☐
Do you understand that each of the sessions will be videotaped for later data analyses?	☐	☐

Who explained this study to you?

_____

Child's Name _____

I agree for my child to take part in this study: YES ☐ NO ☐

Signature of Parent or Guardian _____ Date

_____

(Printed Name) _____

Signature of Witness _____ Date

_____

Signature of Investigator or Designee _____ Date

_____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Assent Form

Project Title:

Intensive Voice Treatment for Children with Cerebral Palsy: Sensorimotor Neuroplasticity and Functional Outcomes

Project Investigators:

Carol A. Boliek, PhD
Jonathan Norton, PhD
Christian Beaulieu, PhD

Why have you been asked to do this?

You have been asked to help in a study because you either have Cerebral Palsy or you are being matched to a child who has Cerebral Palsy. We want to see how your brain, muscles, and lungs work when you are speaking.

What will I have to do?

First we are going to take pictures of your brain using a big magnet called an MRI. You will lie down in a small space and the MRI will take pictures. This will not hurt, but you must lie still. It will take about 20 to 25 minutes. Sometimes the machine is loud, but you can wear headphones while the machine is taking pictures.

Next, we are going to take pictures of how your rib cage, back and tummy muscles work while you are sitting and talking. We will place 10 sticky metal dots on your chest and back. These dots will measure how well your muscles are working. When these dots are on your body, we will get you to sit quietly, talk in a normal voice, and talk in a louder voice. We also will use a video camera to take pictures of you while you are speaking and a microphone which will record what you say.

At the same time we are looking at how your muscles work, we are also going to see how you are breathing. We will place a soft band around your rib cage and another band around your tummy. These will be worn under your shirt and will help us see how much air you use when you are talking. For a very short time, we will also get you to breathe through a small face mask for about 10 breaths.

If you have Cerebral Palsy, you will be asked to work with a speech-language pathologist Four days per week for four weeks. You will work on your voice and your speech and you will play many different speech games and activities. After you are done with the speech therapy, you will be asked to come back to the University of Alberta to take pictures of your brain, muscles, breathing, and also to see how well you are speaking.

How long will this take?

The total time for each University Visit will be about 2 to 3 hours including the time it takes to get the pictures of your brain. We will ask you to come to the University a total of 6 times, but only 3 times to the MRI machine.

Will it help?

By helping us out in this study we will learn about how to help children with Cerebral Palsy have better speech. This is important because then they can do better a school and make friends.

Will it hurt?

Nothing we are asking you to do will hurt. The MRI test will be the hardest because you will need to be still on your back for about 20 to 25 minutes and the noise will sound loud. Everything else is easy and will not be hard for you to do.

Can you quit?

You don't have to take part in the study at all and you can quit at any time. If you want to quit you should tell the researchers or your parents.

Who will know?

No one except your parents and the researchers will know you are taking part in the study unless you want to tell them. Your name and your information will not be seen by anyone except the researchers during the study.

Your signature:

We would like you to sign this form to show that you agree to take part. Your mom or dad will be asked to sign another form agreeing to for you to take part in the study.

Do you have any questions?

You can ask your mom or dad about anything you don't understand. You can also ask any of the researchers at any time during the study.

I agree to take part in the study.

_____ _____

Signature of Research Participant Date

Appendix C

Ethics approval

OCT-06-2006 02:40PM FROM-U OF A HEALTH RESEARCH ETHICS BOARD +7804927808 T-601 P.002/002 F-534

Health Research Ethics Board

213 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
p.780.492.0302 (Health Panel)
p.780.492.0459
p.780.492.0839
f.780.492.7808

ETHICS APPROVAL FORM

Date of HREB Meeting: **August 25, 2006**

Name(s) of Principal Investigator(s): **Dr. Carol Boliek**

Department: **Speech Pathology and Audiology**

Title: **Intensive voice treatment for children with cerebral palsy: sensorimotor neuroplasticity and functional outcomes**

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the subject information material and consent form.

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the REB Panel.

Specific Comments:

OCT - 6 2006

D.W. Morrish, M.D., PhD
Chairman of Health Research Ethics Board
Biomedical Panel

Date of approval release

This approval is valid for one year

Issue #6453

UNIVERSITY OF ALBERTA

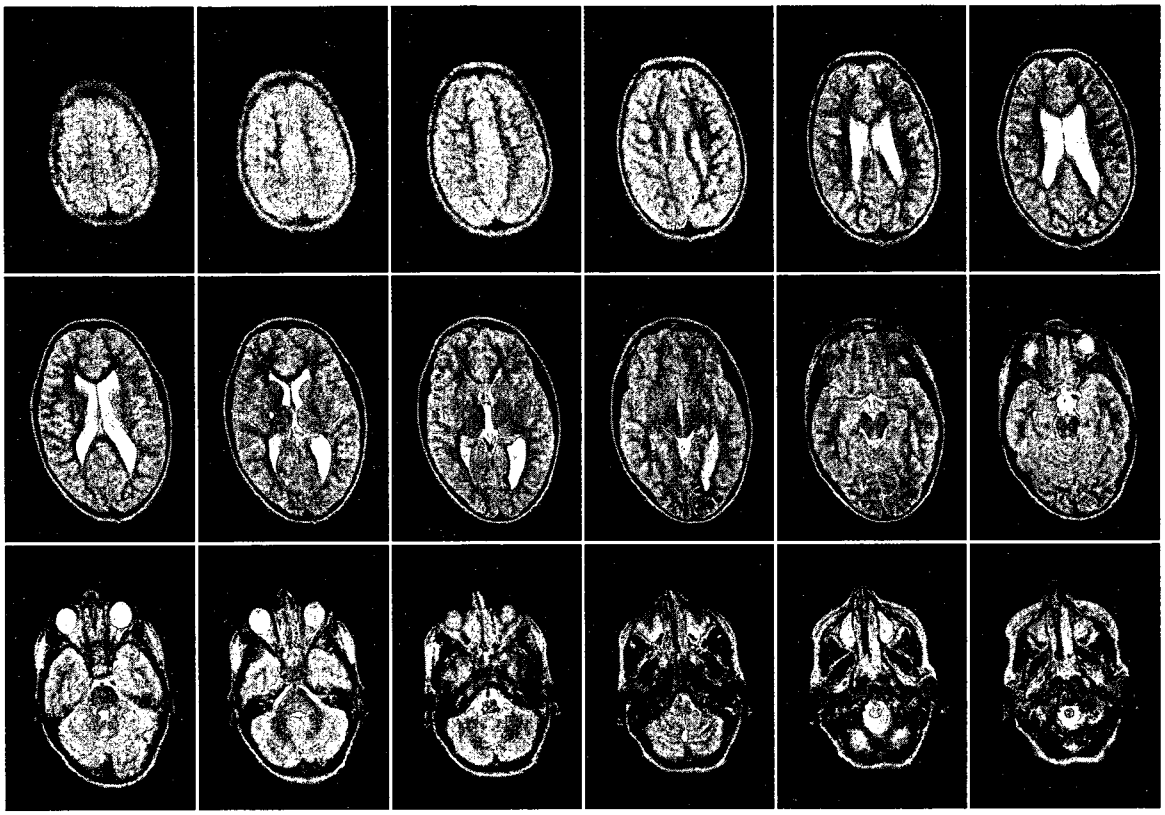
Capital Health
Edmonton and area

CARITAS HEALTH GROUP

Appendix D

T2 scans

Subject F0802E



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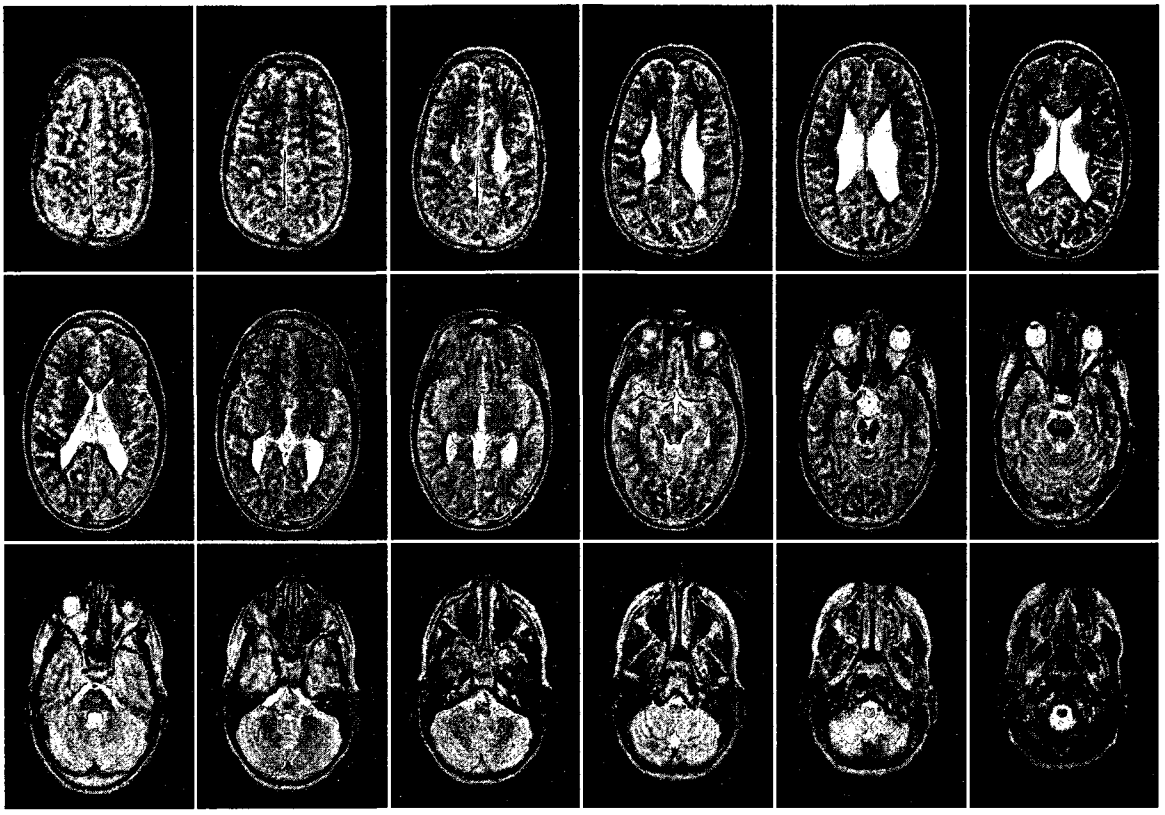

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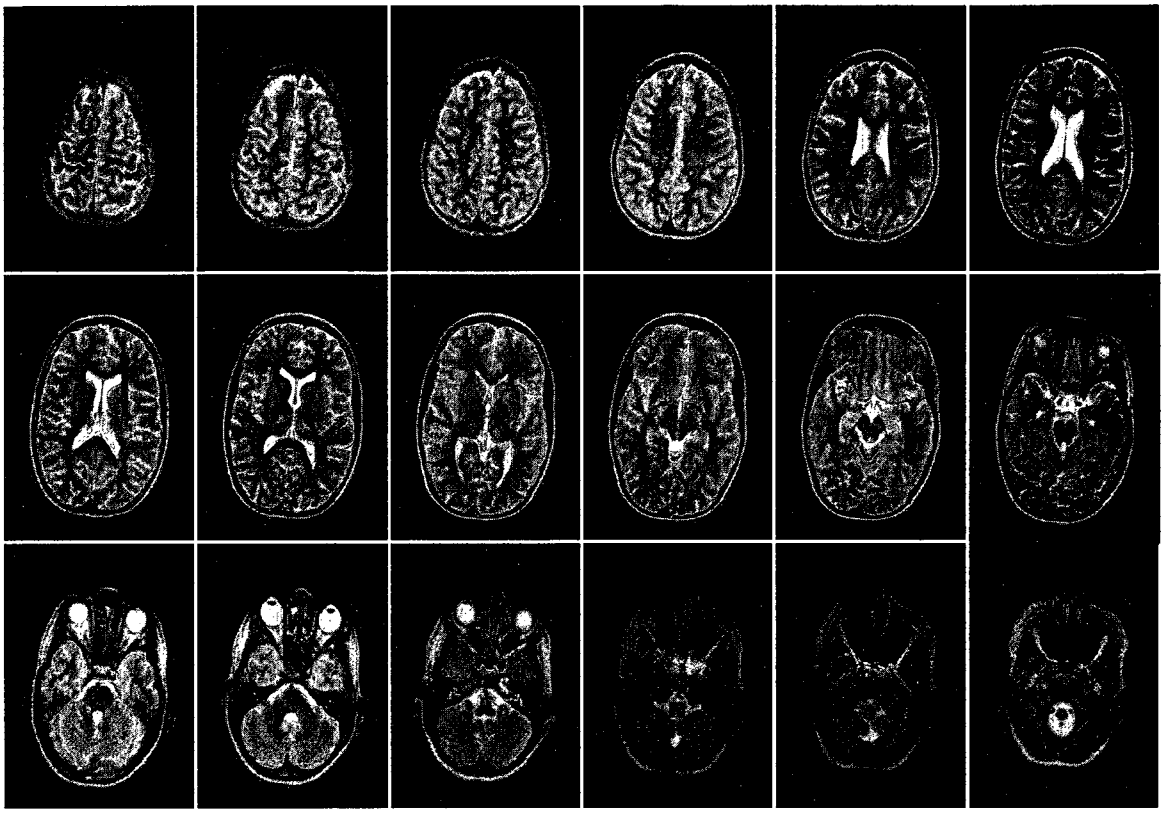

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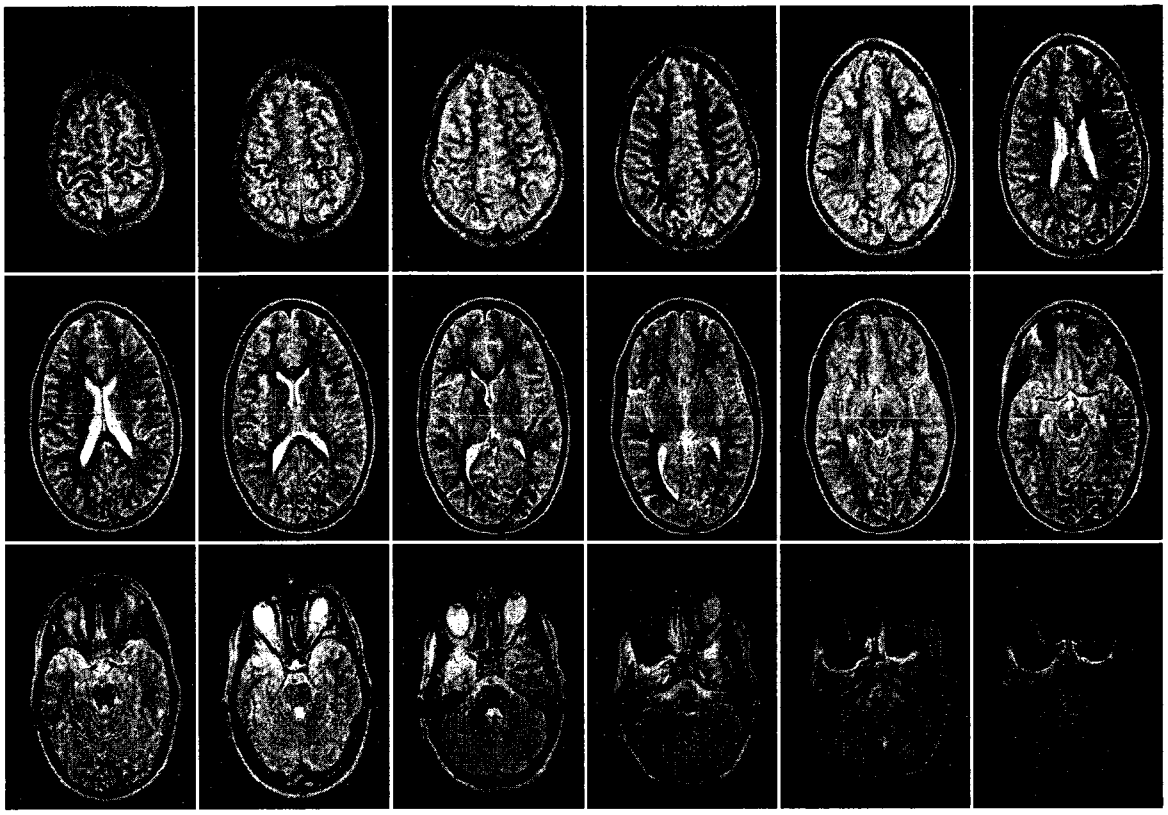

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