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Resting State Functional Magnetic Resonance and Diffusion Tensor Imaging of Hemiplegic Cerebral Palsy Patients Treated with Constraint-Induced Movement Therapy: Predictors and Clinically Correlated Evidence of Neuroplasticity

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Medical Biophysics

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RESTING STATE FUNCTIONAL MAGNETIC RESONANCE AND DIFFUSION
TENSOR IMAGING OF HEMIPLEGIC CEREBRAL PALSY PATIENTS
TREATED WITH CONSTRAINT-INDUCED MOVEMENT THERAPY:
PREDICTORS AND CLINICALLY CORRELATED EVIDENCE OF
NEUROPLASTICITY

(Thesis format: Monograph)

by

Kathryn Manning

Graduate Program in Medical Biophysics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
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London, Ontario, Canada

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Abstract

Hemiplegic cerebral palsy is characterized by unilateral upper limb impairment and patients often compensate by performing most tasks with their unaffected arm. Constraint-induced movement therapy (CIMT) directly combats this learned non-use by casting the unaffected arm and forcing the patient to repetitively practice skills with the hemiplegic limb. Subjects with hemiplegic cerebral palsy were recruited from Holland Bloorview Kids Rehabilitation Hospital, Thames Valley Children's Centre and McMaster Children's Hospital. MRI acquisitions and clinical evaluations were collected at baseline, 1 and 6-months later. The case group participated in a CIMT camp after baseline evaluations and was compared to an untreated control group. Resting state functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) acquisitions quantify global network organization and neural integrity, respectively, and found alterations in multiple resting state network connectivity patterns and significantly different fractional anisotropy and mean diffusivity in the affected corticospinal tract. Asymmetric baseline sensorimotor network organization was predictive of a positive and continuous functional response to CIMT. Clinically correlated network reorganization provides further evidence of neuroplastic mechanisms related to CIMT.

Keywords

Functional magnetic resonance imaging, resting state, diffusion tensor imaging, hemiplegic cerebral palsy, constraint-induced movement therapy, independent component analysis, network, connectivity, pediatrics, neuroplasticity

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1 Introduction

1.1 Cerebral Palsy

1.1.1 Introduction

Cerebral palsy (CP) consists of a group of neurological disorders of the development of movement and posture caused by non-progressive damage to the brain prenatally or in early life (Rosenbaum, et al. 2006). Injury to motor cortical areas and their pathways may inhibit both motor function and development, and may also be associated with the disruption of healthy sensation, cognition, communication and behavior, as well as epilepsy (Rosenbaum, et al. 2006; Carr 1996; Thickbroom, et al. 2001; Hoon, et al., 2009). Brain injuries can occur as a result of abnormal brain development, asphyxia, traumatic brain injury, and complications during the delivery process, or environmental risk factors such as exposures to infections (Kulak, et al. 2006). Nearly half of all cerebral palsy patients were born prematurely and many causes are associated with premature birth complications (Hoon, et al. 2009). CP occurs in about two of every thousand live births, and with improving neonatal care and premature birth survival rates these numbers may increase (Dong, et al. 2012; Numata, et al. 2012; Hoare, et al. 2009).

1.1.2 Hemiplegic CP

Hemiplegic cerebral palsy is the most common subtype of CP and is characterized by unilateral upper extremity motor impairment, though patients often experience other symptoms (Kulak, et al. 2006; Dong, et al. 2012; Winckel, et al. 2013). A brain malformation or periventricular brain lesion in the early stages of prenatal development, or an infarction near the middle cerebral artery can result in neuronal damage to both white and gray matter, including thalamocortical pathways, cortical and subcortical areas (Kuhnke, et al. 2008; Staudt, Gerloff, et al. 2004; Thickbroom, et al. 2001). Arterial ischemic strokes and periventricular venous infarction are the most frequent type of injury in hemiplegic CP patients (Odding, Roebroek and Stam 2006). Healthy development of the infant brain is hindered as the migration of neurons and projections are directly affected by this white matter injury (Odding, Roebroek and Stam 2006). Cortical and/or subcortical lesions are found near motor areas in the hemisphere contralateral to the affected upper extremity, often resulting in weak grasping ability, trouble performing intricate movements, spasticity, and inhibited efficiency (Charles and Gordon 2005, Boyd, Morris and Graham 2001).

Children with hemiplegic CP often compensate for their weak arm by choosing to perform most tasks with their unaffected arm (You, et al. 2005, Hoare, et al. 2009). This can lead to developmental disregard or learned non-use where the affected limb is further inhibited from healthy development (Charles and Gordon 2005; Hoare, et al. 2009; Taub, Ramey, et al. 2004). Many children with hemiplegic CP also exhibit mirror movements where movement of the intended arm is mirrored by the opposite hand (Briellmann, et al.

2002). This is normal in healthy early development, but is significantly prolonged and more severe in children with hemiplegic CP. Both of these common developmental characteristics can make performing bimanual activities even more difficult and frustrating. Individuals with hemiplegic CP often have additional impairments depending on the extent and location of damage, including cognitive, speech, visual, and digestive deficiencies (Odding, Roebroek and Stam 2006).

1.2 Treatment

1.2.1 Clinical Evaluation

Standard tests and questionnaires are often used to quantify motor function and observe any positive changes due to an applied therapy. The evaluation method used depends on the therapist, the age of the patient, the study requirements (if any), and the focuses for that particular patient. Questionnaires are directed towards the patient (if they are old enough to supply reliable answers), the parent and their observations of the child during every day activities, or the therapist who evaluates the patient through standard task protocols (Adams 2009). There are many standardized tests (Table 1-1) that attempt to evaluate aspects of movement and assess any improvements in those specific areas after rehabilitation. These tests permit reliable quantitative comparisons within a subject, as well as between groups or studies while allowing therapists to isolate tasks that are most difficult for a particular patient and focus therapy in those areas.

Table 1-1: A summary of some common clinical evaluations used to assess symptom severity and recovery after an applied treatment. Each evaluation is sensitive to different aspects of function.

Clinical Evaluation	Description
Assessment of Life Habits Scale (Life-h)	Twelve categories of daily personal and social skills
Assisting Hand Assessment (AHA)	How well the hemiplegic hand is used in collaboration with the unaffected arm in bimanual play recorded and observed by therapist
Canadian Occupational Performance Measure (COPM)	Assesses the patient's ability to perform daily tasks and their satisfaction with their progress, individual goals and weaknesses
Children's Hand-use Experience Questionnaire (CHEQ)	Questions directed to the child or parent about the ability to perform bimanual tasks
Jebesen-Taylor Test of Hand Function (JTTHF)	Unilateral hand function timed while performing common daily activities in the form of 7 subtests
Melbourne Assessment of Unilateral Upper Limb Function (MUUL)	Objectively measures unilateral upper limb function in children
Motor Activity Log (MAL)	Twenty tests that assess quality and amount of use with the hemiplegic arm
Pediatric Evaluation of Disability Inventory	Parent and therapist evaluate functional skills
Quality of Upper Extremity Skills Test (QUEST)	Intricate movements, grasping, reaching, and weight bearing
The Gross Motor Function Measure (GMFM)	Therapist evaluates reliable and standard physical tasks
Wolf Motor Function Test (WMFT)	Upper extremity motor ability, quantitatively evaluated for time, performance, functionality, strength

1.2.2 Review of treatments

Rehabilitation is especially difficult for children with hemiplegic CP due to the early onset of brain injury (Staudt, Gerloff, et al. 2004). Unlike later stroke incidence, these patients never truly experience normal functionality so they adapt and compensate by preferring to use their unaffected limb for most activities, which hinders healthy functional development. The role of the therapist and the chosen treatment is to allow the patient to experience and practice activities with the hemiplegic limb and combat these adapted behaviors, which they have developed throughout their early life (Taub, Ramey, et al. 2004).

There are many different types of treatments that attempt to improve various aspects of upper-limb function in CP patients, reduce spasticity, and balance muscle tone (Hoare, et al. 2009; Boyd, Morris and Graham 2001). Traditional physiotherapy and occupational therapy treatments have been moderately effective in improving function according to standardized functional evaluations, however they don't directly address the issue of developmental disregard (Boyd, Morris and Graham 2001). Different types of neurodevelopment therapy have also elicited some motor improvements, but when combined with casting of the unaffected limb results have shown further progress (Law, et al. 1991). Strength training using varying levels of resistance only improved movement time when compared to a zero resistance control group (McCubbin and Shasby 1985). When implementing this type of training with task-driven activities results may translate into overall functional improvement (Dean and Shepherd 1997). Continuous intrathecal baclofen therapy (CITB) and selective dorsal rhizotomy (SDR)

surgery have been shown to reduce spasticity in some cases, and though studies focusing on lower limb function have seen significant functional improvement, no significant improvement has been found in upper limb function studies (Ramstad, et al. 2010). Another invasive procedure such as soft tissue lengthening is useful for correcting deformities, but only report functional improvement in half of the participants (Van Heest, House and Cariello 1999). Neuromuscular electrical stimulation (NMES) has rendered improvements in bimanual task execution, though further improvements were made with case studies of patients treated with NMES combined with temporary splinting (Carmick 1997). A relatively new treatment tool is the use of botulinum toxin type A injections (BTX-A) in the upper limb, which temporarily provide chemo denervation of overactive muscles to allow training of the weak limb using another type of therapy or training. Bimanual training concentrates on activities that require two hands and does not improve unimanual capacity as much as with constraint, and it has been suggested that combining elements of the two therapies may be optimal (Sakzewski, Ziviani, Fabbott, et al. 2011; Dong et al. 2012). Though these treatments have shown improvement in various areas, combining with casting or splinting improves functional results of CP patients (Boyd, Morris and Graham 2001).

1.2.3 Constraint-induced movement therapy

Constraint-induced movement therapy (CIMT) directly attempts to combat learned non-use by physically restraining the unaffected limb thereby forcing the patient to use the

hemiplegic limb (Taub, Crago, et al. 1994). Initial primate studies introduced CIMT as using restraint and excessive practice with the affected limb (Taub, 1980) to address two mechanisms respectively: (1) overcoming learned non-use and (2) inducing cortical reorganization with forced use and repetition.

CIMT involves restraining the unaffected arm for some period of time, allowing the patient to perform daily tasks in the home with the hemiplegic arm alone as well as training with a therapist in the clinic. The standard CIMT developed by Taub (also known as Taub's therapy) involves therapy for 6 hours a day while wearing a restraint 90% of the time over a two-week period (Taub, Ramey, et al. 2004). The length of treatment can vary from a week to many, and the time spent daily with a therapist can also be adapted depending on the age, severity and patience of the participant. In a stroke patient group with severe motor impairment, a longer three-week protocol was implemented and displayed significant clinical results as measured using WMFT and MAL (Bonifer, Anderson and Arciniegas 2005). In cerebral palsy patients, many modifications have been attempted to accommodate for the age of participants and the potentially frustrating nature of the therapy. Juenger and colleagues implemented an intensive protocol during a 12 day program while wearing a sling and glove 10 hours a day, with 2 hours of individual and group level therapy every day (Juenger, et al. 2007), while a study a few years later employed a more feasible protocol with only 4 hours of treatment on weekdays while still wearing a cast 90% of the time (Cope, et al. 2010). There have also been some promising clinical results when the CIMT protocol was further reduced to adapt for a younger patient group (between 1.5 – 4 years) where participants had to wear a restraint glove for 2 hours a day over a period of 2 months

(Eliasson, et al. 2005). Comparing clinical outcome measures such as motor performance, grasping, reaching (Chen, et al. 2012) or according to AHA scores (Eliasson, et al. 2005) before and after CIMT have shown significant improvements when compared to traditional rehabilitation methods. A recent review by Novak et al. found that constraint-induced movement therapy had the most reported evidence of efficacy compared to all other interventions for children with CP (Novak, McIntyre, et al. 2013)

While many different studies have reported success with this therapy using variations of CIMT protocols and outcome measures, individual results are less homogenous. Although an overall improvement in clinical results was found according to group analysis, individual results were varied (Cope, et al. 2010). Subjects were further categorized into groups according to the severity of their spasticity. This revealed that subjects who had very low or high function before treatment showed little to no improvement, while subjects with a moderate level of spasticity and function improved the most. Individuals with lower MUUL scores at baseline showed the most unilateral improvement after training, and age (older) was also a positive predictor for functional improvement (Sakzewski, Ziviani and Boyd 2011). The degree of motor impairment has also been correlated with the gestational age of brain lesion onset (Staudt, Gerloff, et al. 2004). Factors like lesion position, lesion volume, and symptom severity may also influence the efficacy of CIMT for a particular patient, but this has not been well characterized.

1.3 Functional magnetic resonance imaging

1.3.1 Blood oxygenation level dependent signal

The complex organization of the human brain is anticipated based on its imperative role in the body and mind. From a biological standpoint, the brain oversees countless processes from hormone regulation, sensory reception and reaction, and crucial bodily functions that regulate energy distribution, nourishment and maintenance. The brain also handles more abstract psychological responsibilities like memory, emotions and personality. The growing knowledge of the brain is fueled by continually improving technology, optimized methods of analysis and experimental techniques, and the integration of scientists from a slew of different backgrounds. However, the information that is revealed through novel techniques only further demonstrates the complexity and detail of this organ.

The process of signal transfer via neurons involves the movement of action potentials along the axon and the movement of neurotransmitters from other dendrites through ion channels and energy consuming sodium-potassium pumps. The brain consumes a disproportionately large amount of energy for its size, with most of the energy being devoted to restoring the concentration gradients following an action potential, generating inhibitory or excitatory post-synaptic potentials, or maintaining the resting potential of the neurons. Energy is supplied via the vascular system, which transports glucose and other metabolites, and oxygen, which is carried by the hemoglobin molecule

in red blood cells. Upon stimulus onset, a neurovascular coupling mechanism (that is still not fully understood) communicates between active neurons and blood vessels causing the vessels to dilate, allowing a fourth order change in flow rate. This causes a flux of oxygenated hemoglobin to accommodate for the increased rate of oxygen metabolism in the capillary bed near active neurons. The blood oxygenation level dependent (BOLD) contrast is based on this balance between cerebral blood flow (CBF) and oxygen consumption (Ogawa, et al. 1990). The hemoglobin molecule is diamagnetic when oxygenated but as the surrounding active neurons and glial cells consume the oxygen it becomes deoxyhemoglobin (dHb), which is an endogenous paramagnetic molecule that disrupts the local field around the vessel. Ogawa and colleagues, who initially proposed the BOLD contrast, intuitively hypothesized that the increase in oxygen consumption would result in an increase in the amount of dHb, resulting in a decrease in signal. However, after a series of experiments varying the levels of oxygen gas delivered to a rat animal model, the MR signal was found to actually increase in vivo (Ogawa, et al. 1990). The increase in blood flow overcompensates for the neuronal demands (Huettel, Song and McCarthy 2004). During active periods the perturbation of the local magnetic field around the vessel is attenuated because the flux of oxygenated hemoglobin has flushed out the paramagnetic dHb resulting in small increase in the local MR signal with potentially high spatial resolution and global brain coverage.

The MR signal component that is exploited in fMRI is the transverse relaxation because of how it is influenced by the presence of deoxygenated hemoglobin (McRobbie, Moore and Graves 2006). The transverse relaxation, or T2 decay, reflects spin dephasing due to spin-spin interactions. As the magnetic moments are rotated into the transverse

plane, they spin with slightly different frequencies of precession due to field inhomogeneities, causing them to dephase (Haacke, et al. 1999). Gradient echo (GE) EPI is sensitive to changes in T_2^* relaxation time, which includes the effects of these field inhomogeneities as well as magnetic susceptibility. This sensitivity is ideal for focusing on local changes in the relative amount of dHb and is highly sensitive to change at standard field strengths (1.5T and 3T). While neurons are active, the decrease in the relative amount of dHb causes an increase in the ratio of T_2/T_2^* and by choosing an optimal echo time (TE) the signal increase can be maximized.

1.3.2 Task-related fMRI

The most prominent use of the BOLD signal is to identify brain regions that are active during a task. A block design is implemented to allow the comparison of signal intensities between task and no-task states. Initial human BOLD functional MRI (fMRI) experiments were conducted in the early 1990s to evaluate if BOLD percentage changes during activation would be substantial enough for consistent detection and to further understand the basis of this endogenous contrast mechanism. Bandettini implemented a long block design, with a finger to thumb touching task to activate the primary motor cortex. This resulted in a $4.3 \pm 0.3\%$ local signal increase in motor areas (Bandettini, et al. 1992). Shortly thereafter, two groups assessed activation in the visual cortex in response to a flashing LED during a long block design with easily detectable percentage changes in signal between resting and active states (Kwong, et al. 1992, Ogawa, et al.

1992). These relatively small signal changes are typical of task-related fMRI experiments and therefore susceptible to error and noise sources. The vascular origin of the BOLD response also creates both spatial and temporal discrepancies between the underlying electrical neuronal activities. The hemodynamic response (HDR) to neuronal activation is delayed by several seconds, and can be heavily influenced by large vessels that are distal from the location of neuronal activity. Another complication with task-related block designs is the effect of even small amounts of motion on activation patterns. Depending on the experimental design, motion artifacts can be diminished and accommodated for using confounds, smoothing the data, and motion correction. However, when motion is highly correlated with the task being performed and the corresponding hemodynamic response function, this can render the results unusable or unreliable. There have been multiple fMRI studies that have looked at altered activation patterns in cerebral palsy patients while performing a motor task (Briellmann, et al. 2002; Juenger, et al. 2007; Sutcliffe, et al. 2007; You, et al. 2005; Vandermeeren, et al. 2003; Winckel, et al. 2013; Cope, et al. 2010) but there are several challenges associated with this acquisition. Despite training, there may be inconsistencies in how each participant performs the task, even within subject from scan to scan. The rate of movement and the ability to pay attention to the instructions given may not be consistent across a young subject group. Another challenge is dependent on the patient's disease severity and their ability to perform the motor task during the scan with the hemiplegic arm, while keeping head motion at a minimum.

Initially most fMRI experiments concentrated on task-related percent signal changes compared to periods of rest, which appeared to have noise-related signal

fluctuations in the absence of a task. These fluctuations during rest were attributed to system noise and physiological artifacts in both electrophysiological and MR experiments. Initial experiments investigating these underlying signal fluctuations focused on developing methods to remove them in an effort to clean up task-related experiments (Stark and Squire 2001), while some began to concentrate on frequency analysis in an effort to understand if they were in fact a reflection of neuronal activity (Scholvinck, et al. 2010; Gusnard and Raichle 2001; Goense and Logothetis 2008). Some high frequency elements were clearly attributed to physiological artifacts like heart rate and cardiac function, but when concentrating on low-frequency fluctuations below 0.1 Hz, there were unexplained fluctuations (Leopold, Murayama and Logothetis 2003; Horovitz, et al. 2008). Biswal and colleagues compared the activation patterns derived from a finger-tapping motor task to the same subjects' time courses while at rest and not performing any particular task or thought. When low-frequency signals were correlated with the rest of the voxels in the brain, the correlation maps matched closely with the task activation maps (Biswal, et al. 1995). This was amongst the first indications that these signals were organized and neuronal in nature (Ogawa, et al. 1993). Electrophysiological studies (which directly record neuronal activity through multi-unit or local field potential recordings) were found to correlate with BOLD signals within this same low frequency band (Logothetis 2002). These findings gave further support to the idea that these signals are not merely noise but are reflections of temporally and spatially organized neuronal activity.

1.3.3 Resting state fMRI and networks

The BOLD signal recorded in the absence of specific thoughts or tasks is referred to as resting state fMRI. Correlating time series of functionally relevant areas with the rest of the brain reveal patterns of remote organization. These correlations are indicative of functional connectivity. Consistent patterns of structurally isolated connectivity are found in healthy subjects (Damoiseaux, et al. 2006; Smith, et al. 2009) and are referred to as resting state networks (RSN). Recall that the BOLD signal is based on local changes of blood dHb levels in response to neuronal metabolic demands. The most direct way to compare the two signals is through simultaneous fMRI and electrophysiology experiments. Although there have been some inconsistent results between studies, simultaneous local field potential and BOLD recordings in animal models are highly correlated providing strong evidence of the neural basis of these signals (Logothetis 2003; Leopold and Murayama 2003; Pan, et al., 2011).

There are two main types of analysis that reveal networks and the organized underlying functional architecture of the human brain. Seed-based analysis correlates a functionally relevant or structurally derived seed region's time series with the rest of the brain's voxels during rest to reveal remote correlated activity and RSNs (Fox and Raichle 2007). This type of analysis gives the investigator direct control over specific hypotheses with clear, interpretable results. Unfortunately, it is very susceptible to motion and dependent on the seed region size and placement. Independent component analysis (ICA) is a data driven approach that decomposes spatial-temporal components from the BOLD fMRI data and clusters them based on spatial patterns and time courses. This

method is very reproducible when controlling for the dimensionality or number of components derived from the data. Typically a low number of components (20-30) are sufficient for identifying networks while avoiding the separation of single networks into multiple components (Smith, et al. 2009). Components with correlated average timecourses and similar spatial patterns may be justifiably combined into a single component or network.

Similar network patterns are found across different states including wakefulness, sleep, and even while anesthetized. The most repeatable networks are similar to those found in Smith's paper and shown in Figure 1-1, reporting ten resting state networks in functionally relevant areas, along with ten other artifact-related and partial networks (Smith, et al. 2009). These overlapped with functionally relevant areas such as the primary visual, motor and auditory cortices. The first three components reflect visual networks corresponding to the occipitotemporal pathway, medial visual areas, and primary visual cortex. The fourth component reveals the default mode network shown to deactivate during task states and is thought to be responsible for memory and free thought. The fifth component is spatially located over the cerebellum and reflects action and perception mechanisms. The focus of this particular study is the sensorimotor network (the sixth component), which includes the supplementary motor area, sensorimotor and secondary somatosensory cortices, active during bimanual motor task paradigms. The seventh component is the auditory network and the eighth component reveals a network responsible for executive control. The final two components are uncharacteristically lateralized and reflect frontoparietal areas containing functional areas of language and cognition. These networks are reproducible across different states,

subjects, primate species, studies and analytical techniques and are a good candidate for studying alterations in a disease state. Resting state functional connectivity studies have compared Alzheimer's disease, depression, ADHD and autism patient's network organization to healthy controls and have reported significant differences in various spatial patterns and correlation magnitudes (Fox & Raichle 2007; Greicius 2008).

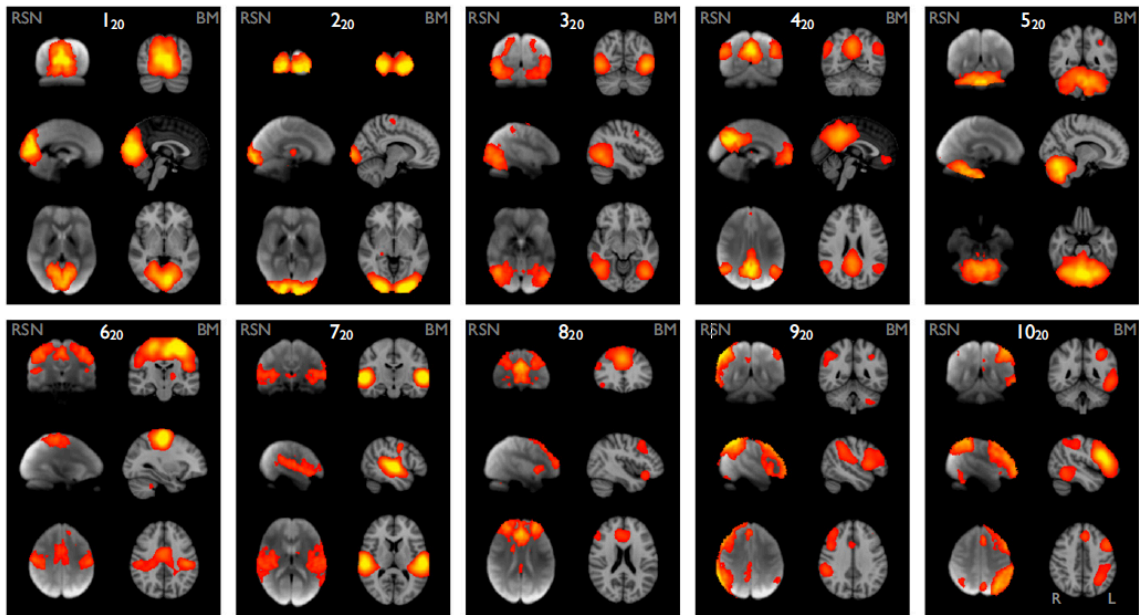


Figure 1-1: Ten resting state networks identified in healthy subjects using ICA with above-threshold voxels colour scaled for z-statistic ($z > 3$). Reprinted with permission from PNAS on behalf of Smith, et al. 2009.

1.3.4 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MRI technique that quantifies the random motion of water molecules and their relative diffusivities along different directions. This

acquisition is sensitive to the integrity of the neuronal fibers in the white matter of the brain as water diffuses parallel to these fibers. A SE-EPI sequence is used in combination with gradients to measure the diffusion along at least six directions in order to define a diffusion tensor. From this tensor the fractional anisotropy (FA) and mean diffusivity (MD) can be calculated. FA quantifies the directionality of water molecule diffusion and is given by

$$FA = \frac{\sqrt{(\lambda_x - \lambda_y)^2 + (\lambda_y - \lambda_z)^2 + (\lambda_z - \lambda_x)^2}}{\sqrt{2(\lambda_x^2 + \lambda_y^2 + \lambda_z^2)}} \quad (1)$$

where λ_x , λ_y , and λ_z represent the eigenvalues along the three principle axes of the diffusion tensor ellipsoid. A value of 0 represents water that diffuses isotropically (any direction) and 1 for anisotropic diffusion (along one direction), reflecting axon myelination, density and integrity (Trivedi, et al. 2008). The MD is simply the average eigenvalue, reflecting the mean squared displacement and diffusion time (Alexander, et al. 2007). This acquisition can be analyzed in a number of different ways. While some studies focus on the FA and MD values at various regions of interest, some use this information for tractography analysis of the fibers illuminating both their organization and the number of fibers involved.

1.4 Neuroplasticity

1.4.1 Introduction

Neuroplasticity reflects the brain's ability to adapt and reorganize neural connections in response to changes in behaviour or injury. This mechanism is particularly evident in the young brain during early development, as seen through the ability to learn new languages or instruments, though adult studies have also shown evidence of neuroplasticity (Park, et al. 2011). Early investigations of neuroplasticity and its relation to stroke incidence and treatment evaluated (a) how the brain reorganizes itself in the presence of brain injuries, lesions, or physical injury and nerve damage (Donoghue, Suner, & Sanes, 1990; Nudo & Milliken, 1996) and (b) how changes in behaviour (specifically limb positioning) can consequently alter cortical maps derived from motor evoked potentials (Gellhorn and Hyde, 1953). This was among some of the first evidence of changes in sensorimotor network representations due to controlled behavioural variations and neuronal injuries. Animal studies throughout the 1980s and 1990s provided many different examples of neuroplasticity following stroke treated using mechanisms found in CIMT (Taub 1980; Byl and Merzenich 2000; Donoghue, Suner, & Sanes, 1990). These studies demonstrate the relationship between physical functional changes and the brain's cortical reorganizations. This also provides strong evidence for the validity of CIMT as a plastic mechanism to improve functionality in both adult stroke patients and young cerebral palsy patients.

1.4.2 Stroke studies and CIMT

Recall that CIMT is based on two mechanisms that attempt to combat learned non-use and increase functionality; restraining the unaffected arm, thereby forcing the use of the weak arm, and repetitive practice. Early investigations of neuronal changes as a result of training were first evaluated using a primate stroke model. Repeatedly practicing skills with the affected hand was found to increase cortical representations of these hand movements, spatially reorganize motor cortices on both hemispheres (as measured by intracortical micro stimulation), and improve behavioural functionality (Taub 1980).

Neuronal changes as a result of therapy have been evaluated using a number of different modalities that attempt to represent the cortical areas associated with hand or arm movements (Mark, Taub and Morris 2006). Assessing these representations in adult stroke patients before and after CIMT allows the investigator to visualize and quantify neuroplasticity, which can then be verified with clinical outcome measures of functional improvement. Transcranial magnetic stimulation (TMS) creates small controlled local electrical currents that can induce depolarization of the surrounding neurons and stimulate activation. By stimulating neural motor areas in an organized way and recording which areas elicit a physical response in the corresponding muscle, one can map cortical organization. Several studies evaluated these measures before and after CIMT and found that the spatial extent of the cortical area controlling the affected hand increased (Liepert, Miltner and Bauder, et al. 1998; Liepert, Miltner and Taub, et al. 2000; Thickbroom, et al. 2001; Staudt, Grodd, et al. 2002). fMRI studies confirmed these findings and have found (with some variability) increased areas of activation in the

affected hemisphere along with decreased activation areas in the healthy hemisphere during hemiplegic arm movements (Levy, et al. 2001; Johansen-Berg, et al. 2002; Schaechter, Kraft, et al. 2002; Dong, et al. 2012; Sheng and Lin 2009; Yin, et al. 2013; Stark and Squire 2001). Liepert et al. studied six adult stroke patients treated with CIMT. They found that motor function significantly improved after treatment in all subjects as measured using MAL (Liepert, Miltner and Bauder, et al. 1998). The motor evoked potential (MEP) amplitudes in the affected hemisphere also significantly increased after therapy, while they remained constant in the unaffected hemisphere. A study a year later used TMS to determine the size of the cortical representation of the abductor pollicis brevis (APB) muscle. This area was significantly enlarged in the affected hemisphere and decreased in the healthy hemisphere after CIMT, similar to other TMS studies of stroke patients treated with CIMT (Kopp, et al., 1999).

This therapy-induced plasticity is a promising result and was replicated in similar studies using fMRI task-induced activation. Stroke patients participated in an fMRI scan before and after CIMT therapy and performed finger tapping (Levy, Nichols, Schmalbrock, Keller, & Chakeres, 2001; Sheng & Lin, 2009), hand flexion-extension (Johansen-Berg, et al. 2002), or wrist movements (Stark, et al. 2011) with both hands separately. Changes in activation patterns can then be evaluated as evidence of neuroplastic reorganization after therapy. These studies found increased ipsilesional activation after therapy during weak arm movements that correlated with significant improvements of motor function based on standard clinical evaluations like grip tests, MAL, WMFT, and JTTHF. In some cases, activation patterns after CIMT were more

concentrated in motor areas then in pre-therapy scans, which showed activation in non-motor areas (Sheng and Lin 2009).

There have been multiple studies that have investigated the changes in resting state connectivity and networks as a result of stroke damage. Depending on the lesion position, time from stroke onset, and stroke severity, there are significant changes between motor networks in stroke patients compared to healthy controls (Golestani, Tymchuk, Demchuk, & Goodyear, 2013; Yin, et al., 2013). Interhemispheric resting state functional connectivity has been correlated with motor recovery and improved behavioural performance after stroke (Carter, et al., 2010; Park, et al., 2011; Varkuti, et al., 2013; James, et al., 2009; Saleh, Adamovich, & Tunik, 2011). This is an important finding that indicates the potential for resting state fMRI as a tool for prognosis of functional recovery in stroke patients (Carter, Shulman and Corbetta 2012). Resting state fMRI has many advantages over task-based studies; it's unrelated to any changes in task-performance or timing, comparable across studies, and applicable to patients of varying symptom severity, age, and even species.

1.4.3 Cerebral Palsy and CIMT

Initial studies of hemiplegic cerebral palsy attempted to understand injury-induced cortical organization in the motor cortex (Carr, Harrison, et al. 1993). These differences are a result of damage to thalamocortical connections and descending corticospinal pathways as well as learned non-use (Hoon, et al., 2009; Grefkes & Fink, 2011). The

activation patterns while performing unaffected-arm motor tasks are similar to those in healthy subjects, with most activation in contralesional motor areas. However, when performing the task with the weak arm activation patterns tend to be inconsistent or remain in the undamaged hemisphere with ipsilateral control (Briellmann, Abbott, Caflisch, Archer, & Jackson, 2002; Vandermeeren, et al., 2003; Thickbroom, Archer, Nagarajan, & Mastaglia, 2001). Mirror movements are also a factor that can elicit activation in the ipsilateral hemisphere. Larger areas of unfocused activation during weak-arm motor tasks have also been observed in areas not normally associated with motor function (Winckel, et al. 2013). Changes in response to therapy using a task-related design are difficult to evaluate in this particular patient group due to the young age group studied and the severe motion artifacts associated with the motor task. One case study investigated the fMRI activation in response to an elbow extension task before and after virtual reality therapy and found improved motor function but seemingly unrelated changes in functional activation patterns based on laterality indices (You, et al. 2005). Task-based functional changes as a result of CIMT have also been studied with similar results compared to stroke fMRI and TMS studies. Increases in ipsilesional activation during weak arm movements (Juenger, et al., 2007; Sutcliffe, Gaetz, Logan, Cheyne, & Fehlings, 2007) and increases in percent activation within motor areas (Cope, et al. 2010) were found in some patients, while others showed no change. Cope et al. then segregated results according to arm function and found that subjects with moderate functionality with their weak arm significantly improved clinically, while subjects with high or low scores did not. These improvements were variably correlated with higher percent signal changes in ipsilateral motor areas during hemiplegic arm tapping.

There have not been any published studies reporting changes in resting state network organization in cerebral palsy patients. One group has quantified the decreased motor and sensory tracts in cerebral palsy patients using diffusion tensor imaging (DTI) and tractography (Yoshida, Hayakawa, et al. 2010), and has now begun to compare these changes with resting state connectivity to show an overall decrease in correlation values between 46 areas of interest (Yoshida, Faria, et al. 2013). Several DTI studies with CP patients have found lower FA and higher MD values in the affected corticospinal tract compared to healthy subjects (Hoon, et al. 2009; Kuhnke, et al. 2008; Yoshida, Hayakawa, et al. 2010).

1.5 Objectives

This study aims to investigate a multitude of neural measures for possible predictors and evidence of neuroplasticity as a result of constraint-induced movement therapy. There are three main objectives of this study. First, it is important to understand the alterations in resting state network organization and the integrity of the affected corticospinal tract in individuals with hemiplegic CP. These investigations may be a powerful tools in understanding impaired motor function as well as other functional symptoms which could be related to altered areas that are near the lesion site. Secondly, by evaluating a number of different clinical and MR measures longitudinally, any changes as a result of CIMT can be compared to a control group and also assessed for longevity. Not all hemiplegic CP patients experience success with CIMT, which is a frustrating process for both caregivers and patients, so the third objective will be to identify neuroimaging measures that predict increased functional gains, so that patients with the best chance of success are selected for CIMT.

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2 Methods

2.1 Study design

This study is a prospective matched-case comparison between hemiplegic cerebral palsy patients treated with CIMT and a control group that did not receive any treatment. The treated group was recruited first with a range of severity levels based on baseline Quality of Upper Extremity Skills Test (QUEST) scores (DeMatteo, et al. 1992), and then an untreated control group was recruited prospectively with severity matched to these baseline QUEST scores (± 15). The CIMT-treated group was assessed clinically and participated in an MRI acquisition at baseline, 1-month after baseline, and 6-months follow-up while the control group was assessed at baseline and 1-month later without participating in the CIMT camp. This longitudinal design allows a clear comparison between groups of patients in terms of the clinical and neural changes after CIMT, as well as an assessment of the longevity of any improvements in hemiplegic CP patients treated with CIMT. Control subjects were only evaluated at two timepoints in order to establish that their clinical and MRI data remained unchanged in contrast to treated subjects.

2.1.1 Recruitment/ patient requirements

Fourteen patients were originally recruited for the CIMT-treated group in this study between the ages of 6 and 18 diagnosed with hemiplegic CP (GMFCS level I, MACS level I) as a result of a middle cerebral artery (MCA) infarct or some other subcortical and/or cortical injury such as intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), for example. They were recruited from three different facilities; Holland Bloorview Kids Rehabilitation Hospital in Toronto, Thames Valley Children's Centre in London, and McMaster Children's Hospital in Hamilton. Patients could not have received any previous CIMT within 9-months of the study, or any botulinum toxin upper limb injections within 6-months of the study. These young patients must be able to comprehend and follow simple instructions, and participate and remain still for the 45-minute MRI scan. Three of these patients did not participate in the MRI portion of the study for various reasons (braces artifact, afraid to enter the MRI, parents were not interested in the MRI sessions), and four of the patients' data were not used due to excessive motion ($> 3\text{mm}$) during the MRI portion of the study. Two included subjects are missing one session of data because of excessive motion during that particular session. Eight control subjects were recruited with severity matched according to CIMT-treated baseline QUEST scores (± 15). Of these control patients, three were excluded because of excessive motion during the scans. The clinical and demographic descriptions of successfully scanned subjects are summarized in Table 2-1. Control and treated groups did not have significantly different age ($T = 1.69, p = 0.12$) or lesion volume ($T = 0.54, p = 0.60$) according to a student *t*-test.

Table 2-1: CIMT-treated and control group subject demographics.

Patient No.	Sex	Age	Ipsilesional Hemisphere	Injury Pattern	Lesion Volume	Baseline QUEST
01-0003	M	13	L	MCA	57.94	65.32
01-0005	M	12	R	MCA	5.91	83.82
01-0012	F	11	L	MCA	8.94	65.70
01-0014	F	6	R	IVH and porencephalic cyst	81.27	79.1
01-0017	M	15	R	PVL and porencephalic cyst	79.54	79.1
05-0007	M	14	R	PVL	10.37	82.49
05-0010	M	11	R	PVL	1.94	75.62
Control 05-0003	M	13	R	Schizencephaly	26.21	68.89
Control 06-0015	M	14	L	Unknown	53.03	35.38
Control 06-0018	F	18	L	Parietal infarct	23.47	62.89
Control 06-0024	M	11	R	Hemispheric infarct	23.42	94.41
Control 06-0028	M	17	R	PVL	1.9	60.33

2.1.2 Ethics

Research ethics approval was obtained from The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB), Toronto Academic Health Sciences Network (TAHSN), Holland Bloorview Research Ethics Board and informed consent and assent were also obtained for all participants at Holland Bloorview Kids Rehabilitation Hospital, Thames Valley Children's Centre, and McMaster Children's Hospital. Ethics approval forms are given in Appendix F.

2.1.3 CIMT treatment

The constraint-induced movement therapy (CIMT) that was applied in this study is an adapted model from the protocol originally developed by Taub and colleagues (Taub 1980) in order to accommodate for the young age of the subject group and to directly address bilateral functionality (Sakzewski, Ziviani, Fabbott, et al., 2011). The three-week protocol was administered with the child wearing a non-removable below-elbow cast on the non-hemiplegic limb for the entire first week followed by a two-week standardized CIMT camp, called "Hand2Hand", developed at Holland Bloorview Kids Rehabilitation Hospital. The objective of this camp was to focus on increasing the affected arm's role in daily activities through improvements in (a) unilateral motor control, (b) strength, (c) speed and efficiency, and (d) bimanual actions. During the first week prior to the camp, children wore a non-removable cast and were forced to perform every day activities in

their home with their affected limb in preparation for the camp. This restraint directly combats the habits and problems associated with learned non-use and is effective for young CP patients, but can be extremely frustrating (Taub, Ramey, et al. 2004; Thorley, et al. 2012). During the two-week CIMT camp, participants worked with occupational therapists for 4 hours a day for four days during the first week of camp where they initially concentrated on unilateral activities with the hemiplegic hand, wearing the constraint for 3 hours per day. During the second week children began to focus on bilateral activities that were incorporated during the final five days, wearing the restraint for an hour per day. The camp was tailored toward young children and early adolescents, with fun and competitive games, group activities, and one-on-one time with the ability to focus on patient-specific goals and training. A ratio of one therapist for every two children was maintained throughout the camp. A full schedule of the camps' activities is shown in Figure 2-1. Activities like squeezing a sponge, manipulating objects in a game setting, and working together with other children involve skills that are useful training for performing daily activities that require reaching, grasping, lifting, and intricate movements. Participants were also able to concentrate on activities and skills that are personally challenging in their daily lives with a therapist one-on-one, and parents and children were encouraged to complete an individualized daily home exercise program at night and on weekends. Constraint therapy is encouraged to casually continue at home and to be formally repeated again later in a clinical setting to promote further improvements and complete specific goals related to daily function (Chen, et al. 2012; Boyd, Morris and Graham 2001). If the skills learned during the camp are not continued the child could regress back to baseline functionality.

Figure 2-1: A schedule of the CIMT camp (Fehlings, et al. 2013)

WEEK 1					
Time	Tuesday July 2, 2013	Wednesday July 3, 2013	Thursday July 4, 2013	Friday July 5, 2013	
8:00 AM	STAFF PREP TIME				
8:30 AM	STAFF PREP TIME				
9:00 AM	Sign In/Ice Breakers Name Tags 1W 135 Keltie & Temine	ADL Goals (B) (1W135) Keltie	Swimming (B) Pool Temine Lead	ADL Goals (1W135)	
9:30 AM		Social Work (1W135) Nadine & Barb		Circuits (U) (1W135)	
10:00 AM	Smoothies (U) (1W135) Temine			ADL Goals (1W135)	Gross Motor (U) 0W300 or Outside Keltie
10:15 AM	Snack	Gross Motor (U) 0W300 (gym) Temine	Snack	Snack	
10:30 AM	Craft (U) (1W135) Keltie	Snack	Circuits (U) (1W135)	Kitchen/Pizza (U) (0W 245) Temine	
11:00 AM	Circuits (U) (1W135) Temine/Keltie	Crafts (U) (1W135) Keltie	Unilateral Games (1W135) & Virtual Therapy w/ Linda		
11:30 AM	Cast Removal	Circuits (U) (1W135)			
12:00 PM	Pick-up/ Clean-up				
WEEK 2					
Time	Monday July 8, 2013	Tuesday July 9, 2013	Wednesday July 10, 2013	Thursday July 11, 2013	Friday July 12, 2013
8:00 AM	Prep	Prep	Prep	Prep	Prep
8:30 AM	SOPHIE Covering				
9:00 AM	ADL Goals (B) (1W135)	ADL Goals (B) (1W135)	ADL Goals (B) (1W135)	Swimming (B) Pool Temine	ADL Goals (B) (1W135)
9:30 AM	Craft (B) (1W135) Temine	Unilateral Games (B) (1W135) Temine	Kitchen/Cupcakes (B) (0W245) Temine/Keltie		Circuits (U) (1W135)
10:00 AM	Kitchen (B) (0W245) Temine	Popsicles for snack!			ADL Goals (B) (1W135)
10:15 AM	Snack	Snack	Snack	Snack	Snack
10:30 AM	Gross Motor (B) (0W300) Sophie	Circuits (U) (1W135)	Gross Motor (B) (0W300) Temine	Circuits (U) (1W135)	Gross Motor (B) (0W300) Temine
11:00 AM	Circuits (U) (1W135)	Gross Motor (B) 1030-11 (0W300) OR outside Keltie	Circuits (U) (1W135)	Unilateral Games (U) & Virtual Therapy w/ Linda (1W135) Keltie	Closing Ceremonies (1W135) Temine/Keltie
11:30 AM	Unilateral Games (B) (1W135) Sophie		Craft (B) (1W135) Keltie		
12:00 PM	Clean Up/Pick Up				

2.2 Assessment

2.2.1 Clinical assessment

Participants were clinically assessed using a number of standard tests and measurements that are sensitive to various aspects of upper limb functionality. The same therapist evaluated the same patient at all timepoints for consistency. Patients were evaluated by an occupational therapist using QUEST, the Canadian Occupational Performance Measure (COPM), dominant and affected hand's grip strength, Assisting Hand Assessment (AHA), and the Jebsen-Taylor Test of Hand Function (JTTHF). The child's parent or guardian also completed a Children's Hand-Use Experience Questionnaire (CHEQ). These assessments are sensitive to various aspects of functional change as a result of an applied therapy. The QUEST measure focuses on a multitude of skills like dissociated movements, grasping, weight bearing, and extending for an overall measure of functional capacity (Thorley, et al. 2012). The COPM measure covers both the performance and satisfaction of the participant while performing three activities they find personally challenging with individually customized goals (Law, Baptiste, et al. 1990). The weak-hand grip strength is a simple quantitative measure of the hand's grip strength, measured in mmHg. This was repeated three times and averaged at each time point. For the AHA scores, a video was recorded while the child carried out casual bilateral play (Krumlinde-Sundholm and Eliasson 2003). A single OT, while blind to subject group or timepoint, evaluated AHA scores by viewing the video recordings of the patient. The OT

rated their bimanual performance based on 22 specific items on a scale of 0-4 to arrive at the total AHA score, which was then scaled as a percentage. The JTTHF is a series of 7 subtests performed by each hand separately and evaluated by the time to complete the task (Jebsen, et al. 1969). The OTs identified that lifting a large, but light object was the task most sensitive to change, and so we focused on that score as well as the total time to complete all tasks to rate efficiency. And finally, the CHEQ evaluation focuses on the effectiveness of the hemiplegic hand during activities that require two hands (Skold, et al. 2011). All these measures attempt to describe various aspects that contribute to normal hand function which are often compromised in hemiplegic CP patients (Adams 2009). These clinical tests are also highly sensitive to changes after an applied therapy. The form used by the OT to evaluate the participants is given in Appendix G.

2.2.2 MRI acquisition

All MRI data was acquired on the 3T MR scanner (Tim Trio; Siemens, Erlangen, Germany) at The Centre for Functional and Metabolic Mapping at the Robarts Research Institute, using a 32-channel human head receive coil. Participants were trained in a mock MRI environment and given clear instructions for performing the task and rest portions of the scan as well as the importance of remaining as still as possible before entering the scanner. A research assistant accompanied the patients into the scan room to monitor movement, encourage the child to remain still throughout the 45min scan, and report on the scan. Three different anatomical images were taken for registration

purposes and in order to best delineate the lesion. An axial T2-weighted turbo spin echo sequence (TE/TR = 95/7770 ms, flip angle (FA) = 120°, matrix size = 320x225, FOV = 256x200mm, No. slices = 35, slice thickness = 3mm), an axial T2-weighted turbo fluid attenuated inversion recovery (FLAIR) sequence (TE/TR = 120/8000 ms, FA = 130°, matrix size = 256x232, FOV = 220x200mm, No. slices = 35, slice thickness = 4mm), and a sagittal T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TE/TR = 2.91/2300 ms, FA = 9°, matrix size = 256x240, FOV = 256x240mm, No. slices = 160, slice thickness = 1mm). Lesion volumes in the ipsilesional hemisphere (opposite the affected arm) were manually delineated using T2-weighted anatomical images with MRIcron software (Rorden, Karnath and Bonilha 2007). Two 5 minute resting state fMRI gradient echo echo-planar imaging (GE-EPI) sequences (TE/TR = 30/2350 ms, FA = 90°, matrix size = 80x80, FOV = 240x240 mm, No. slices = 40, slice thickness = 3mm) were performed while the patient was simply asked to remain still and not fall asleep. Another two 5-minute fMRI GE-EPI scans (TE/TR = 30/2350 ms, FA = 90°, matrix size = 80x80, FOV = 240x240 mm, No. slices = 40, slice thickness = 3mm) were run while the subject performed a lifting/flexing task using the apparatus shown in Figure 2-2. The children were given full instructions on how to perform the motor task, and practiced outside the scan room before their first session using a mock apparatus. A slideshow was presented on a screen during the scan for the purpose of timing the block paradigm, with a directed lift action performed every 2.35 seconds (every TR) during active blocks and indicated rest periods for baseline data. This task was performed with both limbs separately in order to understand which areas are active during movement. Unfortunately, movement artifacts associated with the task

excessively confounded almost all of the task-related fMRI data, making it very difficult to correct (Hajnal, et al. 1999). Performing the task with the affected limb was especially challenging for participants and resulted in even higher motion artifacts and this data was not analyzed further. Finally, a spin echo (SE) DTI sequence ($TE/TR = 85/6800$ ms, matrix size = 100×100 , FOV = 200×200 mm, No. slices = 56, slice thickness = 2mm, $b_1 = 0$, $b_2 = 1000$ s/mm², gradient directions = 30) was used for creating diffusion-weighted images. The total scan time was an hour.

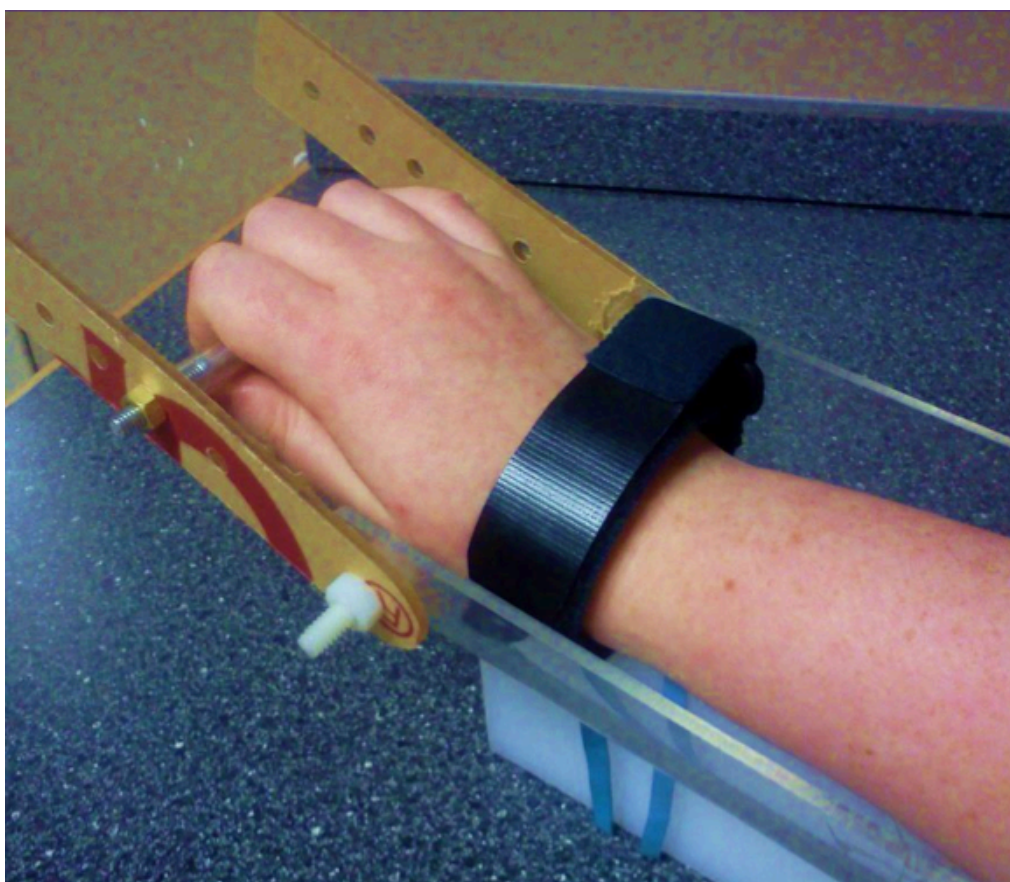


Figure 2-2: fMRI motor task device where the participant is asked to lift and relax the bar while the restraining device attempts to keep arm and head movement to a minimum.

2.3 Analysis

2.3.1 Task-based fMRI analysis

Motion artifacts over 3mm average throughout a single run confounded the majority of task-based data. Some patients found it extremely difficult to perform the task with their affected arm and this strain induced more extreme motion artifacts. Despite training, a simple slideshow instruction video, and a restraining device to minimize any motion besides hand flexing there were still motion artifacts that made the data unusable, even with motion correction algorithms. Excessive motion occurred during the active task paradigm and therefore affected volumes could not be removed in an effort to clean the data. Z-statistical parametric maps showing areas that had increased activity from baseline rest periods highlighted inconsistent areas of activation, even while using the unaffected limb. A reliable data set across multiple timepoints could not be acquired for any subject.

2.3.2 Resting state analysis

I performed all analyses while blind to any clinical information, subject group or results. Resting state EPI data was only included if peak movement was less than 3mm. EPI data was preprocessed using the FMRIB Software Library (FSL)

(<http://www.fmrib.ox.ac.uk/fsl>) using the standard steps (Jenkinson, Beckmann, et al. 2012; Woolrich, Jbabdi, et al. 2009; Smith, Jenkinson, et al. 2004). Both anatomical and resting state data were brain extracted using FSL's brain extraction tool (BET) to remove the skull and non-brain structures (Smith, 2002). Various parameters were used for different subjects and extracted brains were visually inspected to ensure only non-brain structures were removed. Functional data was then preprocessed using the fMRI Expert Analysis Tool (FEAT) with: motion correction using FMRIB's Linear Image Registration Tool (FLIRT) using the middle volume as a reference (Jenkinson, Bannister, et al. 2002), 5mm spatial smoothing, and low and high pass frequency filtering (between 0.01 – 0.1 Hz). Transformation matrices describing functional and anatomical data transformations to a standard space, the Montreal Neurological Institute (MNI) T1-weighted brain image (with 2mm isotropic voxel size), were found using FLIRT and applied to all preprocessed EPI images (Mazziotta, et al. 1995). Further denoising was performed using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), which output 20 components per single session results (Beckmann and Smith, 2004). Components with voxels outside the brain were considered noise or motion artefacts and were manually removed from the data using the *fsl_regfilt* command-line program.

The cleaned and preprocessed functional data was then analyzed to identify the sensorimotor network using two different types of analyses: independent component analysis (ICA) and seed-based analysis (see section 1.3.3). MELODIC was used again on the cleaned data to identify resting state networks (RSN) through probabilistic independent component analysis of the multisession temporally concatenated data

(Beckmann, DeLuca, et al. 2004). Data from all sessions were concatenated per subject with a low model order of 20 to identify the sensorimotor network and avoid splitting networks into multiple components, as seen in previous studies (Abou-Elseoud, et al. 2010; Calhoun, et al. 2001). Components were compared through the *fsl_cc* correlation tool to reveal any components that had been split, though no components exceeded a correlation of 0.1. ICA is a statistical analysis tool that attempts to express a collection of random variables as a linear combination of independent components based on spatial and temporal properties. The concatenated data is represented as a 2D matrix based on n voxels and p timepoints, which are then decomposed into timeseries and spatial maps that describe underlying architecture. Noise is estimated assuming a Gaussian noise distribution and is described elsewhere (Woolrich, Ripley, et al. 2001). Raw component information is transformed to Z-scores dividing by the standard deviation of the estimated noise, and roughly estimates the strength of the linear relationship between the derived timeseries on a voxel-wise basis (Beckmann and Smith, 2004). This average ICA network was then back reconstructed to individual sessions (baseline, 1-month, and 6-months) using FSL's dual regression algorithm to quantify any network changes due to the applied therapy. This method involves multiple linear regression of the component's timecourse and spatial features to obtain individual session and subject-specific spatial maps. Z-scores were statistically thresholded at $p < 0.05$ significance level using FSL's Randomize algorithm and threshold-free cluster enhancement (Nichols and Holmes 2002). Cluster-size thresholds were also applied to this data with a minimum cluster size of 200 voxels (3mm isotropic), though both quantities are reported. Network maps are shown with a z-score threshold of 5.

Before carrying out a seed-based analysis, further motion correction was applied using the *fsl_motion_outliers* tool. Volumes with large motion (> 1mm) were identified and used to create a confound matrix that could then be used within the general linear model (GLM) to remove the effect of these time points on the seed-based analysis, without compromising statistics, temporal filtering, or correlation algorithms. A region of interest (ROI) was chosen from average ICA component-derived motor area within the contralesional hemisphere on a per subject basis due to the large differences in motor area location because of the lesion damage and because task-based results could not be used to identify seed placement. The time course from this region was extracted and correlated with the rest of the brain on a voxel-wise basis to once again visualize the motor network and its connectivity patterns before and after CIMT. Seed-based results from the pair of resting state scans acquired per session were then averaged together per subject.

Several laterality indices were calculated from both the ICA and seed-based network results. The general laterality index (LI) equation used is:

$$LI = \frac{Ipsilesional\ data - Contralesional\ data}{Ipsilesional\ data + Contralesional\ data} \quad (2)$$

where *data* could refer to the number of active (above a z-statistic threshold of 5) voxels, the average signal intensity, or the average z-statistic in those active voxels within extended motor areas defined using the Harvard-Oxford Cortical Structural Atlas (Figure 2-3). A negative LI would indicate a preference to the contralesional hemisphere (or a more unilateral network) due to the subcortical damage in the ipsilesional hemisphere, while an LI approaching 0 would indicate a more bilateral network pattern, as seen in healthy subjects (Damoiseaux, et al. 2006). ROIs were chosen from the supplementary

motor area (SMA), right and left primary and secondary motor areas which were found on a subject by subject basis from the ICA-derived sensorimotor network and, whenever possible, these timecourses were correlated with each other to quantify any connectivity changes.

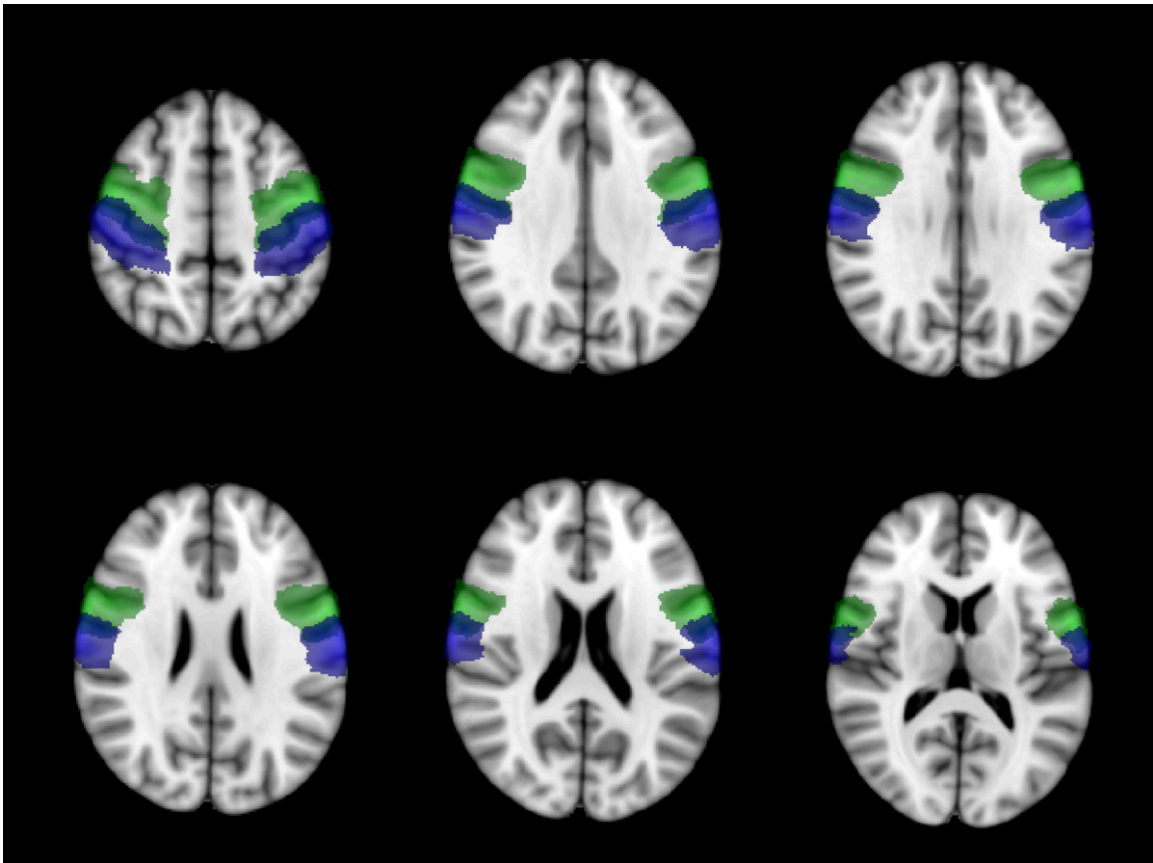


Figure 2-3: Sensorimotor cortex including the primary motor cortex (M1) along the precentral gyrus (green) and primary sensory areas (S1) postcentral gyrus (blue), overlaid on an average standard space MNI image.

2.3.3 Diffusion analysis

All diffusion analysis was completed using FMRIB's Diffusion Toolbox (FDT) (Behrens, et al. 2003). Diffusion weighted data was first eddy current corrected (the diffusion equivalent of motion correction) and a binary brain-extracted mask was created. DTIFIT was then used to fit diffusion tensors to the eddy current corrected data. This step also uses the corrected data to create fractional anisotropy (FA) and mean diffusivity (MD) maps. Average FA and MD values were taken from the lesion and at three common points along the right and left corticospinal tracts (CST) which were manually found using the Johns Hopkins University (JHU) White-Matter Tractography Atlas (Mori, et al. 2005) and confirmed using the individual subject T2-weighted anatomical data. If the JHU region did not match well with the anatomical data, a 5mm circular region was manually delineated. These three areas of interest include the pons, midbrain, and the posterior limb of the internal capsule, similar to previous studies (Marumoto, et al. 2013; Trivedi, et al. 2008) and shown in Figure 2-4.

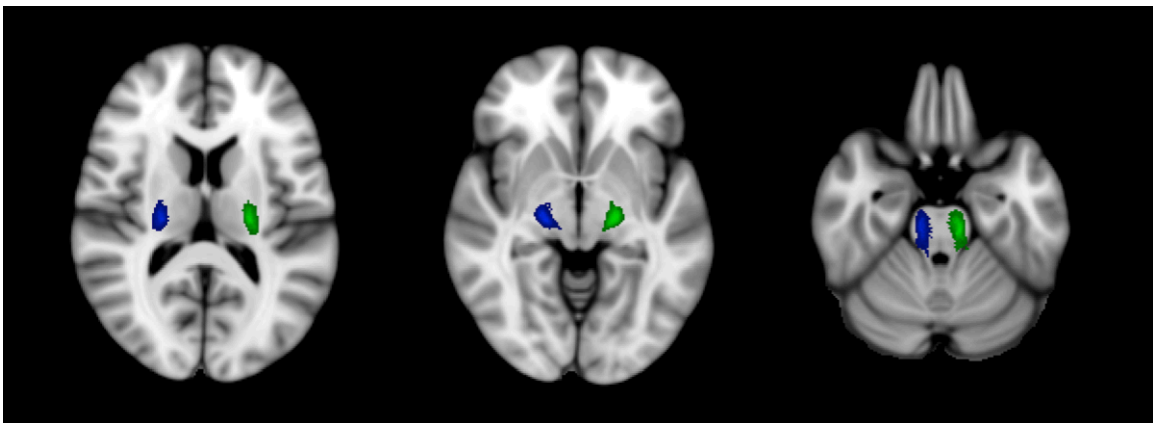


Figure 2-4: Three areas of interest along the right and left CSTs. From left to right: the posterior limb of the internal capsule (PLIC), midbrain, and pons.

2.3.4 Statistical analysis

All data was input into an excel spreadsheet and arranged in columns by session (baseline, 1-month and 6-month follow-up). This spreadsheet was loaded into IBM's Statistical Product and Service Solutions (SPSS) software (SPSS Inc, Chicago, IL, USA), which was used to perform all analysis. Relationships were considered significant when the probability of making a Type I error was less than 5% ($p < 0.05$), though relationships with $p < 0.1$ were considered due to the small sample size.

2.3.4.1 Clinical and MRI changes 1-month and 6-months after CIMT

Both clinical and MRI changes 1-month and 6-months after CIMT were evaluated using a paired samples t-test compared to baseline data. Control subjects' data was analyzed in the same way. Only subjects with successful MRI sessions for at least two timepoints (including baseline) were considered for prediction and correlation analysis.

2.3.4.2 Correlation analysis

The difference between baseline clinical scores before CIMT and 1-month and 6-months later was calculated and put in separate columns in the excel spreadsheet. These clinical changes were correlated with all baseline clinical and neuroimaging data.

2.3.4.3 Evaluating correlated neural and clinical changes

A bivariate Pearson correlation analysis was run with all changes in MRI data and clinical change scores. Clinical change scores that correlated with neuroimaging change scores are strong evidence of neuroplastic mechanisms of recovery, and evaluations at 6-months were also useful in assessing the longevity of any changes.

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3 Results

3.1 Introduction

Though CIMT has been widely successful in improving overall hand function in stroke and CP patients, not all participants experience success (Cope, et al. 2010; Sakzewski, Ziviani, Fabbott, et al., 2011). Baseline characteristics about these patients that predict greater clinical improvements following CIMT could be useful when identifying which treatment is suitable for an individual patient. Several groups have looked at various predictors of therapy-induced clinical success in stroke, traumatic brain injury (TBI), and cerebral palsy patients (Marumoto, et al. 2013; Rocca, et al. 2013; Fritz, et al. 2005; Dong, et al. 2006; Sakzewski, Ziviani, Fabbott, et al., 2011). By evaluating baseline MRI data and its relationship with clinical change scores, we can identify neuroimaging predictors of clinical success following CIMT. To our knowledge, this is the first study to investigate hemiplegic CP patients in order to (a) understand the reorganization of RSNs in light of subcortical and/or cortical damage, (b) identify resting state and diffusion MRI predictors of clinical improvements following CIMT, and (c) reveal plastic mechanisms of clinically correlated resting state changes after CIMT.

3.2 Results

3.2.1 Clinical Results

Most participants in this study experienced some success following the CIMT camp. In particular, CIMT-treated subjects with successful MRI sessions had near-significantly different clinical scores according to a paired-samples t-test of weak grip strength ($p = 0.083$), strong grip strength ($p = 0.098$), CHEQ ($p = 0.083$) and the JTTHF task ($p = 0.083$). They had significantly different scores according to the COPM performance score ($p = 0.004$) and QUEST ($p = 0.007$). Table 3-1 is a summary of all

Clinical Test	Average baseline	Average 1-month	p -value	Average 6-month	p -value	Average control baseline	Average control 1-month	p -value
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subject clinical data that successfully participated in the MRI portion of the study. All average clinical measures indicate different aspects of improved hand function after constraint therapy, except for the AHA score. The untreated control group's clinical scores remained statistically unchanged across all measures as expected, except the CHEQ results that improved significantly one month later ($p = 0.048$). When investigating individual results, almost all subjects improved by some degree clinically after CIMT. Figure 3-1 shows the results of a paired-samples t-test with individual subject scores before and 1-month after CIMT, while Figure 3-2 depicts the average scores, with error bars representing standard error of the mean (SEM). 6-months after therapy only the COPM was significantly different from baseline clinical data ($p = 0.001$) and in general, patients had variable prolonged effects from therapy ranging from maintaining scores, further improvements or regressing back towards baseline. Similar clinical results were found when subjects without MRI data were included and are summarized in Appendix A.

QUEST	74.23 (3.02)	82.46 (2.67)	0.007	79.83 (5.21)	0.248	64.38 (9.44)	66.03 (11.50)	0.742
COPM	2.92 (0.76)	6.67 (0.57)	0.004	6.83 (0.63)	0.001	4.58 (1.34)	3.67 (0.96)	0.288
Weak grip strength	103.57 (23.10)	148.29 (37.25)	0.083	117.90 (30.77)	0.172	168.13 (54.16)	159.33 (58.13)	0.529
AHA Scaled Score	57.86 (10.16)	52.86 (7.09)	0.518	52.57 (9.24)	0.484	-	-	-
JTTHF Total time	295.82 (89.91)	262.55 (91.15)	0.156	278.89 (96.37)	0.391	345.61 (114.08)	283.19 (87.25)	0.130
JTTHF time to lift large/ light object task	30.72 (15.25)	25.63 (15.83)	0.083	28.07 (16.08)	0.512	49.71 (26.75)	31.87 (22.27)	0.426
CHEQ	2.32 (0.41)	3.02 (0.24)	0.083	3.24 (0.20)	0.134	3.05 (0.36)	3.35 (0.29)	0.048

Table 3-1: Average clinical scores for CIMT-treated and control groups at baseline, 1-month and 6-months later. *P* values represent paired samples t-test significance between the differences in baseline and 1-month scores, as well as baseline and 6-months.

While considering the results given throughout this section, it is important to note that some subjects have missing clinical data because it wasn't collected properly or simply wasn't gathered. In the CIMT-treated group, strong grip strength and CHEQ scores were only acquired for 5/7 subjects, while the control group didn't acquire any AHA scores and one subject's follow-up COPM score.

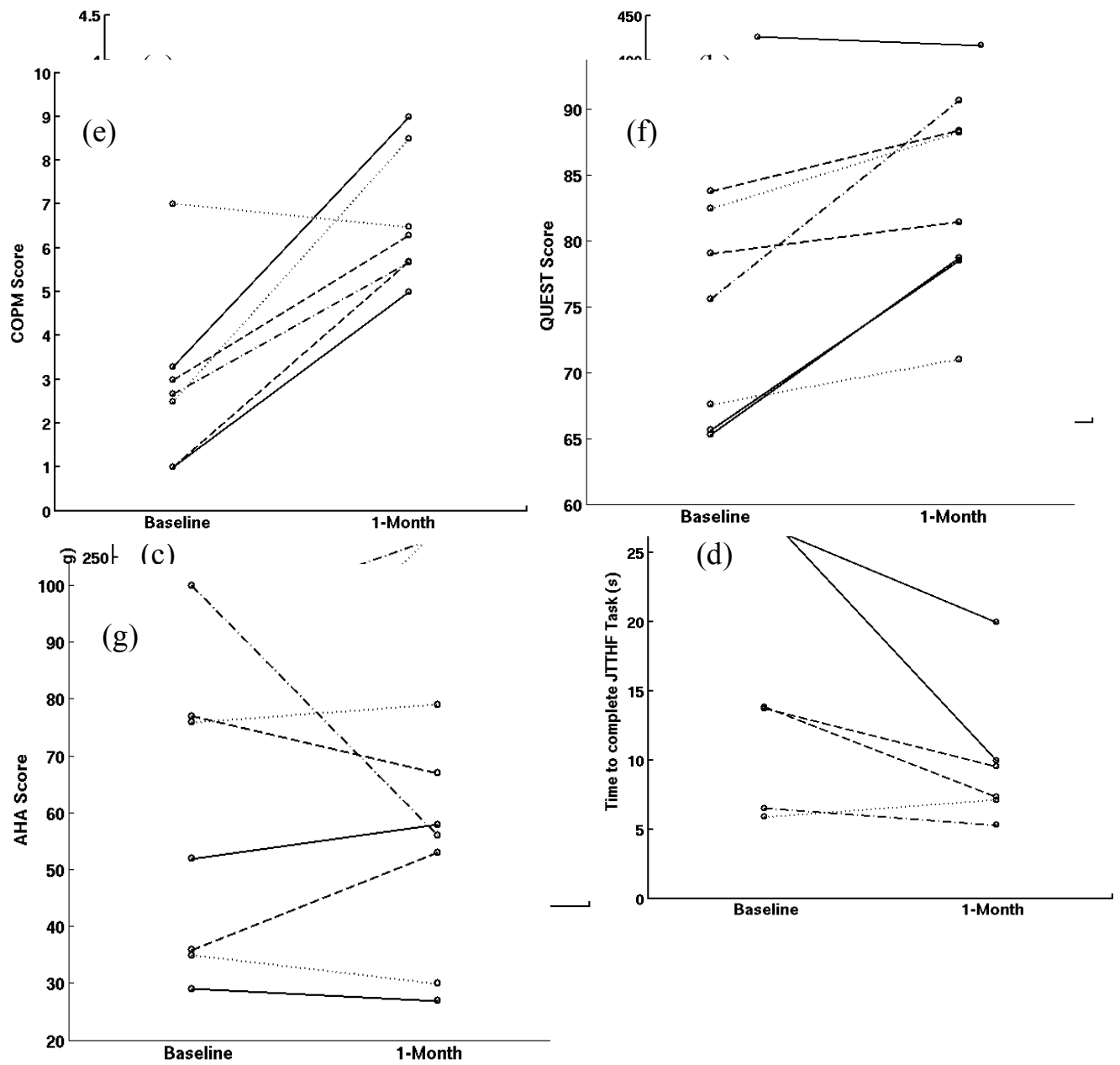
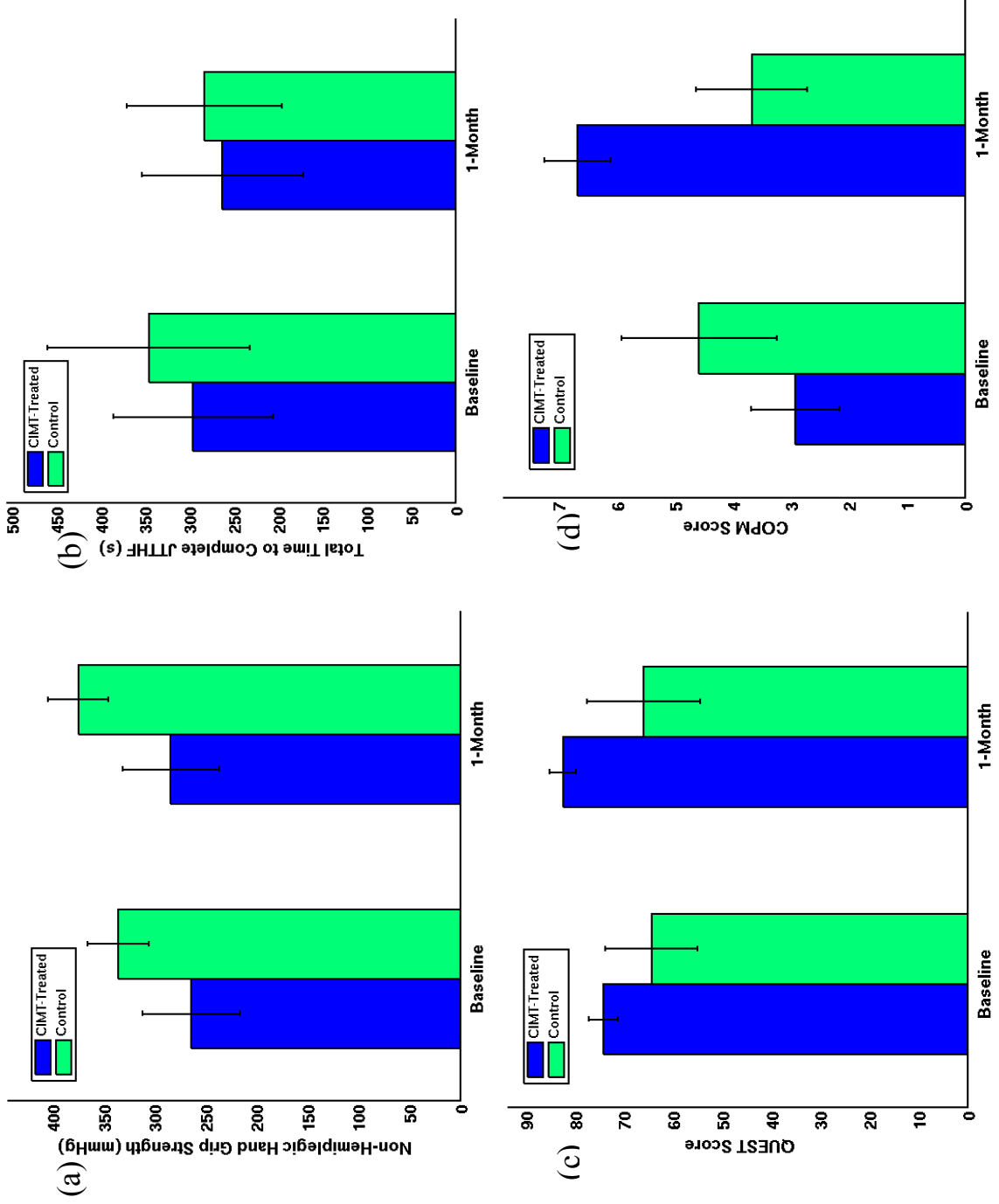


Figure 3-1: Clinical paired samples t-test between CIMT-treated clinical scores at baseline and 1-month, each line represents an individual subject's data.



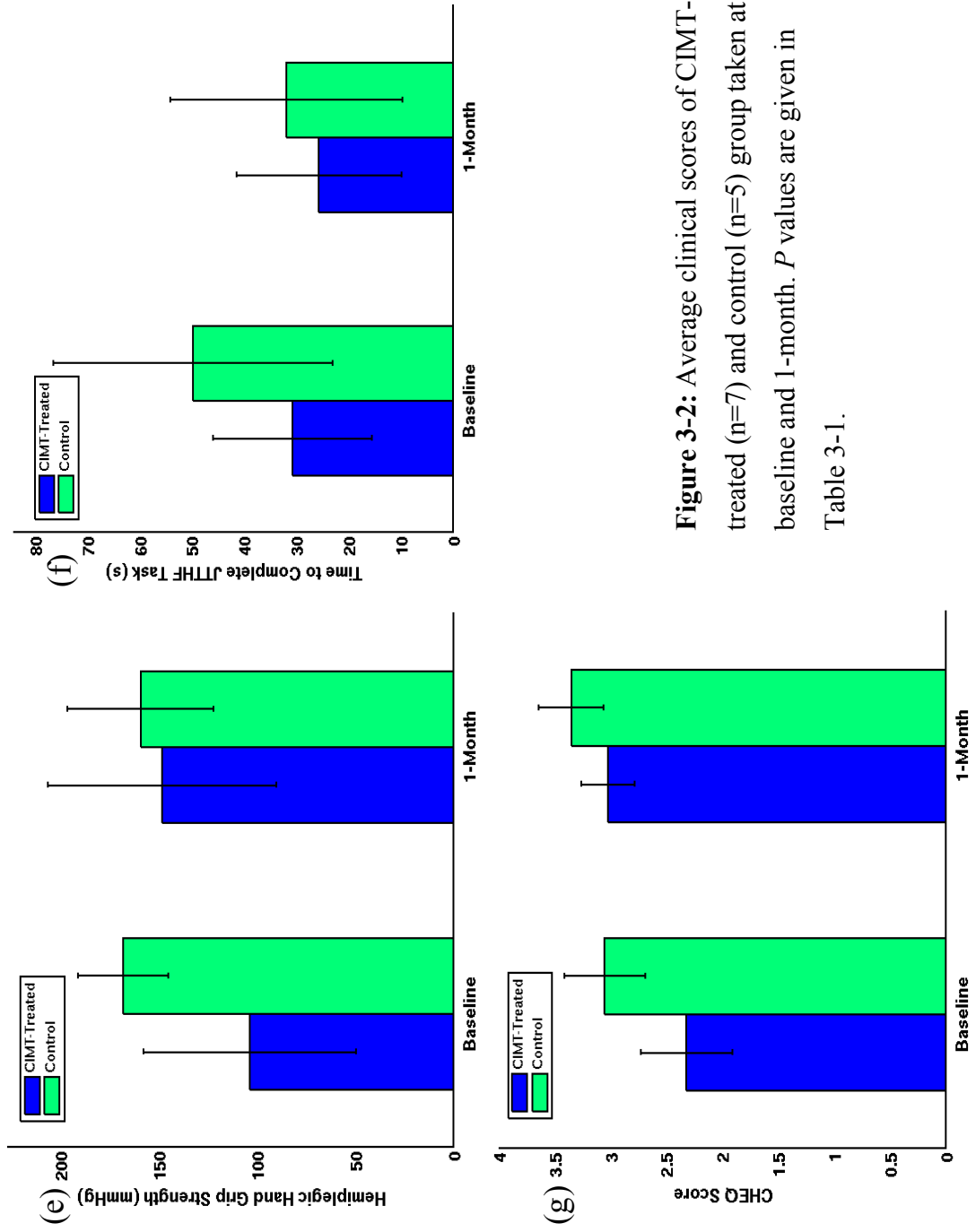


Figure 3-2: Average clinical scores of CIMT-treated (n=7) and control (n=5) group taken at baseline and 1-month. *P* values are given in Table 3-1.

3.2.2 MR Results

3.2.2.1 Anatomical

Several different types of anatomical images are shown in Figure 3-3 for a representative subject; (a) a T2-weighted turbo spin echo, (b) T2-weighted FLAIR, and (c) a T1-weighted MPRAGE image.

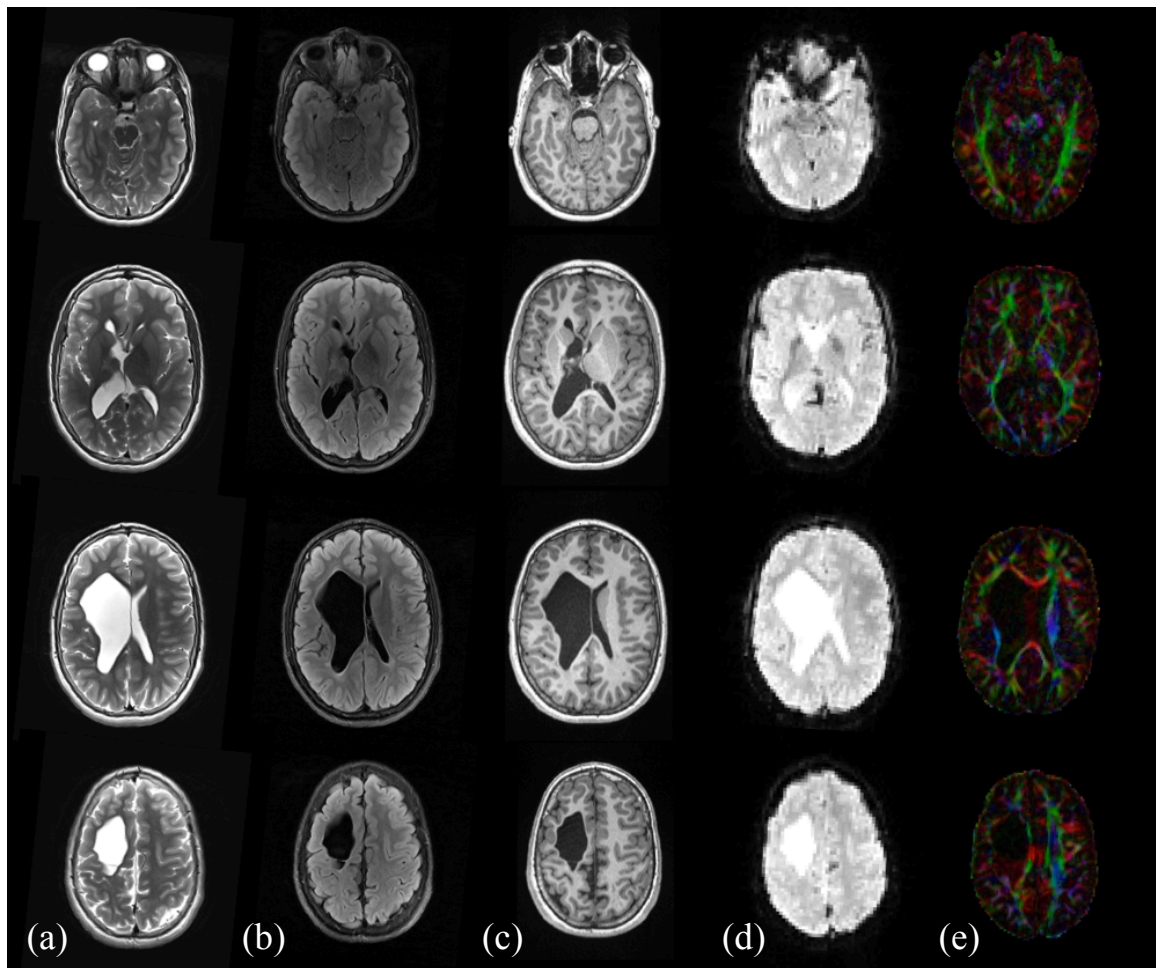


Figure 3-3: Three different anatomical images ((a), (b), (c)), a single EPI volume (d) and an FA color map (e).

These were used for registration of functional EPI and diffusion data (Figure 3-3) to standard space, identifying CST regions of interest, and for lesion volume calculations. Lesion volume is an important clinical measure that quantifies the amount of structural damage in CP patients, though the time of onset (Staudt, Gerloff, et al. 2004) and position of damage (Sterr, et al. 2010) are more indicative of functional damage. The lesion volume for each participant is given in Table 2-1.

3.2.2.2 Reorganization of RSNs in hemiplegic CP

The sensorimotor RSN often had altered connectivity patterns because of the cortical and/or subcortical damage. Hemiplegic CP patients had baseline sensorimotor RSNs that ranged from unilateral connectivity patterns favoring the contralesional hemisphere to bilateral, symmetric RSNs as seen in healthy subjects (Smith, Fox, et al. 2009). The healthy resting state motor network encompasses areas pre and post central gyrus (primary motor and sensory areas respectively) and the supplementary motor area (SMA). Connectivity patterns may be displaced in individuals with hemiplegic CP because of the subcortical injury and the ipsilesional hemisphere is generally less involved, or connectivity patterns are displaced about the lesion. Figure 3-4 (a-d) shows the baseline sensorimotor RSN in a few representative subjects from our study, with areas of connectivity shown in colour and scaled by z-statistic, and overlaid on the corresponding brain-extracted anatomical image.

Though this research focuses on alterations in the sensorimotor RSN, other networks may also be affected depending on the lesion position and volume. For example, the default mode and the lateral visual RSNs may have less ipsilesional hemisphere involvement, as shown in two example subjects overlaid on an MNI standard space brain image in Figure 3-4 (e) and (f), respectively. Hemiplegic CP patients often experience other complications along with upper limb impairment and could be related to these alterations in neural communication.

3.2.2.3 Diffusion results

As observed in previous DTI studies with CP subjects (Thomas, et al. 2005; Hoon, et al. 2009), the affected CST had slightly different FA and MD values at all three individual ROIs with generally lower FA and higher MD in the affected tract compared to the contralesional tract. In particular, when investigating baseline diffusion data from both subject groups there was a significant difference between the FA ($p = 0.010$) and the MD in the midbrain ROI along the CST ($p = 0.034$). Other ROIs had only near significant differences between the FA and MD values of the tracts; the pons FA ($p = 0.127$) and MD ($p = 0.098$) and the posterior limb of the internal capsule (PLIC) FA ($p = 0.101$) and MD ($p = 0.093$). Average FA and MD values for each subject group and tract are shown in Table 3-2.

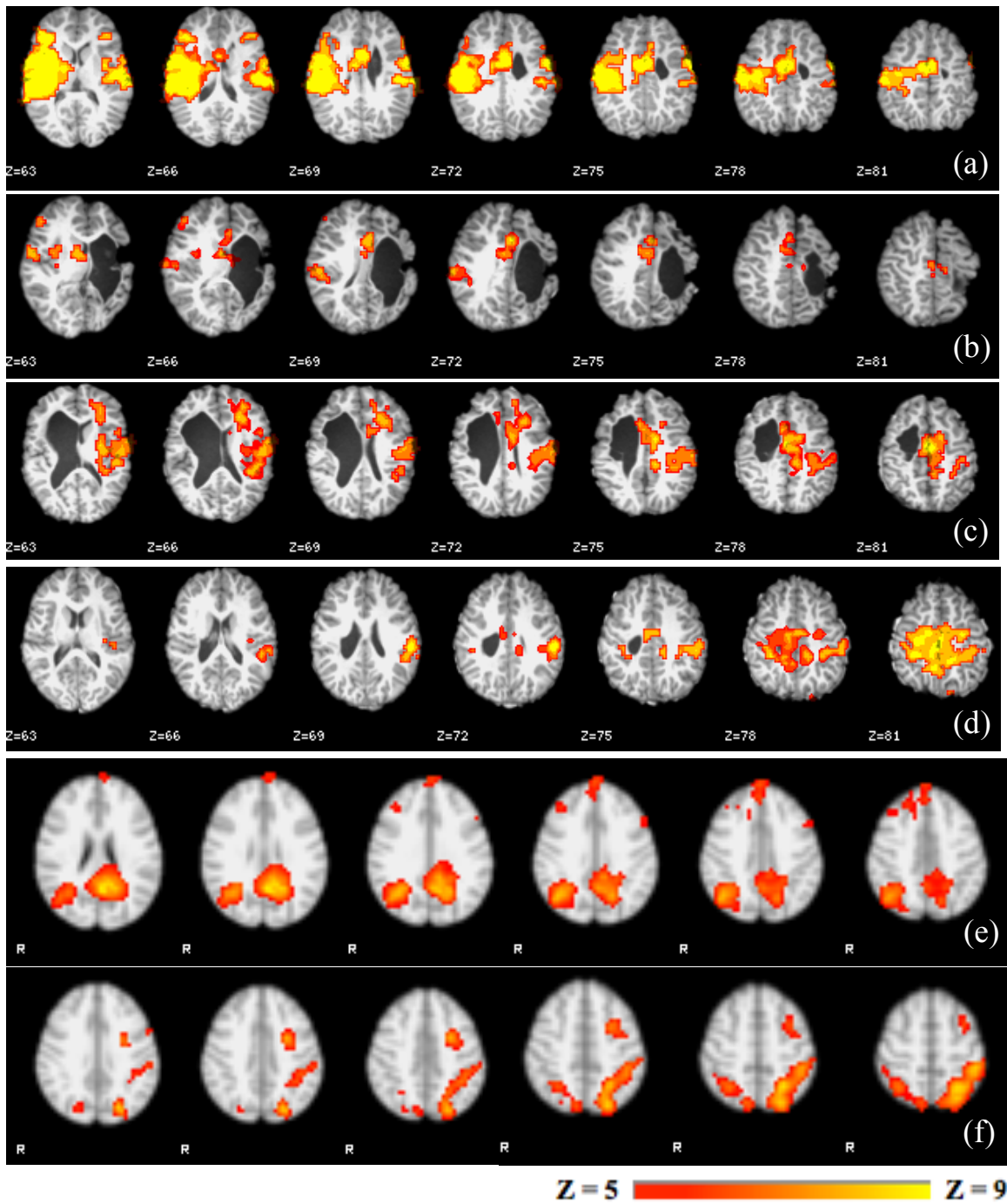


Figure 3-4: Altered baseline resting state connectivity maps in a few representative subjects. Sensorimotor (a-d), default mode (e), and lateral visual RSNs are more unilateral than healthy controls because of lesion damage in the ipsilesional hemisphere, coloured by z-statistic.

Table 3-2: Average diffusion FA and MD values for both groups at three regions of interest along the ipsilesional and contralesional CSTs. Standard deviations are shown in brackets and MD values are 10^{-3} .

ROI	Treated baseline affected	Treated 1-month	Treated 6-month	Control baseline	Control 1-month
FA PLIC affected	0.34 (0.0627)	0.356 (0.0639)	0.331 (0.0747)	0.329 (0.0847)	0.311 (0.0741)
FA PLIC unaffected	0.398 (0.0670)	0.398 (0.0922)	0.392 (0.0714)	0.354 (0.0705)	0.330 (0.0707)
MD PLIC affected	0.926 (0.176)	0.905 (0.216)	0.957 (0.156)	0.883 (0.0995)	0.896 (0.145)
MD PLIC unaffected	0.840 (0.100)	0.854 (0.191)	0.860 (0.144)	0.847 (0.0274)	0.817 (0.0309)
FA midbrain affected	0.337 (0.0572)	0.379 (0.0870)	0.373 (0.0746)	0.406 (0.0999)	0.414 (0.0603)
FA midbrain unaffected	0.469 (0.0593)	0.499 (0.117)	0.465 (0.0396)	0.435 (0.0717)	0.503 (0.0507)
MD midbrain affected	1.33 (0.336)	1.22 (0.420)	1.29 (0.303)	1.17 (0.210)	1.09 (0.147)
MD midbrain unaffected	0.963 (0.208)	0.975 (0.257)	0.997 (0.177)	1.10 (0.282)	0.971 (0.167)
FA pons affected	0.381 (0.0802)	0.387 (0.0965)	0.374 (0.113)	0.358 (0.110)	0.417 (0.0376)
FA pons unaffected	0.458 (0.0399)	0.462 (0.0800)	0.439 (0.0591)	0.424 (0.101)	0.511 (0.0365)
MD pons affected	1.04 (0.282)	1.02 (0.348)	1.08 (0.341)	0.841 (0.389)	0.943 (0.114)
MD pons unaffected	0.810 (0.101)	0.904 (0.230)	0.897 (0.148)	0.833 (0.352)	0.793 (0.0635)

3.2.3 MR predictors of greater functional improvements following CIMT

The clinical change scores referenced here are simply the difference between scores assessed at baseline and 1-month follow-up. Baseline LIs describing the ICA-derived sensorimotor RSN based on the number of voxels in motor areas were most correlated with clinical results, as shown in Figure 3-5. Specifically, the LI based on activated voxels correlated with the COPM change score ($r = -0.748, p = 0.053$) and the JTTHF task ($r = 0.722, p = 0.067$). The LI based on activated voxels with a 200-voxel cluster threshold rendered significant results when correlated with the change in COPM score ($r = -0.814, p = 0.026$). The seed-based sensorimotor network's LI based on signal intensities was similarly correlated with increasing QUEST scores ($r = -0.791, p = 0.034$). The MD in the PLIC ROI of the affected CST was indicative of improved hemiplegic hand efficiency as evaluated by the change in time to complete the JTTHF task ($r = -0.832, p = 0.020$). All correlations between baseline MRI data and clinical changes with $p < 0.1$ are given in Table 3-3.

Lower clinical baseline scores were correlated with clinical changes evaluated using COPM and CHEQ. In particular, the difference in COPM average performance scores was predicted by low baseline COPM ($r = -0.745, p = 0.055$), QUEST ($r = -0.672, p = 0.098$), and AHA ($r = -0.701, p = 0.079$) and the change in CHEQ scores were negatively correlated with the CHEQ baseline score ($r = -0.820, p = 0.089$). As presented in Section 3.2.1, the COPM measure was the only clinical result at 6-months post-CIMT that was significantly different from the baseline scores. All other 6-month clinical data

was not significantly different from baseline ($p > 0.1$) and predictors were not considered. The change in COPM score at 6-months was correlated with the baseline LI based on the number of above-threshold voxels ($r = -0.674, p = 0.097$) and a low baseline QUEST score ($r = -0.705, p = 0.077$). These relationships are similar to the correlations between baseline data and 1-month clinical change scores.

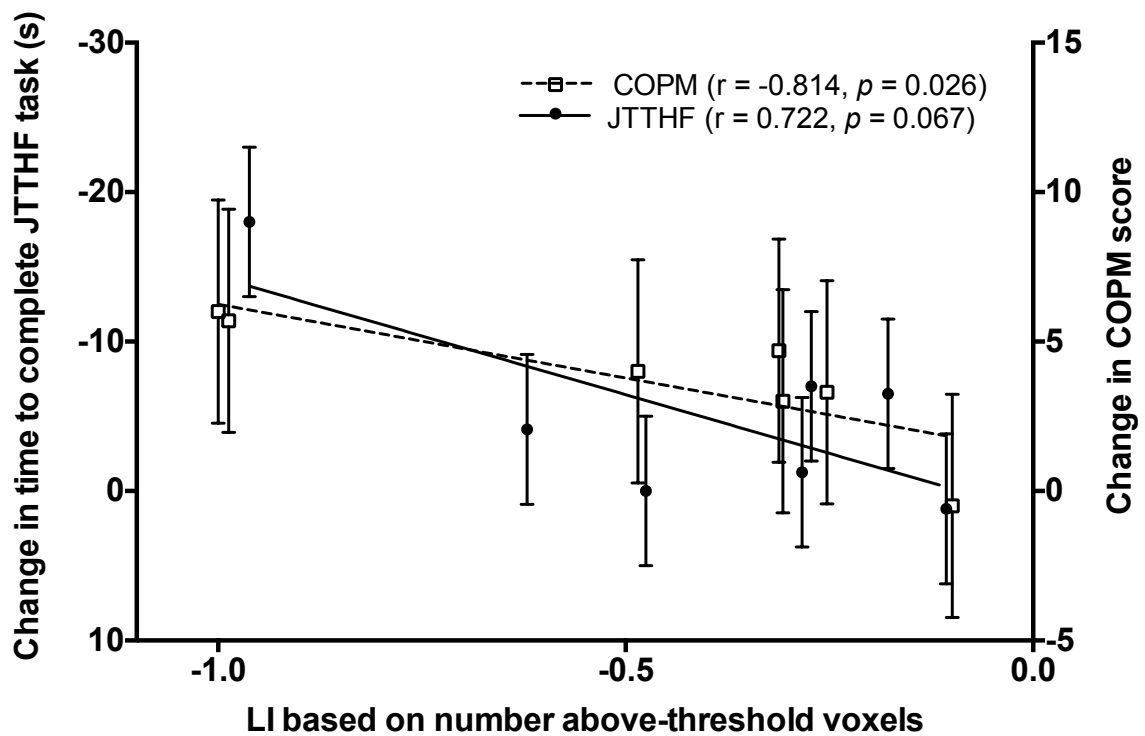


Figure 3-5: The relationship between the change in clinical scores (JTTHF on the left axis, COPM on the right) and a baseline LI based on the number of above-threshold voxels identified as the sensorimotor network.

3.2.4 Correlated changes

All average MRI data is given in Appendix E. The CIMT-treated sensorimotor networks are shown in Figure 3-8 for each subject, and the control group RSNs are shown in Appendix D. According to paired samples t-tests, CIMT-treated subjects had a trend towards significant differences in ICA-derived sensorimotor network reorganization quantified by an LI based on the number of voxels ($p = 0.120$) and the number of voxels with a 200-cluster threshold ($p = 0.070$) at 1-month.

Table 3-3: A summary of the prediction correlation analysis where baseline MRI data correlated with clinical change scores. All correlations with $p < 0.1$ are reported here.

Baseline MRI predictor	Clinical change (Follow-up – baseline score)	Pearson Correlation (r)	Two-tailed significance p - value
Lesion volume	CHEQ	0.837	0.077
LI based on signal intensity (seed-based)	QUEST	-0.791	0.034
LI based on above-threshold voxels	COPM	-0.748	0.053
LI based on above-threshold voxels	Time to complete JTTHF task	0.722	0.067
LI based on above-threshold voxels with minimum cluster size	COPM	-0.814	0.026
FA in the lesion	CHEQ	-0.912	0.031
MD in affected tract's PLIC	Time to complete JTTHF task	-0.832	0.020

At the 6-month follow-up MRI this difference persisted and was significantly different from baseline LIs ($p = 0.036$ and $p = 0.034$, respectively). A regression analysis of the average LI of each group over all timepoints revealed a significant difference between the coefficients or slopes of each group ($p = 0.007$) (Figure 3-6). The correlation decreased between the SMA and both the contralesional ($p = 0.009$) and ipsilesional ($p = 0.056$) motor areas at 1-month follow-up. Seed-based and diffusion data remained statistically unchanged after therapy. Control subjects' MRI data all remained unchanged when comparing baseline and 1-month follow-up data.

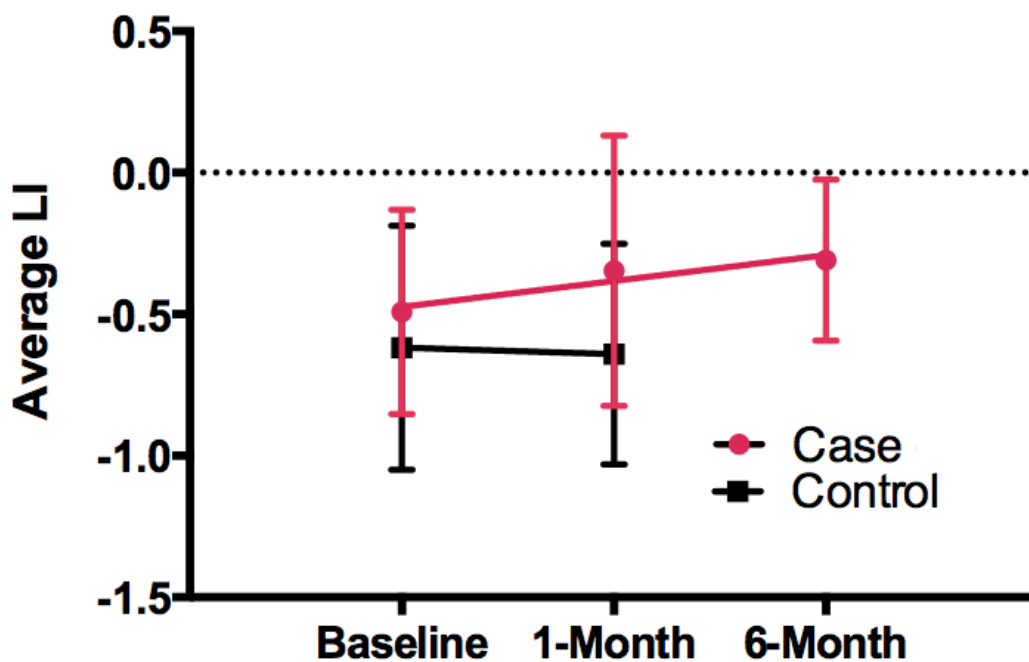


Figure 3-6: Regression analysis of the average LI (with a cluster threshold) for both the CIMT-treated (case) and control groups. The slope of the case group (0.091 (SEM = 0.029) and the control group (-0.020 (0.00)) were significantly different according to a student t-test ($T=3.46$, $p = 0.007$).

3.2.4.1 1-month after baseline

The change in QUEST score was correlated with the change in LI based on active voxels in the ICA-derived sensorimotor RSN at 1-month follow-up ($r = 0.789, p = 0.062$). The change in COPM score was similarly related to the change in LI based on z-statistic ($r = 0.798, p = 0.057$). The change in correlation strength between SMA and ipsilesional motor areas was related to the change in COPM score ($r = 0.739, p = 0.093$).

Correlations between the contralesional motor area and SMA were related to the change in time to complete the JTTHF task ($r = -0.827, p = 0.042$) and the total JTTHF time ($r = -0.850, p = 0.032$).

3.2.4.2 6-months after baseline

The change between 6-months follow-up and baseline LIs based on active voxels with a minimum cluster size of 200 voxels significantly correlated with the change in COPM score ($r = 0.819, p = 0.046$), as shown in Figure 3-7. Control group sensorimotor RSN organization is shown in Appendix D. The correlation with the same LI without a cluster threshold was not significant ($r = 0.739, p = 0.093$). Since COPM was the only score that was significantly different from baseline at 6-months, other correlations are not considered here, though they are reported in Appendix C.

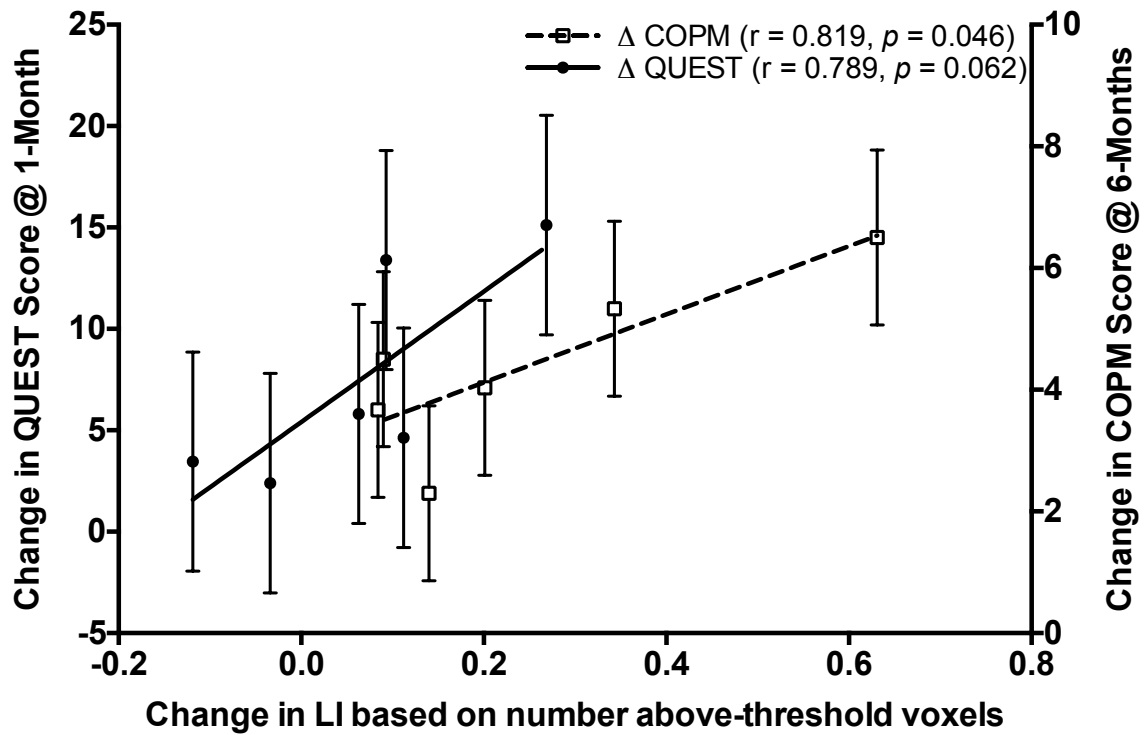
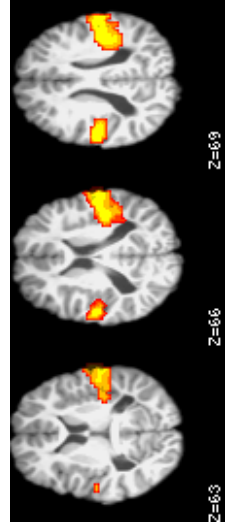
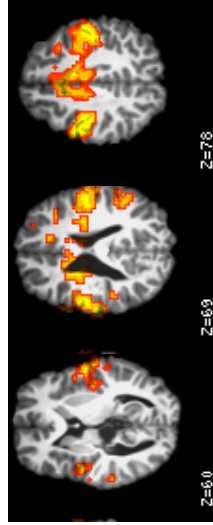
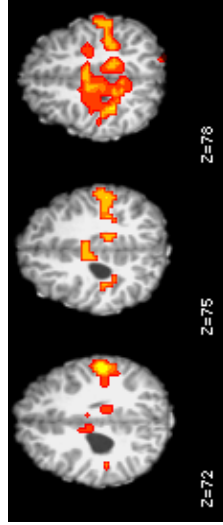
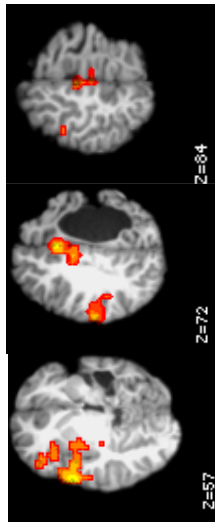
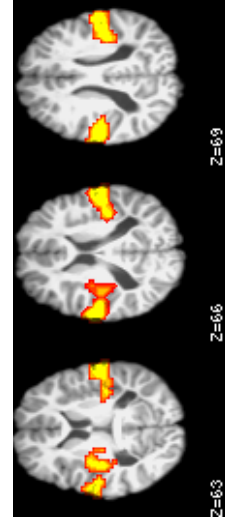
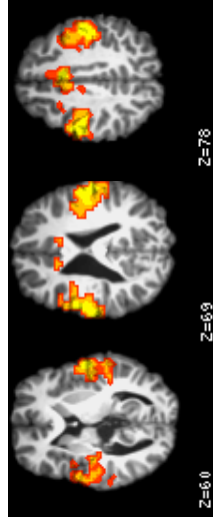
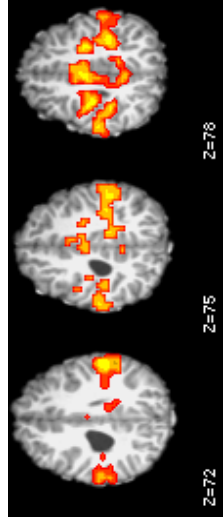
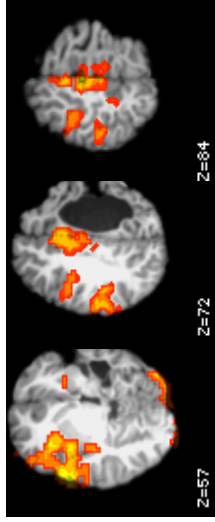


Figure 3-7: Correlated clinical and MR measures. The change in QUEST score at 1-month (shown on the left) and the change in COPM score at 6-months (right) correlated with the change in LI based on the number of above-threshold voxels identified as the sensorimotor network.

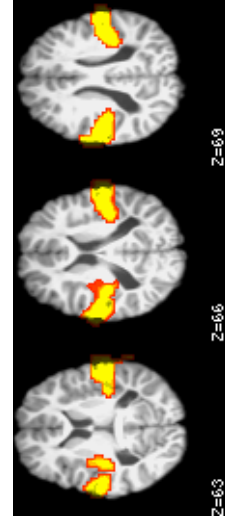
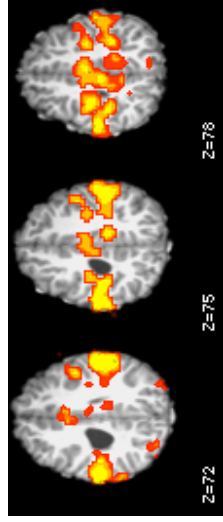
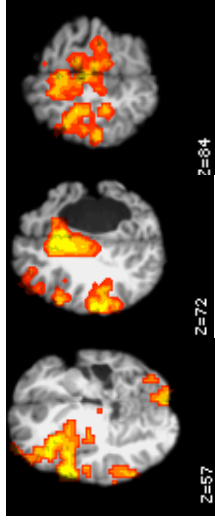
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1-MONTH



6-MONTHS



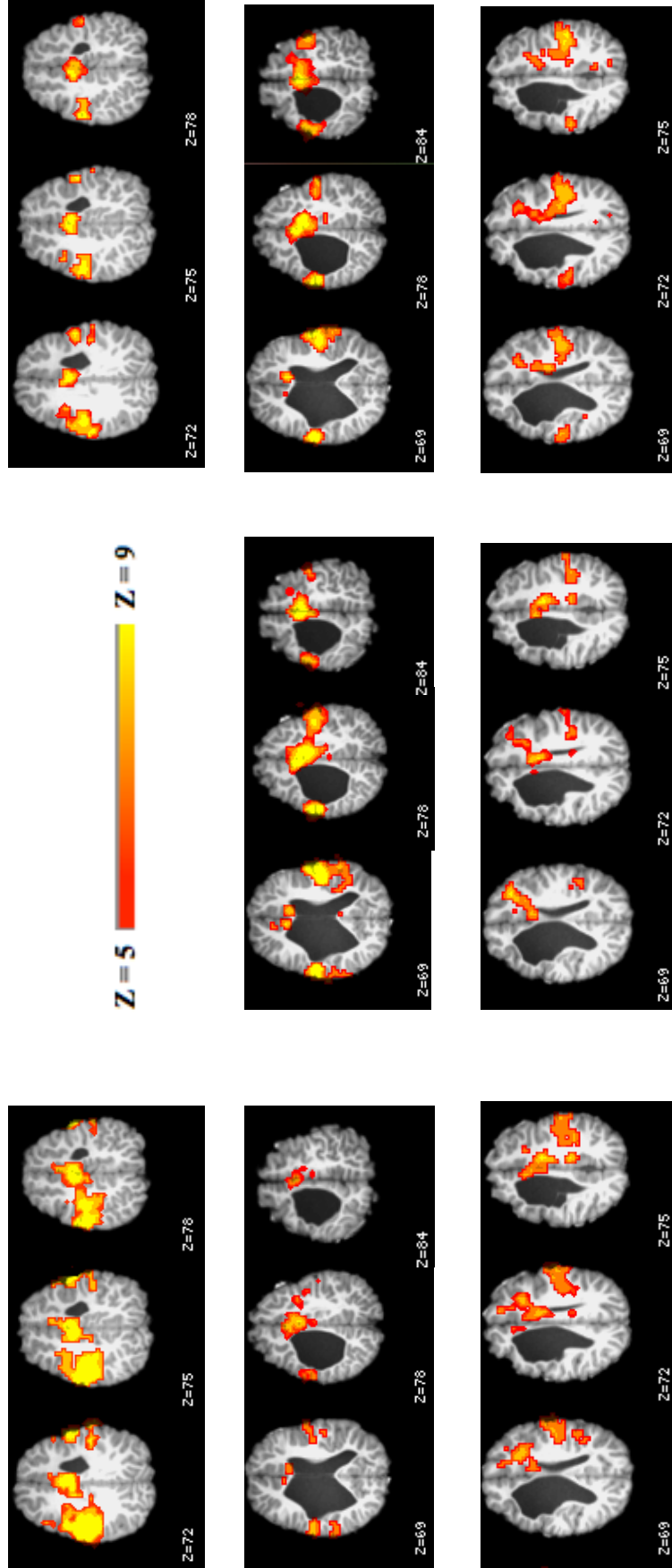


Figure 3-8: ICA-derived sensorimotor connectivity patterns (with a 200-voxel cluster threshold) of each of the CIMT-treated patients at baseline, 1-month and 6-months later. Note: two subjects moved excessively during one session each and their resting state fMRI was not included.

3.3 Discussion

Hemiplegic cerebral palsy patients experience impaired upper limb function and development because of the early onset of subcortical and/or cortical injury. Lesions were found around primary motor areas about the central gyrus and supplementary motor areas near the anterior cingulate. This injury severely affects the young developing brain, and resting state networks spatially reorganize about the lesion or within the unaffected hemisphere exclusively. The sensorimotor RSN connectivity pattern often reorganizes in hemiplegic CP patients, depending on the lesion volume and position. I have also shown that other networks can be affected including the default mode network and the lateral visual network. ICA-derived networks were less affected by motion compared to the seed-based analysis and resulted in clean maps representing sensorimotor connectivity patterns. The diffusion data revealed that the CST in the ipsilesional hemisphere tended to have lower FA values and increased MD, which is consistent with previous studies of hemiplegic CP.

Most patients improved across multiple clinical measures after CIMT, which agrees with previous literature on the effectiveness of this therapy. The modified CIMT camp improved many aspects of hand function that were assessed through these clinical evaluations. Only COPM and QUEST changed significantly however, though this could be attributed to the small group size. AHA scores, which reflect bimanual performance, did not improve after the modified CIMT camp as anticipated, though COPM and CHEQ scores indicated that at least some bimanual skills were improved. The control group's clinical scores all remained unchanged except for the CHEQ questionnaire, which could

have some bias because a parent or guardian completed it, and so the CHEQ score was not a reliable measure of improved bimanual ability. Six-months after CIMT, patient's clinical scores on average returned to baseline except for the COPM measure, which remained significantly different from baseline scores. This result is at first discouraging, but CIMT is more effective if applied multiple times or practice is continued in the home informally (Charles and Gordon 2005). This promotes further improvements and helps maintain the skills already learned through the treatment.

Lower clinical baseline scores were predictive of increased clinical improvements following CIMT. This relationship is important to take into account when considering the MRI baseline characteristics that predict a greater functional response to CIMT. Patients with a more unilateral, further compromised sensorimotor RSN improved the most clinically following constraint therapy. Individuals with symmetric RSNs tended to improve the least. A high MD in the affected CST was also indicative of improved efficiency. These relationships could be influenced by a ceiling effect where patients with lower baseline features have more room to improve compared to patients with high baseline clinical scores and a normal, bilateral sensorimotor RSN. Combining these results with previous literature leads to a model that takes both symptom severity and resting state network connectivity into account when attempting to predict a positive outcome following CIMT.

After CIMT, network connectivity patterns tended to become more bilateral and symmetric, along with improving clinical scores. This is evidence of neuroplasticity and reorganization following constraint therapy, as seen through previous studies using task-related fMRI (You, et al. 2005; Sutcliffe, et al. 2007; Mark, Taub and Morris, 2006) and

other modalities. There were a large number of correlations between changes in clinical data and changes in MRI resting state and diffusion data, which are reported in Appendix B. Many of these contradict each other, so focus was placed on correlations between parameters that changed significantly or near-significantly ($p < 0.1$) after therapy. Correlation strengths decreased after therapy, so the relationships between clinical change scores are relating less decreased network connectivity with improvement. However only one seed was chosen based on the ICA-derived sensorimotor network nodes and though changes in seed placement and size could influence these results, alternate seeds were not pursued to avoid bias. The control subjects clinical and MRI data remained statistically unchanged between baseline and 1-month follow-up. Resting state fMRI acquisition is more practical and reliable when compared to task-based studies, especially in this subject group with a range of symptom severities. Similar to the results of Cope et al., subjects with moderate clinical measures (considered low in our study given the high baseline clinical scores), compromised sensorimotor network connectivity patterns and ipsilesional CST improved the most clinically following CIMT. Consideration of multiple factors like clinical baseline scores, the amount of ipsilesional motor area involvement in network organization, and quantitative DTI measures of neural integrity will together predict a positive response most accurately.

3.4 References

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4 Conclusions

4.1 Summary

Individuals with hemiplegic CP experience impaired hand and arm function because of subcortical and/or cortical injury prenatally or during early development (Rosenbaum, Paneth, et al., 2006). They often compensate for the hemiplegic limb by performing most tasks with their unaffected limb. This behavior can lead to learned non-use, where the hemiplegic limb is further inhibited from healthy development (Charles and Gordon 2005; Hoare, et al. 2009; Taub, Ramey, et al. 2004). CIMT is an effective therapy for individuals with CP or recovering from stroke (Novak, McIntyre, et al., 2013). It directly combats learned non-use by repetitively forcing the participant to use their hemiplegic limb. The adapted CIMT model used in this study was catered to accommodate young children and youths in a camp format with games, challenges and group activities directed towards practicing and improving various aspects of hand and arm function. Though many individuals benefit from this therapy, there are some patients who do not (Cope, et al. 2010). The therapy itself can be demanding and

requires a substantial amount of time and planning for both the family and occupational therapists.

Previous studies have investigated task-based fMRI and DTI for evidence of neuroplastic changes and predictors of success following CIMT in stroke and mild traumatic brain injury with various results because of the multitude of factors involved. Little is known about the global reorganization of network connectivity in light of cerebral palsy related lesion damage. Though some diffusion predictors have been proposed, there is still not a clear understanding of the relationships between neural integrity, disease severity, and clinical outcome. To the best of our knowledge, this is the first study to investigate resting state fMRI predictors of a greater positive response to CIMT in hemiplegic CP subjects and to assess clinically correlated resting state neuroplasticity.

Though task-based fMRI experiments have shown evidence of reorganization both because of injury and treatment, they inherently suffer in both applicability and accuracy due to task-related motion artifacts, consistent patient-suitable tasks, and lack of global information (Carter, Shulman and Corbetta, 2012). Despite training, monitoring, and practice, our subjects struggled to complete the task without moving excessively, especially with their hemiplegic limb. Resting state fMRI and DTI are acquired while the patient is simply asked to remain still. Two different analysis approaches are widely used; seed-based analysis and a data-driven ICA approach. Though the two techniques render consistently similar results the former is strongly affected by motion artifacts, seed placement and size, and a specific hypothesis-based approach (Ma, et al. 2006). ICA is much less affected by noise artifacts and allows the investigator to explore many aspects

of neural organization, and dual regression algorithms allow a clear comparison of networks before and after CIMT (Beckmann, DeLuca, et al. 2004). This is a useful tool that would be easy to implement in a clinical setting and could give valuable information for understanding other symptoms or deciding if CIMT is an appropriate treatment option.

Almost all participants improved across various clinical measures following constraint therapy, however some 6-month follow-up results indicate a regression back towards baseline levels. This is to be expected with CIMT, as it is a treatment that should be repeated, practiced, and continued to maintain functional gains and promote further improvements (Charles and Gordan 2007). The control group's clinical results remained statistically unchanged at the 1-month follow-up evaluation.

Resting state fMRI revealed multiple reorganized baseline network connectivity patterns including the sensorimotor, lateral visual, and default mode RSNs in some cases, where extended areas of the contralesional hemisphere and about the lesion appear to compensate for the areas of subcortical and/or cortical damage. DTI analysis revealed differences between the FA and MD values in the ipsilesional CST compared to the unaffected tract, as shown in previous studies of CP subjects (Trivedi, et al. 2008; Yoshida, Hayakawa, et al. 2010; Thomas, et al. 2005)

Several baseline MRI predictors were correlated with increased functional changes measured through multiple clinical measures. In general, subjects with lower clinical baseline scores, asymmetric sensorimotor organization and increased MD values within the affected CST tended to improve the most after CIMT. Baseline resting state

LI based on the number of voxels in the ICA-derived sensorimotor network were predictive of positive and continuing individualized gains as measured by the COPM. These relationships could be impacted by a ceiling effect because this small group of subjects had high clinical baseline scores (according to QUEST) and some may have had little room to improve. Previous studies of DTI predictors have revealed that more intact tracts promote the reorganization mechanism implied with constraint (Trivedi, et al. 2008). Ceiling and floor effects can make it difficult to come to a consensus on these results across multiple studies, and it has been suggested that focusing on follow-up scores could eliminate this problem (Marumoto, et al. 2013). However, this is not a true testament of individual subject improvement. The result of this study in conjunction with other literature suggests the need for consideration of multiple aspects of an individual patient to determine if CIMT is appropriate. A model that relates baseline disease severity through clinical evaluations, resting state fMRI, and DTI with success after CIMT may give the most accurate prediction of functional improvement. This small study of seven subjects is not large enough to justify performing regression analysis with multiple predictors included, though it was explored. There were some significant relationships that included baseline clinical and MRI scores, however individual factor contributions were only variably significant.

Follow-up scans 1-month after baseline revealed clinically correlated resting state network reorganization after CIMT. This provides further evidence of the neuroplastic mechanisms of this therapy, which compliment previous studies using other modalities and task-based fMRI experiments to reveal neural reorganization in these subjects (Sterling, et al. 2013; Mark, Taub and Morris, 2006). The ipsilesional hemisphere

becomes less involved and regains contralateral control. DTI FA and MD values within both tracts remained statistically unchanged, except in the midbrain ROI. At the 6-month follow-up evaluation, only COPM was still significantly different from baseline clinical scores and was similarly predicted by asymmetric baseline sensorimotor organization and low baseline clinical scores. Network reorganization remained significantly different from baseline LIs, and was correlated with maintained COPM performance measures.

4.2 Limitations

There are several limitations to this study that are important to consider while interpreting results. The main limitation of this study is the size of each subject group. Recruitment efforts were extensive but the subject requirements limited the number of potential candidates while a number could not successfully participate in the MRI portion because of commuting issues, medical reasons, or excessive motion during the scan despite training and monitoring. Resting state analysis was completed for each single subject and group analysis was not possible due to the small amount of subjects and large variation in anatomy and lesion sizes. This group had a small range of high baseline QUEST scores, which also could have influenced results. Consequently, the CIMT-treated group could not be split further into groups of responders and non-responders. However, these limitations did reveal the need for consideration of baseline clinical measures when interpreting resting state fMRI and diffusion predictors of increased functional gains following CIMT in individuals with hemiplegic CP.

4.3 Future Work

To fully understand the relationship between disease severity, neuroimaging predictors and correlated neuroplastic changes a larger group of subjects with a wider range of clinical baseline scores is necessary. It would also be interesting to gather data at multiple follow-up timepoints to understand how often constraint should be repeated, and explore how effective continued practice in the home is compared to the repetition of formal treatments. Resting state fMRI and DTI could easily be implemented in a clinical setting and are applicable to a wide range of subjects regardless of disease severity or their ability to perform a specific task. Information gathered through these two acquisitions could be useful in conjunction with clinical measures to determine if CIMT is an appropriate treatment for a particular subject with hemiplegic CP. Though there are no known negative consequences to CIMT, it requires a huge effort from the patient, their family, the occupational therapist, and the health care system. A clear relationship between multiple baseline predictors and success with this type of therapy would be extremely useful when identifying suitable patients for CIMT.

The effect size was quite large given the number of subjects included in the study. This provides a good indication of the value of resting state fMRI in evaluating these subjects for viable treatments, and for understanding neural reorganization following CIMT. A larger sample size with a greater range of baseline clinical scores would be optimal. A sample size calculation showed that about 25 subjects in each group would be required to reliably have significant differences in resting state fMRI LIs, and though this amount of subjects was attempted, many could not participate for a number of different

reasons like failing to meet inclusion criteria, inability to travel to London for scanning sessions, and excessive motion during the scan itself.

Resting state fMRI has emerged as a reputable tool to study a multitude of disease states including Alzheimer's disease, multiple sclerosis, depression, schizophrenia, stroke, autism, epilepsy, and ADHD (Auer 2008). Future studies of subjects before and after concussion using similar resting state and DTI analysis techniques will be used to understand the neurophysiology of concussion and recovery. Resting state fMRI allows the investigator to explore the global effects of various disease states and injuries. CIMT-induced clinical and resting state fMRI correlated changes are promising evidence of neural reorganization and plasticity in young subjects with hemiplegic cerebral palsy. The relationship between baseline neuroimaging predictors and an increased functional response to CIMT supplicate the need for consideration of multiple baseline characteristics when identifying potential suitable patients.

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Appendices

Appendix A: Average clinical scores of all CIMT-treated (n = 14) and control subjects (n = 8), even if they did not participate or had unsuccessful MRI scanning sessions.

Clinical Test	Average baseline before CIMT	Average 1-month post-CIMT	Average 6-month post-CIMT	Average control baseline	Average control 1-month later
QUEST	75.67 (9.64)	80.32 (10.80)	80.64 (12.07)	60.59 (11.98)	62.97 (16.44)
COPM Performance	3.25 (1.97)	6.75 (1.38)	6.55 (1.80)	3.95 (2.10)	3.78 (1.41)
Weak grip strength	94.35 (49.02)	118.31 (80.08)	107.71 (64.74)	98.67 (74.38)	101.67 (92.10)
AHA Scaled Score	54.07 (21.80)	53.92 (18.08)	52.38 (20.59)	Not collected	Not collected
JTTHF Total Time (s)	338.70 (234.59)	277.00 (200.22)	289.91 (210.26)	503.44 (215.85)	428.74 (197.96)
JTTHF Task (s)	48.12 (48.71)	30.46 (39.18)	36.70 (46.73)	78.50 (52.86)	56.67 (58.04)
CHEQ Performance	1.86 (1.22)	2.34 (1.20)	2.84 (0.82)	2.82 (0.89)	2.64 (0.98)

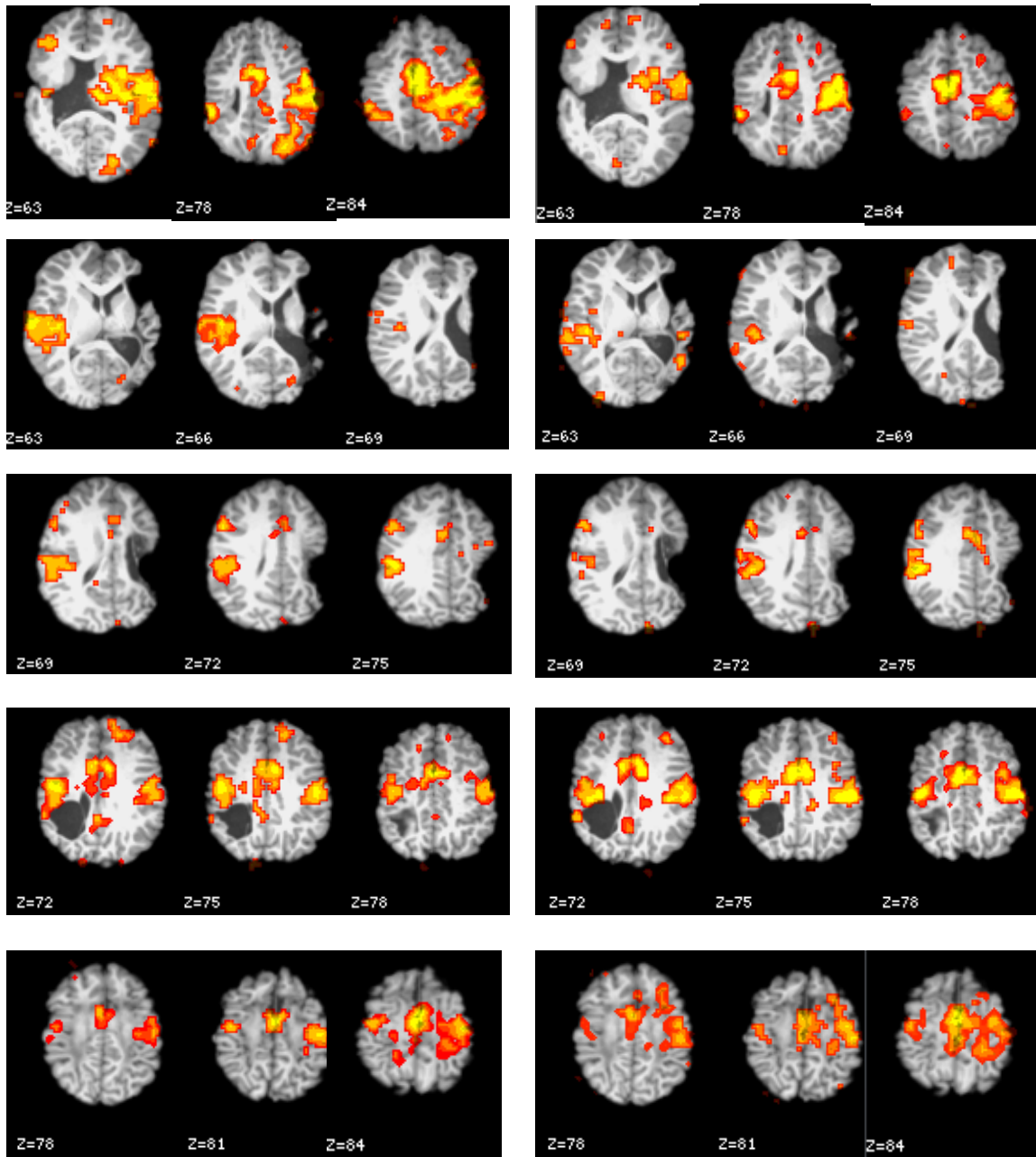
Appendix B: Correlations between clinical and MRI data at 1-month with a two-tailed t-test significance of $p > 0.1$.

Clinical Change @ 1-Month	MRI change @ 1-Month	Pearson correlation coefficient (r)	Two-tailed significance p -value
Weak grip strength	Correlation between SMA and ipsilesional motor area	-0.865	0.026
	MD PLIC (ipsilesional)	-0.701	0.079
	FA midbrain (ipsilesional)	0.854	0.014
	MD midbrain (ipsilesional)	-0.912	0.004
	FA pons (ipsilesional)	0.907	0.005
	MD pons (ipsilesional)	-0.847	0.016
	FA PLIC (contralesional)	0.695	0.083
	FA midbrain (contralesional)	0.779	0.039
	MD pons (contralesional)	-0.722	0.067
COPM	Correlation between SMA and ipsilesional motor area	0.739	0.093
	LI z-statistic	0.798	0.057
	FA midbrain (ipsilesional)	-0.909	0.005
	MD midbrain (ipsilesional)	0.925	0.003
	FA pons (ipsilesional)	-0.797	0.032
	MD pons (ipsilesional)	0.734	0.060
	MD PLIC (contralesional)	0.750	0.052
	FA midbrain (contralesional)	-0.867	0.012
MD pons (contralesional)	0.690	0.086	
QUEST	LI above-threshold voxels	0.789	0.062
	LI z-statistic (seed-based)	-0.888	0.018
CHEQ	FA PLIC (contralesional)	0.691	0.085
	MD PLIC (contralesional)	-0.910	0.004
	FA midbrain (contralesional)	0.803	0.030
JTTHF Task (s)	MD midbrain (contralesional)	-0.691	0.086
	Correlation between SMA and contralesional motor area	-0.850	0.032
	FA pons (contralesional)	0.772	0.042
	MD pons (contralesional)	-0.853	0.015
	JTTHF Total Time (s)	Correlation between SMA and contralesional motor	-0.827

Appendix C: Correlations between clinical and MRI data at 6-months with a two-tailed t-test significance of $p > 0.1$.

Clinical Change @ 6-months	MRI change @ 6-months	Pearson correlation coefficient (r)	Two-tailed significance p -value
Weak grip strength	MD midbrain (contralesional)	-0.765	0.045
	LI z-statistic	-0.774	0.071
COPM	LI above-threshold voxels with minimum cluster size	0.819	0.046
	LI above-threshold voxels	0.739	0.093
	FA PLIC (contralesional)	0.709	0.074
QUEST	LI z-statistic (seed-based)	0.740	0.093
	Correlation between SMA and contralesional motor area	0.821	0.045
	MD midbrain (contralesional)	-0.806	0.028
CHEQ	MD midbrain (ipsilesional)	-0.728	0.063
Time to complete JTTHF task	LI active voxels (seed-based)	0.807	0.052
	FA pons (contralesional)	0.802	0.030
	MD pons (contralesional)	-0.750	0.052
	FA midbrain (ipsilesional)	0.776	0.040

Appendix D: ICA-derived sensorimotor RSN of each control subject at baseline (left column) and 1-month follow-up (right column).



Appendix E: Average MRI data with standard deviations shown in brackets. Paired-samples t-test significance values are shown for both CIMT-treated ($n = 7$) and control groups ($n = 5$).

	LI based on signal intensity	LI based on z-statistic	LI based on the number of voxels with a cluster threshold	LI based on the number of voxels	LI based on signal intensity (seed-based)	LI based on z-statistic (seed-based)	LI based on number of voxels (seed-based)	MRI measure
	0.0316 (0.0380)	-0.0236 (0.0471)	-0.492 (0.361)	-0.414 (0.298)	0.0238 (0.0414)	-0.0393 (0.0332)	-0.473 (0.217)	Baseline
	0.0420 (0.0287)	-0.0213 (0.0264)	-0.347 (0.478)	-0.339 (0.376)	0.0318 (0.0234)	-0.0391 (0.0332)	-0.378 (0.320)	1-Month
	0.87	0.46	0.07	0.12	0.89	0.79	0.58	<i>p</i> -value
	0.0271 (0.0457)	-0.0202 (0.0352)	-0.309 (0.284)	-0.275 (0.264)	0.0218 (0.0444)	-0.0500 (0.0326)	-0.366 (0.352)	6-Months
	0.792	0.406	0.034	0.036	0.70	0.49	0.200	<i>p</i> -value
	0.0126 (0.0703)	-0.0199 (0.041)	-0.619 (0.431)	-0.568 (0.375)	-0.00272 (0.0414)	-0.0583 (0.0188)	-0.515 (0.277)	Baseline
	0.0122 (0.387)	-0.0210 (0.0361)	-0.641 (0.390)	-0.527 (0.250)	0.00214 (0.0429)	-0.0675 (0.0361)	-0.501 (0.205)	1-Month
	0.99	0.94	0.69	0.63	0.73	0.46	0.91	<i>p</i> -value

Correlation between contralateral and ipsilesional motor areas	Correlation between SMA and contralateral motor area	Correlation between SMA and ipsilesional motor area
0.653 (0.201)	0.740 (0.0989)	0.695 (0.182)
0.678 (0.260)	0.589 (0.140)	0.574 (0.166)
0.862	0.009	0.056
0.705 (0.146)	0.666 (0.0630)	0.657 (0.144)
0.235	0.175	0.892
0.666 (0.159)	0.649 (0.137)	0.679 (0.189)
0.538 (0.224)	0.601 (0.148)	0.520 (0.215)
0.326	0.664	0.073

Appendix F: Research ethics approval forms



Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Craig Campbell
 File Number:102272
 Review Level:Delegated
 Approved Local Adult Participants:0
 Approved Local Minor Participants:40
 Protocol Title:Childhood Hemiplegic Cerebral Palsy Integrated Neuroscience Discovery Network CP-NET (REB # 18818)
 Department & Institution:Schulich School of Medicine and Dentistry|Epidemiology & Biostatistics,London Health Sciences Centre
 Sponsor:Ontario Brain Institute

Ethics Approval Date:September 19, 2013 Expiry Date:September 30, 2014
 Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Study End Date		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB-00000940.



Ethics Officer to Contact for Further Information

<input checked="" type="checkbox"/> Erika Basile	<input type="checkbox"/> Grace Kelly	<input type="checkbox"/> Vikki Tran
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Holland Bloorview

Kids Rehabilitation Hospital

Holland Bloorview
Kids Rehabilitation Hospital



A teaching hospital fully affiliated
with the University of Toronto

Holland Bloorview Research Ethics Board Ethics Approval Notification

The Holland Bloorview Kids Research Ethics Board operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, ICH Good Clinical Practice Consolidated Guideline E6, and Health Canada Part C Division 5 of the Food and Drug Regulations

Study Title: Childhood Hemiplegic CP Integrated Neuroscience Discovery Network (CP-NET) Theme IIIa: Constraint Induced Movement Therapy (CIMT)-Neuroimaging predictors of positive response to constraint

File Number: 12-294

Principal Investigator: Darcy Fehlings

Co-Investigators: Ravi Manon, Ronit Mesterman, and Craig Campbell, Jan Willem Gorter

Original Approval Date: March 30, 2012

Expiry Date: March 29, 2013

March 30, 2012

Dear Dr. Fehlings,

The Holland Bloorview Research Ethics Board (REB) has reviewed the above named study on March 5, 2012. This was a full board review and there was a quorum. The board is granting ethics approval for a period of one year. The approval of this study includes the following documents:

- Protocol (March 29, 2012)
- TAHSN Form (received March 28, 2012)
- Participant Information Sheet & Consent Form (March 27, 2012)
- Information Sheet & Consent Form (Parents consenting on behalf of themselves and their child) (March 27, 2012)
- Adverse Event Monitoring Form (March 28, 2012)
- Adverse Event Reporting form (March 28, 2012)
- Phone Script (March 12, 2012)
- Constraint Neuroimaging Data Collection Form (March 12, 2012)
- Constraint OT Data Collection Form (March 12, 2012)

This study must be conducted in accordance with the description in the application and any supplementary documents for which ethics approval has been granted. The REB needs to be notified of any unanticipated or unintentional divergence or departures from the protocol through a "Protocol Deviation Form". Any intentional changes to the protocol need be submitted through an "Amendment Form" to the REB for approval *before* the changes are implemented, except where necessary to eliminate immediate hazards to the participants.

Any adverse events that occur as a result of your study must be reported to the REB by submitting an "Adverse Event/Unanticipated Problem Form".

If the study is expected to continue beyond the new expiry date, you must request another renewal, at least thirty days prior to the expiry date, by submitting an "Annual Renewal Form". When the study is completed or terminated, you need to submit a "Study Closure Form" to the REB.
Best wishes for the successful completion of your project.

Sincerely,

Stephen Ryan, PhD, PEng
Chair, Research Ethics Board

Appendix G: OT Data Collection Form

Holland Bloorview
Kids Rehabilitation Hospital

StudyID: _____
REB #: _____
Date: _____

**Childhood Hemiplegic Cerebral Palsy Integrated Neuroscience Discovery
Network "CP-NET": Constraint Induced Movement Therapy Theme**

Constraint Occupational Therapy (OT) Data Collection Sheet
Form to Complete by OT at Baseline, 1 month, and 6 month assessments
(Please note: 6 month only applies to case group)

1. ADMINISTRATIVE

1.1 Date form completed (yyyy/mm/dd) _____/_____/_____

1.2 Name and professional title of the person who completed the form

1.3 Time of assessment:
 Baseline 1 month 6 months

1.4 Location of assessment: _____

2. GRIP STRENGTH

Grip Strength Scores (as measured by sphygmomanometer)

2.1 Grip Strength Trial 1: _____

2.2 Grip Strength Trial 2: _____

2.3 Grip Strength Trial 3: _____

Average of 3 Grip Strength Trials: _____

3. CANADIAN OCCUPATIONAL PERFORMANCE MEASURE (COPM)





1.			
2.			
3.			

QUEST[®]

Quality of Upper Extremity Skills Test
 Carol DeMatteo, Mary Law, Dianne Russell, Nancy Pollock, Peter Rosenbaum, Stephen Walter

A. DISSOCIATED MOVEMENTS
Shoulder Items






Start Position: sitting in chair no table hands on lap

ITEM "SHOULDER"	SCORE				CRITERIA
	L		R		
	<90	>90	<90	>90	
1. Flexion 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: complete extension wrist: neutral to extension
2. Flexion with Fingers Extended 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: complete extension wrist: neutral to extension
3. Abduction 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: complete extension wrist: neutral to extension
4. Abduction with Fingers Extended 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: complete extension wrist: neutral to extension

✓ X NT 2.

A. DISSOCIATED MOVEMENTS *continued*
Wrist Items





Start Position: sitting at table forearms may be on table

ITEM "WRIST"	SCORE				CRITERIA
	L		R		
	half <range	half >range	half <range	half >range	
1. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: complete extension* <small>*see manual for definition of complete extension</small>
2. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	elbow: at least 10° flexion
3. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete pronation
4. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete supination
5. Flexion 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete supination

✓ X NT 4.

A. DISSOCIATED MOVEMENTS *continued*
Elbow Items



Start Position: sitting in chair no table hands on lap

ITEM "ELBOW"	SCORE				CRITERIA
	L		R		
	half <range	half >range	half <range	half >range	
1. Flexion 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete supination
2. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete supination
3. Flexion 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete pronation
4. Extension 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	forearm: complete pronation

✓ X NT 3.

A. DISSOCIATED MOVEMENTS *continued*
Finger Items



Start Position: sitting at table forearms must rest on table

ITEM	SCORE		CRITERIA
	L	R	
1. Independent Finger Wiggling 	<input type="checkbox"/>	<input type="checkbox"/>	dissociation of all fingers no associated reactions
2. Independent Thumb Movement 	<input type="checkbox"/>	<input type="checkbox"/>	no associated reactions

Grasp of 1" Cube

Start Position: sitting at table cube at distance requiring elbow extension

Note: If Item 1 is performed, then Item 2 should also be scored YES



ITEM	SCORE		CRITERIA
	L	R	
1. Grasp Using Thumb 	<input type="checkbox"/>	<input type="checkbox"/>	shoulder: neutral elbow: extension wrist: neutral to extension
2. Grasp Using Palm 	<input type="checkbox"/>	<input type="checkbox"/>	shoulder: neutral elbow: extension wrist: neutral to extension

✓ X NT 5.

A. DISSOCIATED MOVEMENTS continued
Release of 1" Cube

Start Position: sitting at table cube in child's hand *

* Allowable to put cube in child's hand if he/she can't actively grasp
Note: If Item 1 is performed, then Item 2 should also be scored YES

ITEM	SCORE		CRITERIA
	L	R	
1. Release from Thumb and Fingers 	<input type="checkbox"/>	<input type="checkbox"/>	shoulder: neutral elbow: extension wrist: neutral to extension
2. Release from Palm 	<input type="checkbox"/>	<input type="checkbox"/>	shoulder: neutral elbow: extension wrist: neutral to extension

✓ X NT

Scoring for Part A: DISSOCIATED MOVEMENTS (pages 2-6)

Total ✓ : = a

Total X : = b

Total NT : = c




TRANSFER TO QUEST SCORING SHEET ON PAGE I

6.

B. GRASPS continued
Grasp of 1" Cube

Start Position: sitting at table cube on table within comfortable reach

Note: Once a grasp has been performed, give a YES score for all those below it.
If grasp observed is not listed, then score NO in all boxes and describe it under "Other" below.

ITEM	SCORE		CRITERIA
	L	R	
1. Radial Digital 	<input type="checkbox"/>	<input type="checkbox"/>	wrist: neutral to extension
2. Radial Palmar 	<input type="checkbox"/>	<input type="checkbox"/>	wrist: neutral to extension
3. Palmar 	<input type="checkbox"/>	<input type="checkbox"/>	

Other: _____

✓ X NT 8.

B. GRASPS
Sitting Posture during grasps

Note: Observations for scoring this item should be made while administering the grasp items in the following section.

ITEM	SCORE			
	NORMAL	ATYPICAL		
Head	<input type="checkbox"/>	Left	Right	Flexion Extension <i>circle atypical posture</i>
Trunk	<input type="checkbox"/>	Forward	Lateral	<i>check off position</i>
Shoulders	<input type="checkbox"/>	Retracted	Elevated	<i>check off position</i>

Scoring for Part B1: GRASPS - Sitting Posture (page 7 only)

Total Normal (max. = 3) : = d






Total Atypical (max. = 5) : = e

TRANSFER TO QUEST SCORING SHEET ON PAGE II

B. GRASPS continued
Grasp of Cereal

Start Position: sitting at table

Note: Once a grasp has been performed, give a YES score for all those below it.
If grasp observed is not listed, then score NO in all boxes and describe it under "Other" below.

ITEM	SCORE		CRITERIA
	L	R	
1. Fine Pincer 	<input type="checkbox"/>	<input type="checkbox"/>	wrist: neutral to extension
2. Pincer 	<input type="checkbox"/>	<input type="checkbox"/>	wrist: neutral to extension
3. Inferior Pincer 	<input type="checkbox"/>	<input type="checkbox"/>	
4. Scissor 	<input type="checkbox"/>	<input type="checkbox"/>	
5. Inferior Scissor 	<input type="checkbox"/>	<input type="checkbox"/>	

Other: _____





✓ X NT 9.

B. GRASPS continued Grasp of Pencil or Crayon

Start Position: sitting at table pencil placed midline vertical with point facing child

Note: Child must pick up pencil on his/her own.
Once a grasp has been performed, give a YES score for all those below it.

Circle one of:	L Dominance	R Dominance	L Preference	R Preference
	Circle one of: grasp of Pencil		grasp of Crayon	

ITEM	SCORE		
	L	R	
1. Dynamic Tripod (pencil, grasped distally - precise opposition of thumb, index & middle finger)	<input type="checkbox"/>	<input type="checkbox"/>	
2. Static Tripod (pencil grasped proximally - crude approximation of thumb, index & middle finger)	<input type="checkbox"/>	<input type="checkbox"/>	
3. Digital Pronate	<input type="checkbox"/>	<input type="checkbox"/>	
4. Palmar Supinate	<input type="checkbox"/>	<input type="checkbox"/>	

Other: _____

✓ X NT

Scoring for Part B: GRASPS (pages 8-10)

Total ✓ : = f

Total X : = g

Total NT : = h

TRANSFER TO QUEST SCORING SHEET ON PAGE II

10.

D: PROTECTIVE EXTENSION

Start position: preferably ring sitting or kneeling

Note: Once a position is scored, give a YES score for all those below it.

ITEM	SCORE			
	L	R		
1. Protective Extension - Forward - circle start position:	ring sit	kneeling	other	_____
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
2. Protective Extension - Side - circle start position:	ring sit	kneeling	other	_____
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
3. Protective Extension - Backward - circle start position:	ring sit	kneeling	other	_____
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		

✓ X NT

Scoring for Part D: PROTECTIVE EXTENSION (page 13 only)

Total ✓ : = i

Total X : = m

Total NT : = n



TRANSFER TO QUEST SCORING SHEET ON PAGE IV

13.

C. WEIGHT BEARING

Start Position: prone or 4 point




Note: Once a position is scored, give a YES score for all those below it

ITEM	SCORE		CRITERIA
	L	R	
Circle test position: prone 4 point			
1. Weight Bearing			
			
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>	Thumb must be out of palm for all weight bearing items or they are scored "NO".
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>	
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>	
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>	
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>	
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>	
2. Weight Bearing with Reach			
			
a) Bears weight on LEFT hand with LEFT elbow completely extended and reaches with other arm.	<input type="checkbox"/>		
b) Bears weight on RIGHT hand with RIGHT elbow completely extended and reaches with other arm.		<input type="checkbox"/>	

✓ X NT 11.

C: WEIGHT BEARING continued Sitting

Start position: sitting on floor preferably cross-legged

ITEM	SCORE			CRITERIA
	L	R		
1. Hands forward - circle test position: cross-legged	ring	other	_____	
				
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>	Thumb must be out of palm for all items.	
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
2. Hands by side - circle test position: cross-legged	ring	other	_____	
				
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>	Thumb must be out of palm for all items.	
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
3. Hands behind - circle test position: cross-legged	ring	other	_____	
				
a) elbow extended, hand open	<input type="checkbox"/>	<input type="checkbox"/>	Thumb must be out of palm for all items.	
b) elbow extended, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
c) elbow extended, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		
d) elbow flexed, hand open	<input type="checkbox"/>	<input type="checkbox"/>		
e) elbow flexed, fingers flexed	<input type="checkbox"/>	<input type="checkbox"/>		
f) elbow flexed, hand fist	<input type="checkbox"/>	<input type="checkbox"/>		

✓ X NT

Scoring for Part C: WEIGHT BEARING (pages 11-12)

Total ✓ : = i

Total X : = j

Total NT : = k

TRANSFER TO QUEST SCORING SHEET ON PAGE III

12.

E: HAND FUNCTION RATING

Please rate this child's hand function (circle a number)

Guidelines for scoring hand function:

POOR: minimal independent hand grasps, no active release, unable to combine reach and grasp
GOOD: spontaneous reach, grasp and release, good eye-hand coordination

	POOR										GOOD
Left Hand	0	1	2	3	4	5	6	7	8	9	10
Right Hand	0	1	2	3	4	5	6	7	8	9	10
Bilateral	0	1	2	3	4	5	6	7	8	9	10

F: SPASTICITY RATING

Please rate this child's spasticity

Guidelines for scoring spasticity:

MILD: good spontaneous movement, normal tone at rest, associated reactions present
MODERATE: tone interferes with spontaneous movement, may be present at rest
SEVERE: minimal spontaneous movement, stiff limbs, tone present at rest

	NONE	MILD	MODERATE	SEVERE
Left Hand	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Right Hand	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

G: COOPERATIVENESS RATING

Please rate this child's level of cooperation during this assessment.

NOT cooperative	SOMEWHAT cooperative	VERY cooperative
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

AHA			
Assisting Hand Assessment, English version 4.4			
		score	notes
GENERAL USAGE ITEMS	Approaches objects	4	
		3	
		2	
		1	
	Initiates use	4	
		3	
		2	
		1	
	Chooses AH when closer to objects	4	
		3	
		2	
		1	
ARM USE ITEMS	Stabilizes by weight or support	4	
		3	
		2	
		1	
	Reaches	4	
		3	
		2	
		1	
	Moves upper arm	4	
		3	
		2	
		1	
Moves forearm	4		
	3		
	2		
	1		
GRASP - RELEASE ITEMS	Grasps	4	
		3	
		2	
		1	
	Holds	4	
		3	
		2	
		1	
	Stabilizes by grip	4	
		3	
		2	
		1	
Readjusts grip	4		
	3		
	2		
	1		

GRASP - RELEASE	Varies type of grasp	4		
		3		
		2		
		1		
GRASP - RELEASE	Releases	4		
		3		
		2		
		1		
GRASP - RELEASE	Puts down	4		
		3		
		2		
		1		
FINE MOTOR ADJUSTMENT	Moves fingers	4		
		3		
		2		
		1		
FINE MOTOR ADJUSTMENT	Collimates	4		
		4		
		2		
		1		
FINE MOTOR ADJUSTMENT	Manipulates	4		
		3		
		2		
		1		
COORDINATION	Coordinates	4		
		3		
		2		
		1		
COORDINATION	Orients objects	4		
		3		
		2		
		1		
COORDINATION	Proceeds	4		
		4		
		2		
		1		
FINE MOTOR ADJUSTMENT	Changes strategy	4		
		4		
		2		
		1		
FINE MOTOR ADJUSTMENT	Flow in bimanual task performance	4		
		3		
		2		
		1		
Sum score:				
Scaled score %:		33	Name: 0	Date: 1/01/1900
Comments:				

Tasks	Time to Complete (seconds)	
	Right Hand	Left Hand
6.1 Writing – Copying sentence composed of 24 letters		
6.2 Card Turning – Turning over 5 index cards (3x5 inches)		
6.3 Handling Small Objects – Inserting 2 paper clips, 2 bottle caps, & 2 pennies in a larger can		
6.4 Simulated Feeding – using teaspoon to transfer 5 kidney beans into a larger can		
6.5 Stacking checkers – stack 5 standard size checkers on top of each other		
6.6 Moving light large objects – moving 5 large empty cans onto a board		
6.7 Moving heavy large objects – moving 5 large full cans onto a board		

Curriculum Vitae

Name: Kathryn Manning

**Post-secondary
Education and
Degrees:**

Memorial University of Newfoundland and Labrador
St. John's, NL Canada
2007-2011 B.Sc. Joint Applied Mathematic and Physics

The University of Western Ontario
London, Ontario, Canada
2011-present M.Sc. Medical Biophysics

**Honours and
Awards:**

CST Ronald Lloyd Award, Canadian Scholarship Trust
Foundation, \$7500

Ontario Graduate Scholarship (OGS), Western University, Sept -
Aug 2011

NSERC USRA, Memorial University, Apr - Aug 2010

Faculty of Science Dean's List, Memorial University Sept 2008 -
Apr 2009 and Sept 2007 - Apr 2008

Dr. Leslie Harris Alumni Scholarship, Memorial University, Sept
2007 - Apr 2011, \$16000

District Scholarship (Ward 4), Memorial University, 2007

AP Scholar with Distinction, 2007

**Related Work
Experience**

"A Research and Practice Instructional Course on Constraint
Induced Movement Therapy (CIMT) in Children with Cerebral
Palsy: How can we Develop and Implement a CIMT
Intervention that Works?" Ontario Association of Children's
Rehabilitation Services (OACRS), Oral Presentation.

Research Assistant, Primate fMRI at 7T, Centre for Functional and Metabolic Mapping at Robarts Research Institute, Jan - Aug 2013.

"Brain connectivity measured using the BOLD fMRI signal and electrophysiology", imaging Network Ontario (ImNO Symposium), Poster.

Research Assistant, Peer supervision and manuscript development, Physics and Physical Oceanography Department at Memorial University, Apr - Aug 2011.

Research Assistant, Computational fluid dynamics, programming, simulations, Physics and Physical Oceanography Department at Memorial University, Apr - Aug 2010

Research Assistant, Marine Biology Field Research, Women in Science and Engineering, June - Aug 2006.

Publications:

"Levels of unconsciousness: Isoflurane induces dose-dependent alterations in the connectivity profiles and dynamic properties of the brain's functional architecture", Hutchison, R. M.; Hutchison, M.; Manning, K. Y.; Menon, R.; Everling, S. Cerebral Cortex, Submission number: CerCor-2013-00880

"Modeling the motion and detection of particles in micro cantilever sensor cells", Manning, K.Y.; Butt, N.R.; Alodhayb, A.; Saika-Voivod, I.; Beaulieu, L.Y. Journal of Applied Physics 113. 114501 (2013): 1-8.