Investigating Sensory Plasticity in Hemiplegic Cerebral Palsy following Constraint Induced Movement Therapy

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Rehabilitation Science Institute
University of Toronto

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Abstract

Children with hemiplegic cerebral palsy (HCP) experience upper limb sensory processing and motor deficits. While constraint-induced movement therapy (CIMT) is effective in improving motor hand function in HCP, its impact on sensory function remains under-investigated. The present study evaluates the effectiveness of CIMT on sensory function in children with HCP using neuroimaging and clinical diagnostic tools. Ten children with HCP attended a three-week CIMT intervention with the integration of a sensory component to optimize potential sensory change. Both magnetoencephalography (MEG) and clinical sensory/motor assessments were completed at: baseline (one week prior to CIMT), one and six months post-baseline. Clinical sensory and MEG measures were compared between all three time points. CIMT did not result in significant changes in clinical sensory modalities or MEG somatosensory processing of the affected hand. This is the first study to investigate the effect of CIMT on sensory function utilizing clinical sensory measures and neural processing.

Keywords: constraint-induced movement therapy, hemiplegic cerebral palsy, sensory function, magnetoencephalography
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List of Abbreviations

aPVI: asymmetric periventricular injury, aPVI
CIMT: Constraint Induced Movement Therapy
CP: Cerebral Palsy
EEG: Electroencephalography
ERD: Event Related Desynchronization
ERS: Event Related Synchronization
HBKRH: Holland Bloorview Kids Rehabilitation Hospital
HCP: Hemiplegic Cerebral palsy
HSC: Hospital for Sick Children
MCA: Middle cerebral artery
MEG: Magnetoencephalography
MRI: Magnetic resonance imaging
QUEST: Quality of Upper Extremity Skills Test
S1: Primary Somatosensory Cortex
S2: Secondary Somatosensory Cortex
SAM: Synthetic Aperture Magnetometry
SEF: Somatosensory Evoked Fields
TDC: Typically Developing Children
TFR: Time-frequency representation
VS: Virtual Sensor
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CHAPTER 1

1. Introduction

Cerebral palsy (CP) broadly describes a group of chronic developmental disorders, which impair movement control due to damage to the developing brain. The most common subtype of CP, hemiplegic cerebral palsy (HCP), gives rise to motor and sensory impairments that impact the function of a child’s hemiplegic hand and/or arm (i.e. manual ability). This can disrupt everyday tasks, which in turn can affect their independence and decrease their quality of life. While many treatments have sought to remediate the motor effects of HCP, (e.g. splinting, passive stretching, spasticity medication), constraint-induced movement therapy (CIMT) has proven to be one of the most successful treatments, having the most in evidence to support its effectiveness. CIMT forces the use of the affected limb through immobilization of the unaffected limb (typically via casting or splinting), paired with intensive motor training.

Although CIMT results in clinical benefits, the underlying neural mechanisms remain under investigation with evidence for rebalancing of the sensorimotor networks between the two hemispheres as well as increased activation of the affected motor cortex (M1) post CIMT. Despite sensory and motor function being significantly linked, the main focus of current research has been on motor change (both at a clinical and neural level), thus leaving the potential sensory contributions to CIMT’s impact on increased hand usage largely overlooked and under-investigated.

Sensory input is an essential component for motor function and control. Taub et al. describes how deficits in neuromotor function have profound effects on sensory awareness and responsiveness. Conversely, improper transmission of sensory feedback can also limit a child's ability to maintain proper motor control. Thus, the integration of sensory activities within a CIMT protocol may help to increase sensory function as well as facilitate an increase in motor function. After investigating parent reports and videotaped sessions, Taub and colleagues have indicated that CIMT was capable of ‘new sensory awareness of the hemiparetic extremity’, warranting future research to evaluate these reports objectively. Therefore, sensory recovery may occur following CIMT and contribute to increased use of the affected hand. It is recognized that children with HCP commonly exhibit significant hemiplegic limb sensory deficits in areas of tactile discrimination/registration, proprioception, and stereognosis. The evaluation of clinical
sensory function before and after CIMT has been completed as a secondary exploratory outcome for the specific modalities of tactile discrimination and stereognosis. Despite such sensory assessments revealing no statistically significant change before and after treatment, it is important to note that sensory outcomes have not been the primary area of focus in children with HCP. Assessment of other sensory deficits affecting this population, such as proprioception and kinesthesion, has also not been tested following CIMT. Investigating sensory changes as a primary objective is necessary in order to extensively explore potential changes at both a clinical and neuronal level across all sensory modalities. Therefore, a more focused and rigorous analysis can be directly applied to understanding changes in sensory function following CIMT.

Magnetoencephalography (MEG) is an advanced imaging tool that provides the opportunity to explore sensory and motor neural processing. MEG provides the advantage of both high temporal (timing) and spatial (location) details of cortical somatosensory processing activity in the order of milliseconds after tactile stimulation. Recorded MEG waveforms can provide valuable information about the strength and timing of neural activation in response to tactile stimulation measured by somatosensory evoked fields (SEFs). Furthermore, cortical responses can also be characterized by oscillatory activity at the alpha (8-13Hz) and beta (15-30Hz) frequency range following stimulation. Collectively, SEFs and oscillatory activity can provide complementary understanding of the rhythmic brain activity and the role it plays in sensory processing.

Previous MEG and EEG imaging studies have demonstrated somatosensory deficits with associated reduced cortical brain activity and somatotopic map disorganization of the contralateral primary somatosensory cortex (S1) in HCP in response to pneumatic or electrical stimulation of the affected hand in hemiplegic CP. Altered cortical processing have been characterized as missing deflections, aberrant morphology, longer latencies and lower amplitudes in evoked responses (somatosensory evoked fields, SEFs) to tactile stimulation. In addition, exploration of alpha and beta frequency oscillatory modulations to stimulation have shown decreased power and longer latency durations between suppression and rebound events in children with HCP compared to typically developing children.

To date, two previous MEG studies have specifically addressed somatosensory changes following CIMT at a neural level. A previous MEG case study from our group revealed increased
activation in the contralateral S1 following CIMT after completing a standardized motor task (4-finger extension/flexion). In addition to this, Juenger et al focused on evaluating the selective role of the somatosensory cortex (S1) in functional recovery after CIMT using a somatosensory specific task. An increase in S1 activation in response to tactile stimulation after CIMT training was observed. Their investigation revealed an increase in ‘early-SEF’ at N20 (20ms after stimulation onset) amplitude and reduction in latency in children with contralateral corticospinal projections (projections determined by transcranial magnetic stimulation). Those with ipsilateral projections showed an increase in SEF amplitude only. SEF activation following pneumatic stimulation at P50 (50 ms after stimulation onset) has been shown to be a more reliable indicator of somatosensory processing than N20, which is commonly used in electrical nerve stimulation. Despite providing early evidence to support that CIMT may contribute to improved hand function as a mechanism that enhances sensory input, clinical sensory outcomes were not measured in either study. The inclusion of clinical measures across all modalities can provide valuable information regarding behavioural sensory function.

Clinical sensory outcomes paired with sensory neuroimaging for the evaluation of CIMT on sensory function have never before been completed. In addition, clinical sensory measures have not been a primary focus and all clinical sensory modalities have not been evaluated. By filling these gaps, we aim to add to previous literature and further understand the role that CIMT has on sensory function. The focused exploration of sensory function is important because of the close link between motor and sensory function when using the hand. Furthermore, in order to maximize the CIMT intervention, a focus has been placed on the inclusion of sensory activities in the CIMT program. In addition, the use of MEG and assessment of changes in SEF amplitude and latency of the ‘P50’ response (approximately 50ms after stimulation onset) will add to previous literature, by elucidating changes in S1 processing using a more reliable indicator. This will help to expand our knowledge past responses at N20 (20ms after stimulation onset). Furthermore, investigating alpha and beta band oscillatory modulations can aid in understanding CIMT changes of induced sensory responses. Therefore primary objective of this study seeks to investigate the change in sensory function observed in children with HCP treated with CIMT. By evaluating individuals longitudinally and comparing clinical and MEG sensory measures (SEFs and alpha oscillations) before and after CIMT, we aim to investigate the sensory mechanisms of improved hand and arm function following CIMT. Secondary objectives are: (1) to evaluate the maintenance of any effects at 6 months post therapy at both a clinical and neuronal level; (2) to
evaluate potential clinical and neuronal sensory change in the unaffected hand; and (3) to explore the relationship between motor and sensory improvement following CIMT.
CHAPTER 2: Literature Review

2.1 Cerebral Palsy

Cerebral Palsy (CP) refers to a group of permanent disorders of the development of motor control and posture, causing activity limitations due to a non-progressive impairment of the developing central nervous system.\textsuperscript{26,27} In Canada, CP affects 1 in every 500 live births, and is the most common paediatric physical disability.\textsuperscript{28} The majority of cases of CP result from an injury or malformation to the motor cortical areas and pathways during prenatal development, labour, or early in postnatal development.\textsuperscript{29} The motor disorders of CP are often accompanied by a variety of other potential disturbances including sensation, communication, perception, cognition, communication and behavior.\textsuperscript{30} However, it should be noted that CP is a heterogeneous condition in terms of etiology, as well as in types and severity of impairments. Therefore, CP evolves with time, development, learning, therapies, aging and other factors.\textsuperscript{31}

2.2 Hemiplegia subtype

Hemiplegic cerebral palsy (HCP) is the most common type of CP, affecting approximately one third of individuals diagnosed with CP. HCP is characterized by weakness and limited range of motion of the arm, leg, or both, on one side of the body. In hemiplegia, one side of the body is functionally more impaired than the other, affecting both gross and fine motor function.\textsuperscript{32-34} HCP can result from a variety of brain lesions with respect to timing (during the pre-, peri- or postnatal period), location and the type of structural pathology (cerebral brain malformations, periventricular lesions and cortico/subcortical malformations).\textsuperscript{35,36} Typically, motor impairments are accompanied by spasticity and reduced sensation, with more involvement of the upper limb as opposed to the lower.\textsuperscript{37}

One of the most disabling symptoms in HCP is a unilateral impairment in hand and arm function.\textsuperscript{38} This is often the result of damage to the motor cortex and corticospinal pathways, which are responsible for the fine motor control of the fingers and hand.\textsuperscript{39} During tasks that require fine manipulation, children with HCP often use several fingers to complete the task and have abnormal hand posturing. In addition, reduced sensation can further complicate and impact motor impairment.\textsuperscript{40} These impairments can compromise a child’s ability to reach, grasp, release and manipulate objects, which in turn affects many aspects of their life (e.g. play, self-care, and overall function of daily activities). According to the International Classification of Functioning,
Disability and Health (ICF), impairments are defined as problems in body function or body structures, such as significant deviations or losses and activity limitations. Collectively, these resulting sensory and motor impairments compromise movement efficiency. With respect to the upper limb, this involves the use of one hand over the other with their unaffected upper limb providing compensation over their affected limb. As a result, children with HCP typically learn strategies at an early age to exclusively manage daily tasks with their unaffected hand. This leads to developmental disregard (or learned non-use), which may result in suppressing the development of cortical representations for the affected limb. In turn, this inhibits the healthy development of the affected limb via a decrease in its functional as well as sensory use. The current thesis focuses on the sensory impairments of the upper limb and potential recovery via CIMT intervention in children with HCP.

2.3 Treatment of Hemiplegia: Constraint Induced Movement Therapy (CIMT)

Clinicians dedicate a significant amount of time and resources toward upper limb rehabilitation. This is done by determining the various combinations of impairments at an individual level for children with HCP. Currently, many different treatments exist in efforts to reduce upper limb impairment and enhance function/manual ability. The range of management options include: splinting, casting, passive stretching, facilitation of posture and movement and spasticity medication (which includes Baclofen or Botulinum toxin-A, as well as surgery). The aim of these therapies is to reduce muscle tone and spasticity, improve functional use, and increase range of movement of the affected limb. In 2013, Novak et al., conducted a systematic review of the best available evidence for CP management approaches using the GRADE system. The GRADE system rates treatments based on the quality of evidence and strength of the recommendation for use, which weigh the benefits and trade-offs of using an intervention. Findings were then taken into consideration using the Evidence Alert Traffic Light System (i.e. green means “Go; effective; therefore do it”) to provide knowledge translation guidance to clinicians. Novak et al. reported on compelling evidence from systematic reviews, indicating constraint-induced movement therapy (CIMT) as having not only the highest volume of published evidence, but also the highest GRADE system rating. Therefore these results represent the most effective treatment option for improving hand function at the activities level of the ICF.

CIMT is a relatively new motor intervention that began gaining attention as a potential therapy for children with HCP over a decade ago. Its principle purpose is to increase spontaneous
use of the affected upper limb and as a result circumvent developmental disregard. The two components of CIMT involve: (1) immobilization of the unaffected limb (2) pairing constraint with ‘repetitive practice of therapeutic tasks involving and engaging the affected limb’.44

The foundation of CIMT was derived from ‘the learned-nonuse phenomenon observed in non-human primates’ by Taub and colleagues in 1958.45,46 By surgically abolishing the somatic sensation in one of the monkey’s forelimb via de-afferentation, the monkey was unable to use their forelimb in normal activities regardless of intact motor function pathways.47 This led to increased developmental disregard due to negative and discouraging feedback from their affected forelimb. To encourage the use of the deafferented extremity, the intact forelimb was restricted from movement. Taub suggested that the mechanism considered responsible for the increased use of the affected extremities involved overcoming learned non-use by constraining the unaffected limb. This was then followed by ‘an induced use-dependent cortical reorganization via the repetitive practice of tasks with the affected limb’. Combining the two components of CIMT encouraged the positive reinforcement of the affected limb, in turn, increasing the use of the affected limb and decreasing developmental disregard.6 Based on this work, an adaptation of CIMT for the human population has been developed in an attempt to treat hemiparesis (i.e. those with congenital and acquired stroke, traumatic brain injury and dystonia). Functional improvements have been observed consistently following CIMT.48 Furthermore, studies in adult populations following stroke have demonstrated brain adaptation and plasticity occurring in cortical motor areas controlling movement of the affected limb post-CIMT.49–51 The adult stroke studies suggest that that the core components of this therapeutic approach, including restraint and massed practice, might prove to be effective in reversing the ‘behavioural suppression of movement’ in the affected upper limbs of children with HCP.44 With promising results in the adult stroke population, CIMT has gained popularity in clinical pediatric settings for treatment of HCP.

The standard CIMT developed by Taub for adults with stroke involves 6 hours of therapy a day, of which the restraint is placed for 90% of the time for over a 2-week period. The length of the treatment can range from 1 to 3 weeks and the amount of one-on-one time with an occupational therapist can vary depending on the severity of the impairment, age, and patience of the patient.6 For patients with HCP, many modifications to CIMT have been made to accommodate for the child’s age, daily routine (e.g. school, extracurricular activities) as well as
patience (i.e. children may experience frustration arising from the therapy). Using an intensive therapy protocol (i.e. 12 day period of CIMT, wearing a sling and glove 10 hours a day combined with 2 hours of individual and group therapy everyday), the Wolf motor function test (WMFT) confirmed functional improvement as well as therapy-induced changes of cortical activation. This was assessed using functional magnetic resonance imaging (fMRI). Even studies with a more feasible protocol such as Gordon et al (6 hours of restraint for 10 of 12 consecutive days paired with intense motor practice), have also shown an improvement in upper limb efficiency as well as speed and dexterity using the Jebsen-Taylor test and the Bruininks- Oseretsky Test of Motor Proficiency. Interestingly, studies have also combined CIMT and bimanual therapy which involves 3-hour afternoon sessions occurring 3 days per week for a total of 8 weeks (6 weeks of unilateral and 2 weeks of bilateral activities). This combination can be considered to be ‘modified’ CIMT (mCIMT) which has demonstrated a significant improvement as assessed by the ABILHAND-Kids questionnaire (measures manual ability in self-care activities) as well as the Melbourne assessment of Unilateral Upper Limb Function (measures quality of upper limb movements). Therefore, regardless of modifications to CIMT intervention (traditional constraint therapy and mCIMT), most studies have been successful in demonstrating an improvement of function after intervention through behavioural changes, cortical change or both. Some studies refer to the constraint intervention as modified due to changes in therapy duration (i.e. total number of hours) as well as activities (casting, unilateral, bilateral).

In this present thesis, we use a modified version of constraint therapy that includes the integration of casting, unilateral and bilateral activities into a CIMT treatment protocol. For simplicity, we will continue to refer to this standardized protocol as CIMT throughout the thesis. Further details can be found in the Chapter 3 – Methods.

2.4 Hemiplegic cerebral palsy and sensory impairment

Despite the strong link between sensory and motor function, the main focus of research has been on the enhancement of motor function at both a clinical and neural level. Consequently, sensory contributions to CIMT have been largely overlooked and remain under-investigated. It has been well documented that children with HCP often maintain sensory deficits that limit their ability in tactile discrimination and registration, proprioception, kinesthesia, and stereognosis.
2.4.1 Tactile registration and discrimination

Over 75% of children with HCP have tactile deficits, and over 40% have deficits in both tactile registration (the initial awareness of sensory information) and discrimination (the ability to differentiate/perceive information received through the sense of touch). Many studies have confirmed that tactile performance was poorer on the affected hand of children with HCP than their unaffected hand, and worse in both hands compared to typically developing children (TDC).

Furthermore, Auld et al. have indicated that children with HCP who have tactile registration deficits (measured using the 20-item Semmes Weinstein Monofilament kit) have an increased likelihood to have tactile perception deficits. As a result, an individual would not able to ‘recognize object characteristics, which can reduce their ability to process and use sensory information’. Essentially, this disrupts their interactions with objects in their environment. For example, having a registration deficit increases the likelihood of having a perceptual deficit, as demonstrated by reported lower odds ratios for more difficult tests (e.g. providing light touch to both sides of the arm at the same time and followed by asking if stimuli are detected in both hands).

2.4.2 Stereognosis

Stereognosis is the ability to perceive and identify the shape or form of familiar objects in the absence of visual and auditory information. Group magnitude differences reveal lower median percentage accuracy for the unaffected hand in hemiplegia and diplegia when compared to TDC (40.0%, 37.5%, and 56.25% for identification of common objects, geometric shapes, and letters respectively). Importantly, a recent study has shown that impairment in stereognosis is correlated with impairment in motor function. Namely, a statistically significant correlation was found to occur when comparing stereognosis scores to the Jebsen-Taylor test (which evaluated fine and gross motor hand function using simulated activities of daily living) in the affected hand in children with HCP.

2.4.3 Proprioception and kinesthesia

Proprioception is a ‘complex somatosensory modality that utilizes inputs from muscles, joints, and cutaneous afferent fibers’. These various inputs provide information about hand and body position and contribute towards improving targeted reaching movements. Wingert and
colleagues explain proprioception as typically consisting of 2 important components: 1) the sense of limb movement (kinesthesia) and 2) static limb position (joint-position sense).

Wingert et al., have shown that proprioception deficits in the affected upper limb do exist in children with hemiplegia (sample age range 8-26 years) despite relatively mild motor involvement (GMFCS and MACS Levels I or II). Joint-position sense error was found to be greater in the unaffected upper limbs and was twice the error magnitude of TDC. Despite this difference, observed results did not reach significance. Interestingly, the joint-position sense errors were significantly larger, especially with respect to pronation on the affected side compared to the unaffected. In addition, passive movements to detect kinesthesia were less accurate for the affected hand of the HCP group as compared to their unaffected hand and TDC.

Furthermore, Goble et al., argue that previous studies which address proprioceptive acuity by asking HCP individuals to indicate the direction of the finger movement (e.g. “Did I move your finger/wrist up or down?”) provide limited information about proprioceptive feedback use during functional, goal-directed movement. Therefore, Goble et al., measured proprioceptive feedback during a goal-directed target-matching task. Results revealed a significant increase in affected arm error almost twice as large as the error observed for the unaffected arm. Proprioceptive-guided-matching was more impaired for individuals with right hemisphere damage than those with left hemispheric damage, suggesting that proprioceptive deficits may depend on the side of hemiplegic damage. The importance of hemiplegic laterality is further supported by neuroimaging studies, which have shown a greater right hemispheric activation in frontoparietal temporal areas during tasks requiring kinesthetic processing. Wingert et al. conclude that the proprioceptive deficits could provide rehabilitation clinicians with information about factors contributing to motor impairments. In turn, practicing kinesthetic movements and proprioceptive tasks without vision, could improve perception by repeatedly engaging somatosensory activity.

2.5 Overview of clinical and neuronal functional improvements after CIMT

The effectiveness of CIMT is supported by evidence from randomized control trials demonstrating improved function of the affected limb in children with HCP. Increases in hand function (as measured by the Quality of Upper Extremity Skills Test, Assisting Hand Assessment and Jebsen-Taylor hand function battery) and grip strength, as well as decreases in developmental
disregard (neglect) showcase the value and effectiveness of CIMT.\textsuperscript{1,65} Although CIMT shows promising clinical benefits, the neural correlates behind the observed functional improvements remains poorly understood and are now being actively investigated. Multiple brain imaging techniques have been used to identify different patterns of motor cortical reorganization following CIMT.

The underlying lesions leading to HCP can vary in location, extent and timing of insult. It has been shown that these insults can lead to different reorganization patterns of the corticospinal motor pathways.\textsuperscript{15} Individuals can be categorized into different patterns to understand differential responses. Two types of corticospinal projections to the affected hand can develop: (1) contralateral (crossed) projections from the affected hemisphere or (2) reorganized ipsilateral projections from the contralesional (or unaffected) hemisphere. When describing the primary motor representation, individuals with \textit{ipsilateral projections} share the M1 representation of both hands (affected and unaffected hand) in the contralesional (or unaffected) hemisphere. Those with \textit{contralateral projections} have a M1 representation of their affected hand in the ipsilesional (affected) hemisphere. For the purpose of consistency within the following chapters, contralateral and ipsilateral corticospinal projections will be used to describe the cortical representation of the unaffected and affected hemisphere, respectively.

With strong evidence of neuroplastic changes in improving functionality after CIMT in adults with hemiplegia after stroke, investigating children with HCP has also shown similar neuroplastic improvements after CIMT. Possible mechanisms that have been proposed include the rebalancing of the two hemispheres as well as enlarged motor cortical activation correlating to clinical measures. A recent fMRI study by Manning and colleagues revealed rebalancing of the sensorimotor resting state networks at one and six months after CIMT in children with HCP.\textsuperscript{4} Sensorimotor resting state network reorganization after therapy was also correlated with a change in clinical motor function (Quality of Upper Extremity Skills Test improvement) after CIMT. Our lab has also provided evidence supporting a shift of activity from the unaffected (contralesional) to affected (ipsilesional) cortex, with increased activation of the affected motor cortex (M1) after CIMT (using fMRI analysis, a shift towards a positive laterality indices representing primarily contralateral activation).\textsuperscript{3}

With promising evidence of neuroplastic change following CIMT, changes in response
tends to vary as not all hemiplegic patients experience success with CIMT. Therefore, the need for biomarkers or predictors for those children who are more likely to benefit from CIMT is important. Juenger and colleagues have recently discovered that the type of corticospinal patterns can predict CIMT outcomes. They revealed that individuals with ipsilateral corticospinal projections had a decrease in transsynaptic M1 excitability (measures by TMS) as well as a decrease in synaptic activity during active movements of the affected hand after 12 days of CIMT. However, individuals with maintained crossed contralateral corticospinal projections revealed an increase in both parameters after CIMT. Similarly, in another study, individuals with contralateral projections were accompanied by significant clinical improvement in motor activity; evidenced by an increase in their ability to complete the Wolf motor function test (WMFT) tasks as well as a reduction in the time needed for the execution of the tasks following CIMT. The ipsilateral group showed an increase in WMFT quality score but required more time than before CIMT (i.e. increase in task execution time).

One underlying mechanism that is proposed by Kuhnke and colleagues is the concept of imbalanced interhemispheric inhibition. This concept involves the idea that a more active unaffected hemisphere inhibits activity in the less active affected hemisphere (which negatively impacts hand function via motor function restriction). The ‘rebalancing’ of interhemispheric inhibition in the contralateral group may be contributing by reducing the cortical activity of the unaffected hemisphere (by constraint of the unaffected hand) while increasing cortical activity in the affected hemisphere (by intensive repetitive training). On the other hand, individuals with ipsilateral projections have motor representations located in the same hemisphere, and therefore interhemispheric inhibition cannot be targeted by CIMT. The second proposed mechanism by Kuhnke and colleagues is the interaction of the M1 and primary somatosensory representation (S1) of the affected hand. The S1 representation was found to be preserved in the affected hemisphere for both those with ipsilateral and contralateral cortical projections. It was suggested that the ipsilateral group would however show ‘hemispheric dissociation’ between the preserved S1 in the affected hemisphere and the reorganized M1 in the unaffected hemisphere. Sensory input to S1 (Brodmann areas 3a and 3b) and can be relayed to motor areas in the frontal lobe, via ipsilateral cortical areas 1 and 2 and the thalamus. Thus, in the contralateral group, the transfer of somatosensory feedback from S1 to M1 would likely be more efficient as it would not have to crossover to the opposite hemisphere (through additional synaptic pathways). This would allow for faster processing speed. This second proposed mechanism, sheds light on the importance of
sensory feedback, as the intact sensorimotor loop may be critical for effective motor learning during CIMT. Therefore, it is important to investigate the role sensory function plays in CIMT.

2.6 Magnetoencephalography

Advancements in neuroimaging modalities have provided new techniques to perform functional studies of the brain using a specific task or during resting-state. Functional neuroimaging such as functional MRI (fMRI), hemodynamic-based single-photon-emission computed tomography (SPECT) and positron-emission tomography (PET) provide excellent spatial (location) resolution. However, these modalities have limited temporal (timing) resolution. Magnetoencephalography (MEG) is a neuroimaging technique that provides the advantage of both excellent temporal resolution (in the order of milliseconds) and good spatial resolution (in the order of centimetres).

Often, MEG is compared to another neuroimaging technique called electroencephalography (EEG) given they both measure a ‘neuronal signal’. MEG measures the magnetic components that are generated by the small intracellular currents in neurons of the brain, whereas EEG measures the electrical component of mainly extracellular currents. When using EEG, the conduction of the electrical signal from the neurons to the recording electrodes of the scalp causes distortion of the signal as it passes through various densities (scalp, skull and cerebrospinal fluid). However, in MEG, the propagation of magnetic fields through the head is less influenced by the varying conductivities of the overlying tissues. As a result the spatial resolution is improved to locate the cortical source compared to EEG, resulting in successful localization of brain activity such as the motor and somatosensory areas. Advances in MEG recording technology have led to ‘the development of robust and accurate source modeling analysis techniques and time-specific signal processing’. These features have contributed novel information regarding the nature of both evoked and induced cortical activity within the motor and sensory structures of the brain. Along with its exceptional temporal and spatial resolution, MEG instrumentation is also safe and non-invasive. Furthermore, it is silent and comfortable for a patient and does not require a time-consuming and inconvenient set up of affixing electrodes on the scalp as in EEG. MEG instrumentation allows for the measurement of magnetic brain activity with ‘high sensitivity using advanced noise cancellation’ adjusting for some head motion.

It should also be recognized that MEG does have limitations. For instance, MEG
maintains poor sensitivity to activity occurring deep below the cortex. In addition, the weakness of the brain’s magnetic signal requires a magnetically shielded room. However, very sensitive sensors called superconducting quantum interference devices (SQUIDS) are able to reliably detect these signals. The cost to purchase, install and maintain MEG equipment is high.\(^\text{21}\)
Together, this limits the use and availability of MEG for clinical studies.

Despite some disadvantages, MEG is a useful tool to investigate individuals with cortical malformations and/or brain lesions. Its popularity has steadily increased in clinical research (particularly in the preoperative evaluation of sensory function or epileptic brain activity) and is a promising technique for the evaluation of brain function in patients with brain lesions (e.g. children with cerebral palsy). MEG has been shown to create detailed images of brain activity (both event related fields and oscillatory brain activity) in both adults and children. This has been done not only in regards to movement, but also sensory tasks (e.g. response to tactile/electrical stimulation to the hand).\(^\text{15,18,19,22,69,70}\)

### 2.6.1 MEG analysis

The main purpose of using the MEG is to detect and measure magnetic fields that are generated as well as to determine the brain localization of such activity. Recorded MEG waveforms can provide valuable information about the strength and timing of neural activation in response to a stimulus (e.g. tactile stimulation). These cortical responses can be characterized in the time domain to study event-related fields (ERPs; evoked oscillations) or in the time-frequency domain to study oscillatory activity (induced oscillations). Oscillations differ based on their phase-relationships to a stimulus. Evoked oscillations are phase-locked to a stimulus, whereas induced oscillations are not.\(^\text{71}\) Both these oscillations are described in further detail below.

### 2.6.2 Evoked response: Event-related fields

Event-related fields (ERFs) are systematic positive and negative voltage deflections, which are shown by averaging consistent events that are time-locked to a given stimulus.\(^\text{72}\) An ERF waveform can be extracted using ‘signal averaging’. By averaging across a large number of trials, the “random” activity is canceled out. The presentation of a repeated stimulus leads to the assumption that this produces a repeated series of brain responses that occur at the same time and same location.\(^\text{73}\) Any other brain activity that is not phase or time locked to the stimulus event has
a random phase and therefore decreases with increasing numbers of averages which increases the signal to noise ratio by the square root of the number of trials. Averaging 100-300 trials provides a sufficient signal-to-noise ratio to discern a distinct ERF waveform with reproducible peaks or ERF “components”, which reflect deviations from the pre-stimulus baseline.\textsuperscript{74}

The ERF component peak amplitude and latencies are thought to represent the magnitude strength and efficiency of cortical processing in response to an event, respectively.\textsuperscript{75,76} The stimulus that is used in this study is tactile stimulation to the index finger, allowing for a response in the somatosensory cortex (S1), which is then specifically called, somatosensory evoked fields (SEFs).

### 2.6.3 Induced oscillations: Time-frequency

Typically, brain signals are not stationary. Namely, not all activity related to any given event is phase-locked to the event. Along with evoked responses, induced oscillations occur after stimulation but without phase-locking to the stimulus. Neural oscillations are a reoccurring signal of rhythmic or repetitive neural activity. These oscillations occur from connections between neurons that result in the ‘synchronization of their firing patterns’.\textsuperscript{77} Therefore, induced oscillations cannot be observed when signals are averaged. Consequently, the analysis must be performed on a single-trial basis since averaging would cancel out oscillations due to their random phase relation to the given stimulus (e.g. tactile stimulation). Different oscillatory activity occurs at different frequency ranges (i.e. alpha 8-13Hz, beta 15-30 Hz and gamma 30-70Hz). Therefore, to estimate induced oscillations, time-frequency decomposition is applied to each trial and the resulting absolute signal power averaged across trials.\textsuperscript{71} In addition, the power of the evoked and any background components can subtracted from this total power to reveal changes related mostly to the induced power.

Time frequency analysis thus enables the study of changes in spontaneous cortical oscillations. Their modulations to somatosensory stimulation reflect the reactivity of the ongoing cortical activity to sensory input, by measuring the signal power change over time of a specific frequency band.\textsuperscript{21,78} Spontaneous rhythmic oscillations appear in the frequency bands around 10 and 20 Hz, and are referred to as alpha and beta bands respectively. This recorded “power” is transiently modulated after stimulation reflected by increases and decreases have been termed event-related synchronization (ERS) and desynchronization (ERD) respectively.
Collectively, the role of somatosensory evoked potentials and the modulations of neural oscillatory synchrony in response to somatosensory stimulation can help us to better understand the rhythmic brain activity and the role it plays in sensory processing.  

2.6.4 Source localization

Along with understanding and measuring magnetic field activity, localizing the source of this activity is important. This can be achieved using various inverse modeling methods. One popular method is a spatial filtering procedure called ‘beamforming’. This can be used to generate volumetric, whole-brain source images based on the spatial segmentation of the brain into a three-dimensional (3D) grid using the individual’s structural MRI. This procedure is used to localize the sources of both the event-related magnetic fields and frequency oscillations by ‘modeling the signal from each voxel of the brain while simultaneously suppressing artifacts and any non-event-related sources’. If there are various signals that are occurring at the same time window, beamforming is able to separate the signals by producing a 3D distribution of the magnetic power of the neuronal sources.

2.7 MEG Imaging Evidence of Somatosensory Impairments

In addition to the clinical sensory deficit observations previously described, few HCP studies have used MEG and EEG demonstrating the aberrant processing of the primary (contralateral) somatosensory cortex (S1) in response to sensory stimulation by measuring (1) evoked responses to electrical stimulation of the median nerve or tactile stimulation and (2) cortical oscillatory modulations (alpha and beta frequency bands) to external stimulation.

2.7.1 Abnormal somatosensory evoked responses

To date, there are four published MEG studies that have demonstrated abnormalities of the somatosensory system after tactile or electrical median nerve stimulation in individuals with HCP.

Nevalainen et al have shown contralateral SEF responses to electrical stimulation of the median nerve in children with HCP (n=8, 14.5±2 years) with what they describe as a subcortical brain lesion including lesion types of an infarction, periventricular leukomalacia (PVL), or porencephaly. Abnormal SEF responses included missing deflections, aberrant morphology, longer latencies (delayed time), and lower amplitudes (weak response strength) of evoked responses within 100 ms from stimulation. These characteristics reflect a dysfunction in sensory
information processing of the contralateral S1. Interestingly, in comparison to TDC, HCP children, also had bilateral alterations in evoked responses in both hemispheres, showing the same abnormal SEF characteristics mentioned above in both the affected and unaffected hand. The authors note that this bilateral activation pattern was seen more commonly when stimulating the unaffected hand in comparison to the affected hand. The interpretation of the ipsilateral S1 responses (in conjunction with contralateral activation) in the affected hemisphere was suggested to be the result of altered interactions between the S1 cortices of the affected and unaffected hemisphere via inhibitory transcallosal connections. Tactile stimulation of digits II and V were also evaluated, revealing no significant change in latency or strength between the HCP and TDC cohorts. In addition, the Euclidian distance between the sources for digit II and V after tactile stimulation were significantly shorter in the CP group’s affected hemisphere than in TDC. This reflects a possible fusion of the cortical finger representation areas thought to be caused by a decrease in sensory experience during development (i.e. due to difficulties in fine hand motor control).

Pihko and colleagues also demonstrated that the SEFs to median nerve stimulation were contralateral in all 12 children with HCP, but in contrast to Nevalainen’s study, did not identify bilateral sensory alterations. Identification of similar SEF abnormalities such as longer latencies, abnormal waveform morphology, or the absence of the earliest activation at N20 (20 ms after stimulation onset) were also observed.

Guo and colleagues evaluated six children with spastic CP: two hemiplegic, three diplegic, and one quadriplegic. All of the participants had longer evoked response latencies for N20 and smaller amplitude responses with respect to median nerve stimulation of the index fingers as compared to TDC. These results suggest the delayed latency may be due to a white matter impairment that affects neural conduction and small responses indicate decreased touch sensitivity due to the reorganization of the hand’s representation in the somatosensory topology. Furthermore, SEF waveforms from children with CP had a larger variation in morphology with dull deflections in comparison to TDC’s sharp deflections and consistent latencies.

To date, most studies have used median nerve stimulation to elicit a somatosensory response. However, tactile stimulation has become a more suitable choice of stimulation as it is non painful and reduces movement from the participant yielding a reliable somatosensory response. In a recent multimodal study by Papadelis and colleagues, DTI, fMRI and MEG were
used to understand the function and anatomical sensorimotor network. Using MEG, prominent SEFs contralateral to the tactile stimulation of D1, D3 and D5 were observed in both hands at around 40-50ms in children with diplegic and hemiplegic children. This was shown in all TDC and diplegia CP children as well as 2 out of the 3 HCP children. However, the lowest functioning HCP child revealed an absence of an elicited response at 50ms for all 3 digits of the affected hand. In conjunction with Nevalainen’s study, SEF abnormal somatotopic organization was observed in the affected (or more affected) hemisphere such as missing deflections and aberrant morphology between CP (hemiplegic, diplegic) and TD children. The authors suggest that these alterations could be due to diminished thalamocortical projections from the thalamus to S1 or increased irregular functioning of the somatosensory network. In contrast to previous studies, but in line with Nevalanien, there were no differences in latency for the P50 cortical response for tactile stimulation.

Collectively, these four MEG studies demonstrate processing abnormalities of the contralateral S1 cortex in children with HCP showing that in conjunction with motor deficits, aberrant sensory neuronal processing deficits exist and should be included in the evaluation of response to hemiplegic hand intervention strategies. In contrast to the motor system, the somatosensory representation remains predominately in the lesioned hemisphere (contralateral to the affected hand) as outlined by three of the four studies, similar to TDC. However, even with intact contralateral sensory representation of the S1 cortex, sensory functioning abnormalities still exist in children with HCP. One of the four studies identified bilateral rather than unilateral sensory responses. Importantly, these studies collectively reveal aberrant organization of the somatosensory cortex in children with HCP. These results provide further evidence for the high prevalence of sensory dysfunction in children with HCP by abnormal conduction of sensory information predominantly to the contralateral S1 cortex. This suggests that decreased tactile detection can limit sensory experiences that are important in early brain mapping of the somatosensory brain structures. Thus, the association between sensory and motor deficits in individuals with HCP is important to explore.

2.7.2 Somatosensory cortical oscillations (alpha and beta bands)

In addition to evoked activity, the MEG has been used to evaluate spontaneous cortical oscillations and their modulations to somatosensory stimulation. These studies provide an initial understanding of the reactivity of the ongoing primary sensorimotor cortical activity between
children with HCP and TDC. This reveals spontaneous rhythmic oscillations recorded in the S1 cortex that appear in narrow frequency bands centered around 10 and 20 Hz, referred to as alpha and beta bands, respectively. It has been previously shown that both alpha and beta oscillations can be modulated by somatosensory stimulation.\textsuperscript{21} Stimulation of the median nerve, for example, leads to an initial post stimulus suppression at 100-300 ms (event-related desynchronization) followed by a rebound (event-related synchronization). Patterns of reactivity of somatosensory oscillations, represented by suppression and rebound plays an important role in understanding the underlying neural effects of tactile registration and perception on alpha and beta rhythm after stimulation of the sensory cortex in children with HCP.

Recently, Pikho et al demonstrated that the reactivity of both the alpha and beta-band sensorimotor cortical oscillations to contralateral median nerve stimulation was reduced in the affected hemisphere.\textsuperscript{17} In children with HCP, suppression and rebound strength of both alpha and beta frequency bands were smaller in the affected than the unaffected hemisphere; showing no differences between hemispheres of TDC. Hoon et al, suggests that this decrease in suppression and rebound of the oscillations could be due to thalamocortical sensory connections or increased aberrant functioning of the sensorimotor networks.\textsuperscript{82} Indeed, Papadelelis et al’s diffusion tensor imaging (DTI) findings revealed structural deficits in thalamocortical fibers projecting from the thalamus to the pre-central and post central gyri in children with HCP.\textsuperscript{15} Furthermore, in two of the three children with CP who had ipsilateral motor representation, the beta band modulations were absent in both the affected and unaffected hemispheres following stimulation to the affected hand. This suggests the existence of abnormal sensorimotor network interactions in these individuals.

It is important to note that the neural basis of the somatosensory and motor oscillations and their reactivity is complex and not completely understood. Traditionally, movement-related reactivity of the alpha band has been attributed to the postcentral (somatosensory) gyrus, while the precentral (motor) cortex contributes to beta-band oscillations.\textsuperscript{69} However, it has been suggested that alpha- and beta-band oscillations could theoretically be generated in the SI cortex.\textsuperscript{83} For example, when only tactile stimulation was used to modulate the oscillations, the suppression in alpha band and rebound in beta band were localized to somatosensory and motor cortices, respectively.\textsuperscript{69} However, as both primary motor and somatosensory cortices seem to be able to generate oscillations in alpha and beta bands, the modulations measured with MEG
probably reflect complex interactions in the sensorimotor networks. This includes both motor and somatosensory cortices, highlighting the interplay and association between both modalities.

2.8 Sensory-motor hand function association in children with HCP

It is well known that the planning and execution of proper hand function relies on grip strength, in-hand manipulation, and tool use. Importantly, the underlying upper extremity sensation associated with all these actions are also required for appropriate hand function. When severe sensory deficits exist, individuals tend to neglect the affected limb and as a result it can result in a decline in upper limb function. In addition to this neglect, motor learning can be further impaired caused by a decline or absence of ascending afferent fibers. Sensory retraining interventions aim to enhance sensory abilities, and have been used in the treatment of patients with stroke. Despite this, similar studies involving the effectiveness of sensory enhancement in children with HCP are still required.

There are very few studies that have actually examined whether there is a relationship between sensation and hand function in children with HCP. However, those that have studied this relationship have shown the importance of sensation on performance of precision grip in children with HCP compared to controls. It can be argued that sensory input should be important for the adjustment of grip and scaling of forces. For example, a strong positive correlation has been shown for sensory modalities (such as: stereognosis and 2-point discrimination) and pinch strength (as measured by a dynamometer), grip force adaptation, and grip force rate scaling (anticipatory control of force output). This therefore gives evidence to support the importance of sensation and motor control of fingertip force during grip. Hemiparetic pediatric literature has also shown that sensory and motor improvements are correlated after motor training. For example, Robert and colleagues have demonstrated that improved upper limb kinematics during motor recovery training (reach and grasp task) has also been associated with improved proprioception and tactile registration thresholds in a HCP cohort. However, studies have also argued that sensory deficits may be caused by underlying secondary effects elicited by motor limitations. For example, it has been shown that the motor performance errors of children with CP are linked with neural synchronization within the somatosensory cortices. This suggests that the motor impairments seen in children with HCP may be partly due to deficient processing by the sensorimotor cortices and related error checking networks. Impaired sensory feedback would
therefore limit the child’s ability to execute a motor plan properly, thereby increasing performance errors. This is a novel concept that has only recently been explored.

Similarly to motor neuronal recovery after CIMT in adult stroke patients, sensory studies of adults with a presumed MCA infarction have shown that improved hand function after CIMT correlates with neuronal sensory recovery. Following CIMT in a selected population of chronic stroke patients with moderate hand paresis, normal sensory examination, and somatosensory evoked potentials, improved hand function was closely correlated with the fMRI activation peak changes within the contralateral S1. Therefore, the more hand function improved, the more peak activation within the S1 changed. Laible and colleagues suggests that motor recovery implicates S1 involvement which could be due to the enhancement of corticospinal fibers or the dynamic processing between the S1 and the remaining M1 regions. In addition, an fMRI study of stroke patients with MCA lesions revealed an increase in fMRI signal change correlating with improved hand function within the cerebellum (bilaterally), the contralateral secondary somatosensory cortex (S2), and the contralateral dorsal premotor cortex. This occurred following a two week home therapy program based off of CIMT principles. It is noteworthy that the S1 was not explicitly evaluated in this particular study. Collectively, these studies suggest that if altered recruitment of sensorimotor cortical plasticity within the ipsilesional S1 or S2 is associated with motor recovery during a motor task, then perhaps CIMT can enhance sensory processing. This in turn can be an underlying factor for motor recovery. Adults with stroke who have an acquired lesion with previous normal motor and sensory function are quite different from children with HCP who have developed with the lesion and have not had a baseline normal experience. Therefore, it is important to specifically study neuroplastic changes within the sensorimotor regions of the brain in individuals with HCP.

Taub explains how deficits in neuromotor function have profound effects on sensory awareness and responsiveness. In their study, parental reports and videotaped sessions indicate that CIMT demonstrated new sensory awareness of the hemiparetic extremity, warranting future research to evaluate these reports objectively. CIMT research in HCP has focused predominantly on the motor response, however, the importance of sensory change to facilitate motor performance cannot be overlooked.
2.9 MEG and clinical sensory studies and CIMT

With the potential role of an aberrant somatosensory system impacting motor function, understanding such underlying sensory mechanisms may provide valuable information underlying recovery in therapy such as CIMT.

The evaluation of clinical sensory function before and after CIMT has only been evaluated in specific modalities such as tactile discrimination and stereognosis, showing no statistical significance. Furthermore, the evaluation of clinical sensory function has been completed as a secondary exploratory outcome for the specific modalities such as tactile discrimination and stereognosis. Despite such sensory assessments revealing no statistically significant change before and after treatment, it is important to note that sensory outcomes have not been the primary area of focus in children with HCP, with studies continuing to focus on functional changes.\textsuperscript{12,13} Other sensory deficits affecting this population, such as proprioception and kinesthesia, have not been evaluated after CIMT.

As seen previously, advanced neuroimaging techniques can evaluate sensory neural processing change. To date, two studies have investigated neural sensory improvement using MEG in HCP children after CIMT. Our previous MEG single case study of a child with an MCA lesion, revealed changes in proprioceptive responses in the contralateral S1 following CIMT after completing a standardized motor task (4-finger extension/flexion).\textsuperscript{22} This suggested the improvement was a result of increased sensory input from the affected limb.

Juenger and colleagues focused on the \textit{selective} role of the somatosensory cortex (S1) in functional recovery after CIMT using a somatosensory specific task, showing an increase in S1 activation in response to tactile stimulation after CIMT training.\textsuperscript{23} Their investigation revealed an increase in ‘early-SEF’ at N20 (20ms after stimulation onset) amplitude and reduction in latency in children with contralateral corticospinal projections. Those with ipsilateral projections showed an increase in SEF amplitude only. These results support the interpretation of increased synaptic activity of S1 after CIMT in children with HCP.

However, the use of clinical sensory outcomes paired with advanced neuroimaging techniques to evaluate changes in sensory processing in HCP children after CIMT have yet to be evaluated. This will allow for an investigation of the relationship between sensory feedback with
CIMT at both a central and functional level. An assessment of changes in SEF amplitude and latency at ‘P50 (50 ms after stimulation onset) will also help to elucidate changes in the S1 processing and expand our knowledge past responses at N20 (20ms after stimulation onset).\textsuperscript{17,19}
CHAPTER 3: Objectives and Hypotheses

While our understanding of the clinical and neuronal mechanisms of motor recovery after CIMT is improving, the impact in CIMT on sensory function is under-investigated.

The **primary objective** of this study focuses on how sensory function changes in children with HCP treated with CIMT. By evaluating individuals longitudinally and comparing clinical and MEG sensory measures before and after CIMT, we aim to investigate the mechanistic sensory role of improved hand and arm function following CIMT level.

**Secondary objectives** are: (1) to evaluate the maintenance and longevity of any effects at 6 months post therapy at both a clinical and neuronal level; (2) to evaluate potential clinical and neuronal sensory change in the unaffected hand; and (3) to evaluate a possible correlation between clinical and MEG sensory outcomes and functional improvement.

**Primary Research Question:** For 10 children recruited in a prospective cohort with HCP, will CIMT result in an improvement in clinical sensory outcomes and MEG somatosensory cortex neural activity (measured by peak SEF and oscillatory modulation), post CIMT?

**Hypotheses:** Using a sensory enhanced CIMT protocol, clinical (2-point discrimination, tactile registration, stereognosis, proprioception and kinesthesia) and neural outcomes (SEF and alpha/beta oscillations) from baseline to post CIMT are expected to improve.
CHAPTER 4: Methods

4.1 Participants

10 participants (eight males and 2 females) between the ages of 5 to 13 years diagnosed with HCP as a result of a vascular cortical and/or subcortical injury, were recruited from Holland Bloorview Kids Rehabilitation Hospital (HBKRH).

All participants had to meet the following inclusion criteria for entry into the study:

1. Diagnosis of hemiplegic CP secondary to an MCA infarct or subcortical vascular injury
2. Age between 5 and 14 years
3. Ability to co-operate, understand, and follow simple instructions for neuroimaging tasks and remain still for about 45-60 minutes
4. No previous participation in a CIMT camp within 9-months of study entry or Botulinum toxin upper limb injections within 6-months of study entry was classified as exclusion criteria. Other exclusion criteria included non-removable ferromagnetic materials that may cause artifacts in the MEG (e.g. braces, retainers, pacemakers, piercings, surgical screws, etc).

The present research study was approved by the Bloorview Research Ethics Board and the Sick Kids Research Ethics Board. Informed consent and assent were obtained from the guardian of each child.

4.2 Study Design

This is a prospective cohort study with clinical and MEG imaging outcomes obtained at 1 week before CIMT (baseline), at 1 month (+/- week) after baseline (post CIMT) and 6 months after baseline (6 month post CIMT). Such a longitudinal design will allow for the detection of potential changes in clinical and MEG measures over the short-term and long-term for each child.
4.3 CIMT Intervention

A 3-week CIMT protocol was administered, requiring the participants to wear a non-removable, below-elbow cast on the non-hemiplegic limb for the first week in the home/community (24 hours per day). This was followed by a 2-week modified CIMT camp called “Hand2Hand”, which was developed at Holland Bloorview Kids Rehabilitation Hospital. The children wore a removable cast for the majority of camp-time during the first week and for 1 hour per day during the second week. Children worked with occupational therapists in a group setting for 4 hours a day, 5 days per week (40 hours total). The intervention concentrated on unilateral motor and sensory activities with the hemiplegic hand in the first week and bilateral motor and sensory activities during the second week. Activity modifications were progressively scaled to ensure a level of challenge based on individual ability levels (i.e. either grading down or up depending on the participant's ability and progress throughout the camp). The camp program sustained a ratio of 2 children per occupational therapist and they were encouraged to practice for 1 hour each night at home.

To enhance the sensory component of the CIMT camp and optimize potential change in

<table>
<thead>
<tr>
<th>Visit 1 Baseline</th>
<th>Visit 2 CIMT Intervention</th>
<th>Visit 3 Post CIMT</th>
<th>Visit 4 6 Month post CIMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ST assessment</td>
<td>Casting of ‘strong’ arm (24 hours for 1 week) at HBKRH</td>
<td>1 month (+/- week) after baseline</td>
<td>6 months after baseline</td>
</tr>
<tr>
<td></td>
<td>CIMT camp (5 hours/day for 2 weeks) at HBKRH</td>
<td>OT tests (2-3 hours) at HBKRH</td>
<td>OT tests (2-3 hours) at HBKRH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEG at HSC (1 hour)</td>
<td>MEG at HSC (1 hour)</td>
</tr>
<tr>
<td>1 week before baseline</td>
<td>MRI (brain image) at HSC (10 minutes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OT tests (2-3 hours) at HBKRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MEG at HSC (1 hour)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. CIMT intervention and clinical and imaging assessment timeline. HSC = Hospital for Sick Children, HBKRH = Holland Bloorview Kids Rehabilitation Hospital.
sensory function targeted sensory activities were integrated focusing on tactile, stereognosis and proprioceptive modalities (activities included matching textures/shapes, Wii Fit games for proprioception, object hunt (i.e. participants would ‘feel’ for different objects with different textures and shapes, in tubs filled with various mediums such as soapy water or beans/rice) (Appendix A). The schedule of the camp’s activities are shown in Appendix B.

4.4 Clinical Evaluation of sensory function

All sensory tests were performed with the tested hand obstructed by an opaque curtain or blindfolded. Participants were assessed using a number of standard tests and measurements that are sensitive to various aspects of upper limb sensory and motor functionality. The same therapist evaluated the same patient at all time points for consistency.

4.4.1 Tactile registration

Tactile registration was evaluated using the 5-item Semmes-Weinstein Monofilament kit. The monofilaments were applied at a 90 degree angle against the tip of the index finger of the affected and unaffected hand until bowing occurred. Filaments were held in place for two seconds and participants were instructed to notify the evaluator if they felt any sensation of touch by saying “yes” or “no” (scores 0–4, where 4 = normal, 2 = diminished protective touch, and 0 = no sensation). Starting with the monofilament of value 2.83 (lower side of normal sensation), the monofilament is applied to the skin surface of the finger three times, with one or more correct responses taken as an affirmative response, as indicated by the original test methodology by Bell-Krotoski, et al. Null stimuli were also used to find false positive responses. The Semmes-Weinstein Monofilament test has established reliability (test-retest reliability ICC of 0.96), and high content validity and consistently high intra-rater reliability (0.79-0.96).

4.4.2 Two point discrimination

The two point discrimination test was used to measure an individual’s ability to perceive two points of stimuli presented simultaneously. Using the prongs of a Disk-Criminator spaced exactly 5 mm apart, prongs were gently pressed onto the finger pulp of the thumb, index, and middle finger, five times each. At random a paperclip was pressed with either one or both tips into the fingertip. The child was asked to identify whether they felt one or two points. A total score out of 15 for each hand (affected and unaffected) was determined. Two point discrimination has also established very high interrater (ICC=0.92) and test-retest reliability.
4.4.3 Stereognosis

Stereognosis test was administered to evaluate tactile identification of familiar objects. Of the 12 objects, six are matched in pairs of similar size and shape (e.g. pencil/pen, coin/button, paperclip/safety pin) while six object pairs differed from each other significantly (e.g. key/clothespin, marble/comb, spoon/ball). The evaluator randomly selected six objects of which 3 were from similar pairs and 3 from the non-similar objects. The objects were placed in the child’s hands in random order, and only unilateral exploration was permitted. Participants were then shown a picture of all 12 objects and are asked to point to the image of the object or answer verbally. The number of objects correctly identified with the affected and unaffected hand was recorded. The total score range was from 0 to 6. This test has established interrater reliability (ICC=0.78) and test-retest reliability (ICC=0.86).

4.4.4 Proprioception

To assess proprioception (joint-position sense) of the upper limb, a sensitive parametric protocol is used. This protocol has previously been used on participants with hemiplegic and diplegic CP by Wingert et al, to report differences between the affected and unaffected hand, as well as between children with HCP and TD children. This involves the use of a semigoniometer, to measure forearm orientation angles in the transverse plane (Figure 1). Participants were blindfolded and asked to complete a series of proprioceptive-matching trials, in which the unaffected and affected hand are passively extended (evaluator used the pointer while participant holds the handle) to the 10 predetermined target angles, held for 2 seconds and returned to the start position (0 degrees) along the semi-goniometer axis. All chosen angles were within participant’s forearm pronation and supination range to avoid range of motion deficits. After a verbal ‘match’ cue, participants are asked to actively replicate the target position with the same arm. The magnitude (degrees) and direction (pronation/supination) of error between performance and target location is recorded for each trial to the nearest degree for both the affected and unaffected hand.

4.4.5 Kinesthesia

Using the control rod of the proprioceptive device, kinesthesia was measured by direct passive rotation of approximately 0.5°/s with a maximum displacement of 4°. Direction was
pseudorandomly selected per trial, with half of the trials moving in one direction and half in the other direction. Participants reported movement direction (left or right indicating pronation or supination) immediately after movement was applied. Performance accuracy was calculated based on the number of correct responses in 10 trials for unaffected and affected hand.

![Image](image1.png)

**Figure 1.** Proprioceptive/kinesthesia device used by Wingert et al (2009). Similar custom built device was used in this study, allowing for rotation around the axis of a 'semi-goniometer' to measure forearm orientation angles in the transverse plane.

### 4.5 Clinical Evaluation of hand motor function

Participants were clinically evaluated between all 3 timepoints, baseline and post CIMT and 6 months post CIMT. The Quality of Upper Extremity Skills Test (QUEST) is a standard test used for clinical evaluation of functional capacity. The QUEST is a criterion-referenced measure of upper extremity function evaluating a child’s quality of movement in four domains: dissociated movements (isolated joint movement that is not part of a pattern of spastic synergy), grasp, weight bearing and protective extension. QUEST scores are calculated as percentages with a maximum score of 100. Higher scores represent better quality of function. A change of 5 points on the QUEST is considered a minimal clinically important response. QUEST scoring was done for only the hemiplegic extremity.

### 4.6 Tactile Stimuli

A controlled pneumatic tactile stimulator was used to deliver precisely calibrated non-painful somatosensory tactile stimuli to the tips of digit II of both hands using compressed-air-
driven inflatable plastic membranes (1cm diameter, 4D-Neuroimaging, San Diego, CA). All components were MEG compatible. Stimuli were activated under computer control used to generate rapid (10-ms rise-time) pulses of compressed air and were repeated 400 times per arm during MEG scanning. During this time the child viewed their favorite movie or video to maintain their level of vigilance and reduce head and eye movements. The inter-train interval (ITI) was set to 1-1.5s with a repetition rate of 25 Hz. Such vibrotactile stimuli have been shown to evoke a reliable somatosensory steady-state response.24,25,93

4.7 MEG recordings

MEG signals were recorded in a magnetically shielded room using a 151 channel whole-head MEG system (CTF, VSM MedTech Ltd) with continuous head motion monitoring. All scanning was completed in the MEG suite at the Hospital for Sick Children. Participants were comfortably positioned in a supine position with arms resting on either side to minimize head motion. In addition, a head cushion was placed in the MEG scanner to decrease movement artifact (Figure 2). Three fiducial landmarks were placed on the nasion, left and right pre-auricular points in order to locate the participant’s head position relative to the sensor array. These fiducial coils were replaced with MRI markers for the MRI scan required for co-registration. In addition, aid of digital photographs, allowed for an accurate co-registration of the 3 time point datasets. Electromyography (EMG) electrodes were placed on both forearms and video recording of participants were performed during the MEG scan to identify and remove trials with arm movements. The sampling rate of the MEG recording was 600 samples/second (bandwidth=0-1000Hz).

4.8 MRI scanning

MRIs were obtained with a 3T Siemens scanner. For MEG source modeling, standard 1mm isotropic T1-weighted images were obtained using a magnetization prepared gradient-echo sequence (MP_RAGE) with parallel acquisition technique (GRAPPA). MEG images were superimposed onto the co-registered MRI for better anatomical accuracy during source localization.
4.9 MEG data processing/analysis

4.9.1 Pre-processing

MEG trials containing large eye, or limb movements were removed prior to analysis based on video recordings. In addition, trials with head movements deviating from the baseline more than 1 cm were discarded. This was typically due to muscle artifact and eye blinks. Continuous MEG data were segmented into 1s epochs (1.5s before and 1.5 ms after tactile stimulus). Each epoched dataset was time locked to the presentation of tactile stimulus.

4.9.2 Source localization

4.9.2.1 Somatosensory evoked source localization analysis

To identify the source location of SEF activity to tactile stimulation, beamformer analysis was conducted using a scalar Event Related Beamformer algorithm filtering the data from 1-50Hz and then applying the beamformer at 5ms time intervals. This algorithm is implemented in the BrainWave toolbox developed at the Hospital for Sick Children.
Beamformed images can be viewed as a maximum-intensity projection (glass brain) volumetric image in Montreal Neurological Institute (MNI) coordinates after normalizing the beamformer image to the MNI template brain using SPM8. MNI coordinates were scaled to the Talairach brain atlas using the mni2tal script. The coordinates for Brodmann area 3 (BA3) were identified by locating the peak activation around 50ms after tactile stimulation (this proposed timing of interest is explained in sections below). This region of interest is known to be the main sensory receptive area for sense of touch. Stimulation of the affected and unaffected hand for most participants had typical brain response pattern location representing a posterior-anterior current flow in the primary somatosensory cortex BA3 could be identified. However, location of the unaffected hand were more variable. Therefore, all locations within +/- 5mm from areas labeled BA3 using Talairach coordinates were accepted.

4.9.2.2 SAM beamformer analysis

Location source analysis for alpha frequency power change was implemented using the Synthetic Aperture Magnetometry (SAM) algorithm (Robinson and Vrba, 1999) implemented the BrainWave toolbox. SAM images generate images of source power summed over individual trials. Specifically, pseudo-t images were created for alpha (8-13Hz) frequency bands. Pseudo-T generates the normalized power, a difference (subtraction) of the source power in the baseline from the source power in the active time windows selected. These images of percent power change over time were created using a sliding active window of 300ms duration defined at 50ms intervals starting from stimulus onset (0ms) to 300ms. The same fixed 300ms was used for the baseline window (-400ms to -100ms). The volumetric images were spatially normalized to the MNI template brain using SPM8 and then averaged across participants. Group averages were then scanned for maximum peaks of power changes.

4.9.3 Identifying Somatosensory evoked fields (SEFs)

Within the first 150 ms interval, SEFs can be elicited by non-painful tactile stimuli characterized by a prominent positive peak around 40-50ms (P50) after stimulus onset. Although this peak was clearly observable in TDC as well as the unaffected hand in CP children, peak detection of the affected hand was especially difficult for the affected hand of CP individual SEF averages. Therefore, mean amplitudes were computed in the time-window 35-70ms to determine the P50 component. It has been previously shown that the P50 SEF components
generated in the affected hemisphere might appear delayed and distorted. Thus a peak P50 detection in the CP population is difficult in the grand averages at exactly 50ms. Therefore, a larger time window would allow for the analysis of P50, if present. Each subject's averaged sensor plot was used to find peak sensory latencies at all 3 time points (baseline, post CIMT and 6 month post CIMT, in turn helping to generate a more appropriate latency range for this group of children (Appendix C).

To characterize the SEF components, peak latency and amplitude were quantified. To quantify changes in peak amplitude of the magnetic brain activity, the global field power scores of all channels at the P50 peak were recorded. Once P50 was identified, a standard peak picking procedure was followed to measure group averaged peak and corresponding latency for the P50 component. The dipole source moments (source strength) measured in nanoampere-meters (nAm) and corresponding latencies measured in milliseconds (ms) were recorded. SEF amplitude will provide information regarding neuronal activity strength and SEF latency will provide information regarding cortical processing efficiency of the somatosensory cortext.

4.9.4 Oscillations

The reactivity of the somatosensory oscillations in the alpha and beta band were analyzed. Time-windows where coordinates of maximal source % power change were localized and then used to extract single-trial source activity over time. This was done in individual participants using the peak location in the SAM group images and using an automatic search within a 10 mm search radius from the group peak location to locate each individual’s peak location. Time series were band-filtered between 7-13Hz (alpha band) and 15-30Hz (beta band) and were used to generate a time-frequency representation (TFR) plot (wavelet cycles = 7, Frequency step = 0.5 Hz). TFR plots are used to assess changes over time across frequency bands. Power was averaged across the alpha and beta frequency band to generate an envelope of the time-course of event related desynchronization (ERD) or event-related synchronization (ERS). Peak amplitude (relative to baseline) for suppression and rebound of the alpha and beta oscillation were measured by using the % power change time-courses integrated across subject-specific time windows. In this way, power, 'amplitude envelope' was calculated by computing the area under the curve or above the curve (ERD or ERS respectively). Group comparisons of baseline, post CIMT and six-month time points on the time-courses were performed for both alpha and beta oscillations.
4.10 Statistical analyses

All statistical analyses were performed using IBM’s Statistical Product and Service Solutions (SPSS) software (version 21).

4.10.1 Behavioral effects of CIMT

*Primary objective:* Clinical sensory changes at post CIMT to baseline were evaluated using a parametric paired sample t-test or a non-parametric Wilcoxon signed-rank test for the affected and unaffected hand based on whether the outcome was continuous or ordinal. A Bonferroni correction of the p value was set at p<0.01 rather than p<0.05 as there are 5 sensory outcome measures.

*Secondary objective:* 6-month data was compared to baseline and post CIMT follow-up data using a parametric repeated measures ANOVA or a Friedman test (non-parametric ANOVA) to evaluate the longevity and maintenance of any changes for both the affected and unaffected hand (p<0.01).

4.10.2 MEG effects of CIMT

*Primary objective:* MEG changes (SEF amplitude and latency/ alpha integrated power and latency durations) at post CIMT to baseline were evaluated using a paired samples t-test for the affected and unaffected hand.

*Secondary objective:* (1) Six-month CIMT data was compared to baseline and post CIMT follow-up data using a repeated ANOVA to evaluate the longevity and maintenance of any changes for both the affected and (2) unaffected hand.

4.10.3 Relationship of Motor and sensory CIMT effects

*Secondary exploratory objectives:* To explore the association between motor and sensory change following CIMT, a bivariate Pearson correlation was run with the QUEST change score (representing CIMT motor response) and all change scores/values in MEG measures (SEF amplitude and latency) and clinical sensory measures (2PD, tactile registration, stereognosis, proprioception and kinesthesia). Change scores were calculated by subtracting baseline scores from post CIMT scores.
CHAPTER 5: Results

5.1 Participant Characteristics

10 children diagnosed with HCP, 8 males and 2 females (7 right hand affected and 3 left hand affected, mean age: 11.8 years, age range 5-13 years) completed the study. Demographic descriptions for all participants are summarized in Table 2.

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Sex</th>
<th>Age</th>
<th>Affected Hand</th>
<th>Injury Pattern</th>
<th>GMFCS Level</th>
<th>MACS Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>12</td>
<td>Left</td>
<td>MCA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>6</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI *</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7</td>
<td>Right</td>
<td>aPVI *</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>7</td>
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<td>aPVI</td>
<td>I</td>
<td>II</td>
</tr>
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<td>M</td>
<td>9</td>
<td>Left</td>
<td>aPVI</td>
<td>I</td>
<td>II</td>
</tr>
</tbody>
</table>

Table 2. Participant Demographics. *Denotes participants who did not complete neuroimaging component of the study. Injury pattern: Asymmetric periventricular injury, aPVI; Lateral Lenticulostriate Infarction, LLS; Middle cerebral artery, MCA.

All 10 participants completed the three clinical assessments. However, some participants did not complete specific sensory tests. For the kinesthesia and proprioception test, nine out of the ten participants completed all three time points for kinesthesia and proprioception (reported in the clinical results section below). Eight participants out of ten completed all three imaging assessments. Two participants did not complete the imaging assessments due to presence of epileptiform background activity which obscured sensory responses and one due to fear of entering the MEG/MRI scanner.

All 10 participants were casted for the first week of CIMT intervention. Seven out of ten
participants successfully completed the following two week (5 hr/day) camp CIMT intervention without interruptions. Participant 8 was absent 1 day due to a cold. Participant 5 was absent 1 day due to the stomach flu. Participant 3 was absent during the second week of camp due to a planned trip however, a customized home program with sensory and motor activities was provided by the occupational therapist. For this individual, compliance to the hours of recommended therapy were followed with 4-5 hours/day including a focus on more bilateral activities (consistent with the 2nd week of camp which focused on bilateral activities).

5.2 Clinical sensory outcomes

Results shown below are mean +/- standard deviation or median with minimum to maximum ranges. Measures of central tendency are stated. It is important to note that when considering the results presented throughout this section, some participants have missing results for specific tests (due to participant not cooperating or found too difficult to complete, physically or cognitively). Therefore, the sample size (n) for each test is stated.

5.2.1 Affected hand sensory outcomes

A paired samples t-test or a non-parametric Wilcoxon signed-rank test was conducted to determine CIMT effects from baseline to post CIMT for 5 sensory modalities of the affected hand: two point discrimination, stereognosis, tactile registration, kinesthesia and proprioception. Analysis revealed that CIMT intervention did not lead to any statistically significant change on all 5 sensory modalities of the affected hand from baseline to post CIMT (Bonferroni correction, p < 0.01). All 10 participants were included in the group means/medians, except 1 participant was not added to proprioception and kinesthesia results (did not complete due to lack of cooperation/concentration). Mean with standard deviation and median (Mdn) with range clinical scores with statistical analysis results for the affected hand are presented in Table 3. Following the table, are detailed results from the paired sample t-test (means) or a non-parametric Wilcoxon signed-rank test (medians) analysis comparing baseline to post CIMT values:
<table>
<thead>
<tr>
<th></th>
<th>2PD</th>
<th>Tactile Registration</th>
<th>Stereognosis</th>
<th>Proprioception</th>
<th>Kinesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(out of 15) n=10 mean (SD)</td>
<td>(out of 4) n=10 median (range)</td>
<td>(out of 6) n=10 median (range)</td>
<td>(angle error difference ) n=9 mean (SD)</td>
<td>(% accuracy) n=9 mean (SD)</td>
</tr>
<tr>
<td>Baseline</td>
<td>9.8 (4.1)</td>
<td>3.0 (1-4)</td>
<td>3.0 (0-6)</td>
<td>16.9° (8.4)</td>
<td>61.7 (27.6)</td>
</tr>
<tr>
<td>1 month</td>
<td>10.3 (3.7)</td>
<td>3.0 (2-4)</td>
<td>3.0 (0-6)</td>
<td>12.3° (7.1)</td>
<td>70.0 (21.8)</td>
</tr>
<tr>
<td>6 month</td>
<td>9.2 (4.5)</td>
<td>3.0 (0-4)</td>
<td>3.0 (1-5)</td>
<td>12.3° (7.3)</td>
<td>77.9 (22.8)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>F_{2,18} = 0.79, p = 0.47</td>
<td>$\chi^2(2) = 0.20$, p = 0.37</td>
<td>$\chi^2(2) = 0.18$, p = 0.42</td>
<td>F_{1,220} = 1.70, p = 0.21*</td>
<td>F_{2,18} = 2.33, p = 0.13</td>
</tr>
</tbody>
</table>

| p-value | t(9)=1.00, p=0.34 | z=-0.45, p=0.66 | z=-0.58, p=0.56 | t(8)=-2.61, p=0.03 | t(8)=1.03, p = 0.33 |

Table 3. Mean/median clinical sensory scores at baseline, post and six month post CIMT of the affected hand. Paired t-test or Wilcoxon signed-rank test compare mean or median values respectively from baseline to post CIMT (Bonferroni correction p<0.01). Repeated measures ANOVA or Friedman test (non-parametric alternative to the one-way ANOVA with repeated measures), compare across the three timepoints (baseline, post CIMT, and six month post CIMT); * Greenhouse-Geisser correction applied when Mauchly's test of sphericity was violated.

**Two point discrimination**

Two point discrimination mean scores remained consistent from 9.8 ± 4.1 baseline to 10.3 ± 3.7 post CIMT. There were no outliers and the data was normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p=0.08), respectively. CIMT intervention did not elicit statistically significant changes in two point discrimination scores of the affected hand from baseline to post CIMT, t(9)=1.00, p=0.34. Mean group two-point discrimination scores are graphically represented in **Figure 3a**, with individual subject results reflecting mean values (**Figure 4a**).

**Tactile registration**

Tactile registration median scores of the affected remained consistent from baseline (Mdn =3.0; range: 1-4), to post CIMT (Mdn = 3.0; range: 2-4). A Wilcoxon signed-rank test revealed that CIMT intervention did not elicit a statistically significant difference between baseline and post CIMT tactile registration scores of the affected hand, z=1.47, p=0.14. Median
group tactile registration scores are graphically represented in Figure 3b, with individual subject results reflecting mean values (Figure 4b).

**Stereognosis**

Stereognosis median scores of the affected remained consistent from baseline (Md =3.0; range: 0-6), to post CIMT (Md= 3.0; range: 0-6). A Wilcoxon signed-rank test revealed that CIMT intervention did not elicit a statistically significant difference between baseline and post CIMT stereognosis scores, z=-0.58, p=0.56. Median group stereognosis scores are graphically represented in Figure 3c, with individual subject results reflecting mean values (Figure 4c).

**Proprioception**

The mean magnitude of error between performance and target location was used to determine proprioception accuracy (a decrease in error) before and after CIMT. Proprioception magnitude error decreased from 16.9° ± 8.4 baseline to 12.3° ± 7.1 post CIMT. There were no outliers and the data was normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p>0.05), respectively. CIMT intervention did not elicit statistically significant changes in proprioception scores of the affected hand from baseline to post CIMT, t(8)=-2.611, p=0.03 once a Bonferroni correction was applied. Mean group proprioception scores are graphically represented in Figure 3d, with individual subject results reflecting mean values (Figure 4d).

**Kinesthesia**

Kinesthesia accuracy score of the affected hand increased from 61.7% ± 27.6 baseline to 70.0% ± 21.8 post CIMT. There were no outliers and the data was normally distributed, as assessed by boxplot and Shapiro-Wilk test (p> 0.05), respectively. CIMT intervention did not elicit statistically significant changes for the affected hand from baseline to post CIMT, t(8)=1.031 p = 0.33. Mean group kinesthesia scores are graphically represented in Figure 3e, with individual subject results reflecting mean values (Figure 4e).

**5.2.2 Six months post intervention for affected hand**

Using a repeated measures ANOVA or a Friedman test (non-parametric ANOVA), 6 months post CIMT effects were also investigated to evaluate any potential long term impact (compared to baseline and post CIMT respectively) of all 5 sensory modalities. CIMT intervention did not elicit statistically significant changes for two-point discrimination, tactile registration, stereognosis proprioception and kinesthesia across all 3 time points. Therefore, a
post hoc analysis was not applied. Refer to Table 3 above for the parametric and non-parametric ANOVA results.
Figure 3. Graphical representation of mean clinical sensory scores at baseline, post and six month post CIMT of the affected hand; a) two-point discrimination, n=10 d) proprioception, n=9 e) kinesthesia, n=9 and median scores for b) tactile registration of the index finger, n=10 c) stereognosis, n=10. Error bars represents standard deviation error.
INDIVIDUAL SUBJECT CLINICAL SENSORY RESULTS: AFFECTED HAND

Figure 4. Graphical representation of subject-specific clinical sensory scores at baseline, post and six month post CIMT of the affected hand; a) two-point discrimination b) tactile Registration of the index c) stereognosis d) proprioception e) kinesthesia. Each line represents an individual’s clinical scores (total of 10 participants). Note tactile registration provides clinical scores at each time point, as participant data points are overlapped in graph and view of individual scores are obstructed.
5.2.3 Unaffected hand sensory outcomes

As part of our stated secondary objectives, sensory effects of the unaffected hand from baseline to post CIMT were assessed. A paired sample t-test or a non-parametric Wilcoxon signed-rank test were conducted to determine CIMT effects from baseline to post CIMT for five sensory modalities of the unaffected hand: two-point discrimination, stereognosis, tactile registration, kinesthesia and proprioception. Analysis revealed that CIMT intervention did not lead to any statistically significant change for all five sensory modalities of the unaffected hand from baseline to post CIMT (Bonferroni correction, p < 0.01). All 10 participants were included in the group means or median, except 1 participant was not added to proprioception and kinesthesia results (did not complete due to lack of cooperation/concentration). These participants were the same participants who did not complete the test for their affected hand. Mean/median clinical scores with statistical analysis results for the unaffected hand are presented in Table 4. Following the table, are detailed results from paired sample t-test (means) or a non-parametric Wilcoxon signed-rank test (medians) analysis, comparing baseline to post CIMT values:

<table>
<thead>
<tr>
<th></th>
<th>2PD (out of 15) n=10 mean (SD)</th>
<th>Tactile Registration (out of 4) n=10 median (range)</th>
<th>Stereognosis (out of 6) n=10 median (range)</th>
<th>Proprioception (angle error difference) n=9 mean (SD)</th>
<th>Kinesthesia (% accuracy) n=9 mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.3 (2.9)</td>
<td>3.0 (2-4)</td>
<td>6.0 (3-6)</td>
<td>12.2c (5.3)</td>
<td>80.0 (21.8)</td>
</tr>
<tr>
<td>1 month</td>
<td>13.4 (3.3)</td>
<td>3.0 (2-4)</td>
<td>6.0 (3-6)</td>
<td>81.9c (2.6)</td>
<td>78.9 (16.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>t(9) = 0.26, p = 0.80</td>
<td>z = -0.45, p = 0.66</td>
<td>z = -0.82, p = 0.41</td>
<td>t(8) = -2.15, p = 0.06</td>
<td>t(8) = -0.15, p = 0.89</td>
</tr>
<tr>
<td>6 month</td>
<td>14.6 (1.3)</td>
<td>3.0 (2-4)</td>
<td>6.0 (4-6)</td>
<td>8.3c (5.4)</td>
<td>78.9 (22.0)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>F1,1,11 = 1.582, p = 0.24*</td>
<td>χ² (2) = 0.25, p = 0.88</td>
<td>χ² (2) = 0.40, p = 0.82</td>
<td>F2,16 = 0.02, p = 0.98</td>
<td>F2,16 = -2.61, p = .011</td>
</tr>
</tbody>
</table>

Table 4. Mean/median clinical sensory scores at baseline, post and six month post CIMT of the unaffected hand. Paired t-test or Wilcoxon signed-rank test compare mean or median values respectively, from baseline to post CIMT (Bonferroni correction p<0.01). Repeated measures ANOVA or Friedman test (non-parametric alternative to the one-way ANOVA with repeated measures), compare across the three time points (baseline, post CIMT, and six month post CIMT); * Greenhouse-Geisser correction applied when Mauchly's test of sphericity was violated.
Two point discrimination

Two point discrimination scores of the unaffected hand remained unchanged from 13.3 ± 2.9 baseline to 13.4 ± 3.3 post CIMT. There were 4 outliers (participant 5, 8, 9 and 10), however, the data were normally distributed, as assessed by boxplot and Shapiro-Wilk test (p=0.04). Inspection of their values did not reveal them to be extreme and they were kept in the analysis. *CIMT intervention did not elicit statistically significant changes in 2-point discrimination of the unaffected hand from baseline to post CIMT, t(9)=0.264, p=0.80.*

Tactile registration

Tactile registration scores of the unaffected hand remained consistent from baseline (Mdn =3.0; range: 2-4), to post CIMT (Mdn= 3.0; range: 2-4). *A Wilcoxon signed-rank test revealed that CIMT intervention did not elicit a statistically significant difference between baseline and post CIMT tactile registration scores, z=-0.45, p=0.66.*

Stereognosis

In addition, Stereognosis scores of the unaffected hand remained consistent from baseline (Mdn =6.0; range: 3-6), to post CIMT(Mdn= 6.0; range: 3-6). *A Wilcoxon signed-rank test revealed that CIMT intervention did not elicit a statistically significant difference between baseline and post CIMT stereognosis scores, z=-0.82, p=0.41.*

Proprioception

The mean magnitude of error decreased from 12.2° ± 5.3 at baseline to 8.1° ± 2.6 post CIMT. There were no outliers and the data were normally distributed, as assessed by boxplot and Shapiro-Wilk test (p>.05), respectively. *CIMT intervention did not elicit statistically significant changes in proprioception of the unaffected hand from baseline to post CIMT, t(8) =-2.150, p =0.06.*

Kinesthesia

Kinesthesia accuracy scores remained consistent from 80.0% ± 21.8 baseline to 78.9% ± 16.1 post CIMT. There were no outliers as assessed by boxplot. The data were normally distributed at baseline and post CIMT time point, as assessed by Shapiro-Wilk test (p>.05). *CIMT intervention did not elicit statistically significant changes in kinesthesia accuracy for the unaffected hand from baseline to post CIMT, t(8) = -0.147, p = 0.89.* In comparison to the affected hand, CIMT did not show a trend towards kinesthesia of the unaffected hand.
5.2.4 Six months post intervention for unaffected hand

6 months post CIMT effects were also investigated to evaluate any potential long term impact (compared to baseline and post CIMT respectively) using a repeated measures ANOVA or a Friedman test (non-parametric ANOVA). Overall, CIMT intervention did not elicit statistically significant changes for two-point discrimination, tactile registration, stereognosis, proprioception and kinesthesia, with scores remaining consistent from baseline to post CIMT to six month post CIMT. Therefore, a post hoc analysis was not applied. Refer to Table 4 above for the ANOVA results.

5.2.5 Unaffected and affected hand baseline sensory comparison (additional exploratory analyses)

To assess the baseline sensory function between the affected and unaffected hand at baseline, an independent t-test (parametric) or Mann-Whitney U-test (non-parametric) was performed. This was done to determine baseline differences in sensory function between the affected and unaffected hand. There were statistically significant differences between 2-point discrimination ($t(9)=-2.8$, $p=0.02$) and stereognosis ($U = 85.5$, $z = 2.9$, $p = 0.01$), respectively, of the unaffected hand and the affected hand at baseline. Tactile registration ($U = 53.0$, $z = 0.2$, $p = 0.85$), proprioception ($t(8)= 1.5$, $p = 0.18$) and kinesthesia ($t(8)= -1.9$, $p=0.09$) did not show statistical differences.

5.2.6 Motor functional behavioural outcome

There were no significant differences between baseline and post CIMT on the change in Quality of Upper Extremities Skills test (QUEST), $t(9)=2.00$, $p=0.08$. However, 5 out of 10 participants improved scores by a minimally important clinical amount (increase by 5 points). Furthermore, 6 months post CIMT functional effects were also investigated for longevity and maintained effects (compared to baseline and post CIMT respectively) using a repeated measures ANOVA. There was one outlier at post CIMT (participant 6) as assessed by boxplot. Inspection of their value did not reveal them to be extreme and they were kept in the analysis. Furthermore, the QUEST scores were normally distributed at each time point as assessed by Shapiro-Wilk test ($p>0.05$). Overall, CIMT intervention did not elicit statistically significant functional changes, with QUEST scores remaining consistent from baseline to post CIMT to six month post CIMT, $F(2,18)= 2.21$, $p=0.27$. Individual subject scores for baseline, one and six months post CIMT are given in Table 5.
5.3 MEG neuroimaging results

5.3.1 Somatosensory evoked responses

Selection of anatomical locations for SEF source analysis

It has been shown that Brodmann area 3 (BA3) is involved in early somatosensory processing in response to tactile and median nerve stimulation to the upper hand extremities, both in CP and healthy populations.\textsuperscript{66-99} In this study, BA3 was the expected location for source activation using the criteria: 1) beamformer peak activation localized for the SEF P50 component within +/- 5mm from the postcentral gyrus, based on Talairach atlas labels incorporated into the BrainWave analysis software (\texttt{www.talairach.org})\textsuperscript{100} and 2) an identifiable maximum P50 source magnitude within a latency range of 35-65ms. Average source location and the corresponding magnitude are shown in Table 6 for both the affected and unaffected stimulated hand. Individual source locations revealed +/- 5mm from the post central gyrus, except for two participants who revealed displaced or reorganized somatotopic organization. Such reorganization has been documented in children with HCP in response to tactile stimulation (Appendix D).\textsuperscript{15} Reorganized location was verified to represent activation in response to tactile response. Two source locations, both left and right hemispheric locations, are reported at each time point. This is to distinguish the source location between the right hand affected participants (n=6) and the left hand affected participants (n=2). Source location was contralateral to the stimulated hand.

<table>
<thead>
<tr>
<th>Participant number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90.34</td>
<td>58.72</td>
<td>60.65</td>
<td>39.89</td>
<td>52.88</td>
<td>11.98</td>
<td>70.08</td>
<td>39.88</td>
<td>51.97</td>
<td>32.96</td>
</tr>
<tr>
<td>Post CIMIT</td>
<td>92.97</td>
<td>64.58</td>
<td>62.21</td>
<td>58.85</td>
<td>45.22</td>
<td>10.76</td>
<td>79.8</td>
<td>54.82</td>
<td>48.9</td>
<td>44.8</td>
</tr>
<tr>
<td>Change score (baseline – post CIMIT)</td>
<td>2.63</td>
<td>5.86*</td>
<td>1.56</td>
<td>18.96*</td>
<td>-7.66</td>
<td>-1.22</td>
<td>9.72*</td>
<td>14.94*</td>
<td>-3.07</td>
<td>13.06*</td>
</tr>
<tr>
<td>Six month</td>
<td>84.32</td>
<td>65.58</td>
<td>71.5</td>
<td>48.29</td>
<td>69.67</td>
<td>12.98</td>
<td>63.16</td>
<td>32.26</td>
<td>56.64</td>
<td>46.02</td>
</tr>
<tr>
<td>Change score (baseline – six month)</td>
<td>-6.02</td>
<td>6.86</td>
<td>10.85</td>
<td>8.4</td>
<td>16.79</td>
<td>1.00</td>
<td>-6.92</td>
<td>-7.62</td>
<td>4.57</td>
<td>13.06</td>
</tr>
</tbody>
</table>

Table 5. Mean QUEST scores at baseline, post CIMIT and 6 month post CIMIT. Change scores from baseline to post CIMIT as well as change scores from baseline to 6 month post CIMIT are shown in the grey rows. *Indicate individuals who improved by a clinically relevant amount from baseline to post CIMIT.
Table 6: Source location with corresponding Talairach coordinates in the affected and unaffected hemisphere at all 3 time points (baseline, post CIMT and six month post CIMT), including magnitude for peak identification. *Denotes location within 5 mm of post central gyrus. Two locations are represented for each time point/stimulated hand as there are 6 right hand affected participants (n=6) and 2 left hand affected participants (n=2). Subject-specific coordinates can be found in Appendix D Table A (affected hand) and B (unaffected hand).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Source Location</th>
<th>Coordinates</th>
<th>Magnitude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFFECTED HAND</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASELINE</td>
<td>L Postcentral Gyrus, BA3* (n=6)</td>
<td>-30, -18, 32</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>R Precentral Gyrus, BA4* (n=2)†</td>
<td>22, -21, 54</td>
<td>1.38</td>
</tr>
<tr>
<td>POST CIMT</td>
<td>L Precentral Gyrus, BA4 (n=6)</td>
<td>-26, -17, 51</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>R Sub-Gyral (n=2)†</td>
<td>30, -18, 32</td>
<td>1.80</td>
</tr>
<tr>
<td>SIX MONTH</td>
<td>L Postcentral Gyrus, BA3 (n=6)</td>
<td>-34, -29, 47</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>R Postcentral Gyrus, BA3 (n=2)</td>
<td>34, -22, 36</td>
<td>2.80</td>
</tr>
<tr>
<td><strong>UNAFFECTED HAND</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASELINE</td>
<td>R Postcentral Gyrus BA4 (n=6)†</td>
<td>42, -17, 43</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>L Postcentral Gyrus, BA3 (n=2)</td>
<td>-46, -17, 47</td>
<td>1.82</td>
</tr>
<tr>
<td>POST CIMT</td>
<td>R Postcentral Gyrus BA3 (n=6)</td>
<td>46, -17, 43</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>L Postcentral Gyrus (n=2)</td>
<td>-38, -26, 29</td>
<td>3.39</td>
</tr>
<tr>
<td>SIX MONTH</td>
<td>R Postcentral Gyrus BA3 (n=6)</td>
<td>46, -17, 43</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>L Postcentral Gyrus, BA3* (n=2)</td>
<td>-42, -26, 33</td>
<td>2.87</td>
</tr>
</tbody>
</table>
Virtual sensor peak identification for P50

The identified group Talairach coordinates with the highest magnitude (within latency range 35-65ms) were used to generate a group averaged time course of source activity (also termed virtual sensor or VS plots). These group-averaged virtual sensor plots were used to determine the time course of brain activity, identifying the SEF P50 amplitude (first prominent peak) and corresponding latencies in the identified peak location. Figure 5 provides an example of a virtual plot generated from the specified source location, depicting the group averaged SEF waveform time course (with P50 identified).

5.3.1.1 Affected hand

It was observed that the P50 component did not reach peak strength at exactly at 50ms in all subjects. The averaged trials sensor plot waveforms (before the source localization beamformer was applied) were used to estimate when/where exactly the P50 component occurred for each individual. A clear SEF ‘P50’ component of the somatosensory evoked magnetic field was identified for the majority of participants in both their affected (6 out of 8 subjects) and
unaffected hand (5 out of 8 subjects) at baseline. This allowed for a determination of when the response occurred in time (range of latency, ms) at the individual level (Appendix C). In line with previous somatosensory EEG and MEG studies in children with HCP, a latency range rather than a specific time point has been used. This has been done as peak detection can be difficult at specific time points (i.e. 50ms). Using a range allowed the capture of a mean peak latency range for our population sample and was determined to be from 35 to 65ms after tactile stimulation (0ms). Using the individual subject VS plots, mean SEF peak amplitude (moment, nAm) and corresponding peak latency (s) were generated for each participant for each SEF waveform.

Effects of CIMT on SEF P50 amplitude and latency were examined. A paired sample t-test was conducted to determine the strength (amplitude) and latency of the neural magnetic activation in response to tactile stimulation from baseline to post CIMT (significance was set as p<0.05). Eight participants were analyzed (6 right hand affected and 2 left hand affected). Left and right affected participant data was combined, unless otherwise specified for waveform purposes. Data are mean ± standard deviation, unless otherwise stated.

**CIMT effects on SEF P50 amplitude from baseline to post CIMT**

SEF amplitude of the affected hand remained consistent from baseline (14.4± 5.2) to post CIMT (14.6 ± 6.7), shown in the SEF waveforms in Figure 6. There were no outliers and the data were normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p>0.05), respectively. *CIMT intervention did not elicit statistically significant changes in SEF P50 amplitude of the affected hand from baseline to post CIMT, t(7)= 0.14, p=0.90.* There was no identifiable SEF response in the S1 region ipsilateral to the stimulated hand.
CIMT effects on SEF P50 latency from baseline to post CIMT

SEF peak latency of the affected hand remained consistent from baseline (0.04s ± 0.005) to post CIMT (0.04s ± 0.004), which is shown in the SEF waveform in Figure 6. There were no outliers and the data were normally distributed, as assessed by boxplot and the Shapiro-Wilk's test (p>0.05), respectively. *CIMT intervention did not elicit statistically significant changes in SEF latency, indicating no detectable cortical processing differences for tactile stimulation delivery to the affected hand after CIMT, t(7) = -1.28, p=0.24.*

5.3.1.2 Unaffected hand

CIMT-induced effects of the unaffected hand SEF amplitude and latency measures were also explored from baseline to post CIMT.

SEF amplitude of the unaffected hand remained consistent from baseline (12.8 ± 5.7) to post CIMT (13.1 ± 6.2 shown in the SEF waveforms in Figure 7. There was one outlier (participant 9) detected, however, inspection of their value did not reveal them to be extreme and were kept in the analysis. The data were normally distributed, as assessed by the Shapiro-Wilk's test (p >0.05). *CIMT intervention did not elicit statistically significant changes in SEF P50 amplitude of the affected hand from baseline to post CIMT, t(7) = 0.19, p=0.85.*
SEF peak latency of the unaffected hand remained consistent from baseline (0.04s ± 0.004) to post CIMT (0.04s ± 0.003) which is shown in the SEF waveform in Figure 7. There were no outliers and the data were normally distributed, as assessed by boxplot and the Shapiro-Wilk's test (p>0.05), respectively. **CIMT intervention did not elicit statistically significant changes in SEF latency, indicating no detectable cortical processing differences for tactile stimulation delivery to the unaffected hand after CIMT, t(7) = -1.00, p= 0.35.**

![Figure 7](image.png)

**Figure 7.** Grand averaged SEF waveform at baseline (black line) and post CIMT (dark red line) of the unaffected hand, P50 (first prominent peak identified). SEF waveforms are observed for the source localized contralateral to the stimulated unaffected hand. P50 SEF amplitude and peak latency at baseline and post CIMT remain the same (no significant changes) for the unaffected hand.
5.3.1.3 SEF responses at 6 months post CIMT

Using a repeated measures ANOVA, 6 months post CIMT effects were also investigated to evaluate any potential long term impact (compared to baseline and post CIMT respectively). Overall, CIMT intervention did not elicit statistically significant changes in SEF P50 amplitude and latency for the affected and unaffected hand, with amplitude and latency values remaining consistent from baseline to post CIMT to six month post CIMT. Therefore, a post hoc analysis was not applied. Figure 8 demonstrates grand averaged SEF waveform at baseline (blue), post CIMT (grey) and six month (red) post CIMT of the (a) affected hand, P50 and (b) unaffected hand. Table 7 summarizes all group averaged mean SEF amplitude and latency for P50 for both the unaffected and affected hand at all 3 time points. Subject-specific values for the affected and unaffected hand can be found in Appendix D, Table A and B.

<table>
<thead>
<tr>
<th></th>
<th>Affected Hand (n=8)</th>
<th>Unaffected Hand (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEF amplitude (nAm)</td>
<td>SEF latency (s)</td>
</tr>
<tr>
<td>Baseline</td>
<td>14.4 (5.2)</td>
<td>0.04 (0.005)</td>
</tr>
<tr>
<td>1 month</td>
<td>14.6 (6.7)</td>
<td>0.04 (0.004)</td>
</tr>
<tr>
<td></td>
<td>t-test</td>
<td>t-test</td>
</tr>
<tr>
<td></td>
<td>t(7)=0.14,</td>
<td>t(7)= -1.28,</td>
</tr>
<tr>
<td></td>
<td>p=0.90</td>
<td>p=0.24</td>
</tr>
<tr>
<td>6 month</td>
<td>11.3 (5.3)</td>
<td>0.04 (0.01)</td>
</tr>
<tr>
<td></td>
<td>F_{2,14}=3.86,</td>
<td>F_{2,14}=0.31,</td>
</tr>
<tr>
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<tr>
<td></td>
<td>12.4 (6.2)</td>
<td>0.04 (0.003)</td>
</tr>
<tr>
<td></td>
<td>t(7) = 0.19,</td>
<td>t(7) = -1.00,</td>
</tr>
<tr>
<td></td>
<td>p=0.85</td>
<td>p=0.35</td>
</tr>
<tr>
<td></td>
<td>12.4 (7.0)</td>
<td>0.04 (0.004)</td>
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<td></td>
<td>F_{2,14}=0.11,</td>
<td>F_{2,14}=1.93,</td>
</tr>
<tr>
<td></td>
<td>p=0.89</td>
<td>p=0.18</td>
</tr>
</tbody>
</table>

Table 7. Summary of mean MEG P50 amplitude and latency values at baseline, post CIMT and six month post CIMT for both the affected and unaffected hand. Repeated measures ANOVA, with Mauchly's test of sphericity, assessed significance over the three time points.
5.3.2 Oscillations

5.3.2.1 Alpha band oscillations

Reactivity of the primary somatosensory alpha band oscillations in response to tactile stimulation

Analyses of brain oscillatory activity in the alpha frequency band were performed on the tactile stimulus locked (induced response) datasets for 7 out of 8 participants (6 right hand and 1 left hand affected) at baseline, post CIMT and six months post CIMT. Left hand affected participant 10 did not demonstrate a distinct group alpha-band reactivity in the contralateral hemisphere to stimulation in all but one participant (left hand affected participant 10). Thus, participant 10 (left hand affected) was removed from the analysis. We investigated the effects of CIMT on the modulation of alpha-band (8-13Hz) oscillations of both the affected and unaffected hand before (baseline) and after CIMT (post CIMT and six month post).

Figure 8. Grand averaged SEF source waveform at baseline (black line), post CIMT (dark red line) and six month post CIMT (blue line) of the (a) affected and (b) unaffected hand, P50. SEF waveforms are observed contralateral to the unaffected hand stimulated. Tactile stimulation onset at 0ms. SEF waveforms for each time points can be viewed individually in Appendix E.
Localization of the alpha band (8-13Hz) ERD

Alpha event-related desynchronization (ERD) was localized to the sensory regions, specifically to the contralateral postcentral gyrus (BA3 if present). Group SAM localized coordinates of the alpha ERD are listed in Table 8 for all 3 time points (baseline, post CIMT and six month post CIMT) along with peak Synthetic Aperture Magnetometry (SAM) normalized power (pseudo-t, a difference of the source power in the baseline from the source power in the active time windows selected) for both the affected and unaffected stimulated hands. Note that two source locations, both left and right hemispheric locations, are demonstrated at each time point. This is to distinguish the source location between the right hand affected participants (n=6) and the left hand affected participants (n=1). Source location is contralateral to stimulated hand. In addition, localized group peaks are displayed on the glass brain in Figure 9.
Table 8. Sam-localized alpha ERD coordinates on the group average image at baseline, post CIMT and six months post CIMT for both the right hand affected (n=6) and the left hand affected (n=1) participants. Source localization is separated into left and right hand affected to show specific region of interest (Left or Right BA3). *Denotes location +/- 5 mm from the post central gyrus.

<table>
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<th>Timepoint</th>
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<td>R Precentral Gyrus, BA4 (n=1)*</td>
<td>50, -13, 43</td>
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</table>
Figure 9. SAM image of tactile stimulation localization of alpha (8-13Hz) ERD on the group average image for right hand affected participants (n=6) for both the (a) affected and the (b) unaffected hand. * denotes left Postcentral Gyrus, ** denotes right Postcentral Gyrus Stimulation localization is contralateral to stimulated hand. Left hand affected participant not shown.
**CIMT effects on sensory alpha-band event related desynchronization (ERD)/suppression**

Table 9 below summarizes group averaged mean integrated % change in power for the alpha band ERD as well as corresponding ERD onset/offset, latency duration and maximum peak for the affected hand at baseline and post CIMT for the affected and unaffected hand. There was no alpha rebound (ERS overshoot following ERD) at any of the 3 time points for both the affected and unaffected hand, thus only alpha suppression was evaluated.

*Alpha ERD power quantified for comparison before and after CIMT effects*

Using the generated tactile stimulation time-frequency (TFR) plots, clear alpha band suppression (ERD) was shown for the group average following tactile stimulus presentation, **Figure 10a**. The TFR time-course (**Figure 10b**) demonstrates an ERD peak following tactile stimulus at 0ms.

To quantify differences in the magnitude of alpha ERD, the source power (% change in power) was integrated over the chosen time course to obtain the area under the curve, using 17 millisecond time windows. In addition, latency comparisons were made using ERD onset and offset times (defined as the overall ERD duration in response to tactile stimulation). An example of the group average time course of alpha (8-13Hz) suppression of the left postcentral gyrus of the right hand affected participants are shown in **Figure 10b**, defining the onset and offset of ERD suppression and the integrated source power at baseline.
CIMT effects on alpha-band ERD integrated power

Using a paired t-test, alpha-band ERD integrated % change in power (area under the curve) was compared from baseline to post CIMT for the affected and unaffected hand.

Affected hand

ERD power of the affected hand decreased from baseline (-7634.4 ± 5955.9) to post CIMT (-5593.8 ± 4013.0) shown in Figure 11. There were two outliers (participant 1 and 4), however, the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. Inspection of their values did not reveal them to be extreme and they were kept in the analysis. Comparing CIMT-induced changes of alpha ERD power of the affected hand revealed no significant intervention group effects involving alpha ERD power from baseline to post CIMT for the affected hand, t(6)= 1.04, p=0.34.

Figure 10. a) TFR plot of virtual sensors extracted from the left post central gyrus (6 right hand affected participants). Strong alpha suppression is indicated by the black box. Stimulus onset is presented with the vertical dashed line. b) Grand average time course of alpha suppression (8-13Hz) in the affected post central gyrus BA3 at baseline. ERD onset and offset are indicated. The area under the curve represents the ‘integrated % change in power’ of alpha suppression.
Unaffected Hand

ERD power of the unaffected hand decreased from baseline (-7733.8 ± 5743.9) to post CIMT (-4996.2±1860.6) shown in Figure 12. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. Comparing CIMT-induced changes of alpha ERD power of the unaffected hand revealed no significant intervention group effects involving alpha ERD power from baseline to post CIMT for the unaffected hand, t(6)=1.04, p=0.34.

**Figure 11.** Grand average time course of alpha suppression (8-13Hz) of the post central gyrus at baseline and post CIMT for the affected hand (n=7). Tactile stimulus onset is at 0s. Error bars reflect standard mean error.
Comparing alpha-band ERD minimum peak, onset/offset and latency duration

Using a paired t-test, alpha-band ERD minimum peak, onset/offset and latency duration was compared from baseline to one-month post CIMT for the affected and unaffected hand.

Affected hand

The minimum peak of the alpha-band suppression was also compared from baseline to post CIMT. The minimum peak decreased from baseline (-25.7 ± 19.2) to post CIMT (-22.7 ± 13.4) in response to tactile stimulation to the affected hand. There was one outlier (participant 1), however, the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. Inspection of their value did not reveal them to be extreme and they were kept in the analysis. *A paired t-test revealed no significant change in peak latency duration of the alpha-band suppression following CIMT for the affected hand, t(6)=0.51, p=0.63.*

The ERD onset latency was initiated slightly earlier at post CIMT (-0.2s ± 0.2) in comparison to baseline (-0.02s ± 0.3) in response to tactile stimulation of the affected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed no significant change in ERD onset latency duration following CIMT for the affected hand, t(6)=1.51, p=0.15.*

![Figure 12](image-url). Grand average time course of alpha suppression (8-13Hz) of the post central gyrus BA3 at baseline and post CIMT for the unaffected hand (n= 7). Tactile stimulus onset is at 0s. Error bars reflect standard mean error.
onset latency following CIMT intervention for the affected hand, \( t(6)=-1.88, p=0.31 \).

The ERD offset latency was initiated slightly later at post CIMT (0.5s ± 0.4) in comparison to baseline (-0.8s ± 0.2) in response to tactile stimulation of the affected hand. There was one outlier (participant 9) and the data was not normally distributed as assessed by Shapiro-Wilk's test (p=0.03). Inspection of the outlier’s value did not reveal them to be extreme and they were kept in the analysis. *A paired t-test revealed no significant change in ERD offset latency following CIMT for the affected hand, \( t(6)=-1.46, p=0.2 \)*.

The group peak latency duration (onset to offset) of the alpha-band suppression was also compared from baseline to post CIMT. Peak latency remained consistent from baseline (0.8s ± 0.3) to post CIMT (0.7s ± 0.2) in response to tactile stimulation to the affected hand. There were two outliers (participants 4 and 9), however, the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. Inspection of their values did not reveal them to be extreme and they were kept in the analysis. *A paired t-test revealed no significant change in peak latency duration of the alpha-band suppression following CIMT for the affected hand, \( t(6)=-0.63, p=0.55 \).*

**Unaffected hand**

The minimum peak of the alpha-band suppression was also compared from baseline to post CIMT. The minimum peak decreased from baseline (-26.9 ± 14.3) to post CIMT (-19.1 ± 5.8) in response to tactile stimulation to the unaffected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed no significant change in peak latency duration of the alpha-band suppression following CIMT unaffected hand, \( t(6)=1.15, p=0.29 \).*

The ERD onset latency was consistent from baseline (-0.01s ± 0.1) to post CIMT (-0.07s ± 0.1) in response to tactile stimulation of the unaffected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed that no significant change in ERD onset latency following CIMT for the unaffected hand, \( t(6)=-1.10, p=0.31 \).*

The ERD offset latency was consistent from baseline (0.7 ± 0.2) to post CIMT (0.7s ± 0.2) in response to tactile stimulation of the unaffected hand. There was one outlier (participant
3), however, the data were normally distributed, as assessed by the boxplot and Shapiro-Wilk's test (p>0.05), respectively. Inspection of their value did not reveal them to be extreme and they were kept in the analysis. *A paired t-test revealed no significant change in offset ERD latency following CIMT for the unaffected hand, t(6)= -0.34, p=0.75.*

The group peak latency duration (onset to offset) of the alpha-band suppression remained consistent from baseline (0.7s ± 0.2) to post CIMT (0.8s ± 0.2) in response to tactile stimulation of the unaffected hand. There were no outliers and the data were normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed no significant change in peak latency duration of the alpha-band suppression following CIMT for the unaffected hand, t(6)=0.28, p=0.79.*

*Alpha band suppression reactivity at 6 months post CIMT*

Using a repeated measures ANOVA, 6 months post CIMT effects were also investigated to evaluate any potential long term impact (compared to baseline and post CIMT respectively). Overall, CIMT intervention did not elicit statistically significant changes for ERD power, minimum peak, onset/offset or latency duration for both the affected hand and unaffected with values remaining fairly consistent from baseline to post CIMT to six-month post CIMT. Therefore, a post hoc analysis was not applied. **Table 9** summarizes all group averaged mean integrated power for alpha band ERD as well as corresponding ERD onset, offset and latency duration for both the unaffected hand and affected hand at all 3 timepoints. Furthermore, grand-average time course of alpha suppression (8-13Hz) for the (a) affected hand and (b) unaffected hand are shown in **Figure 13**.
<table>
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<tr>
<th></th>
<th>Integrated ERD power</th>
<th>Minimum peak</th>
<th>Latency onset</th>
<th>Latency Offset</th>
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Table 9. Summary of mean group averaged mean integrated power for alpha band ERD as well as corresponding ERD onset, offset and latency duration for both the affected and unaffected hand. Paired t test compare mean values from baseline to post CIMT. Repeated measures ANOVA, with Mauchly's test of sphericity, compare significance over time points, baseline, post CIMT and six month post CIMT. * Greenhouse-Geisser correction applied when Mauchly's test of sphericity was violated. **Post hoc pairwise comparison revealed no significance between all 3 time points.
Figure 13. Grand average time course of alpha suppression (8-13Hz) in the post central gyrus BA3 at all 3 timepoints (baseline, post CIMT and six month post CIMT) for the (a) affected hand and (b) unaffected (n= 7). Tactile stimulus onset is at 0s. Error bars reflect standard mean error.
5.3.2.2 Beta band oscillations

Reactivity of the primary somatosensory beta-band oscillations in response to tactile stimulation

Beta oscillation analyses were performed on the tactile stimulus locked (induced response) datasets for all 8 participants (6 right hand and 2 left hand affected) at baseline, post CIMT and six months post CIMT. We investigated the effects of CIMT on the modulation of beta-band (15-30Hz) oscillations of both the affected and unaffected hand before (baseline) and after CIMT (post CIMT and six month post).

Localization of the beta band (8-13Hz) ERD

Beta event-related desynchronization (ERD) was localized to the sensory regions, specifically to the contralateral postcentral gyrus (BA3 if present). Group SAM localized coordinates of the alpha ERD are listed in Table 10 for all 3 time points (baseline, post CIMT and six month post CIMT) along with peak values (pseudo-t) for both the affected and unaffected stimulated hands. Individual source locations revealed +/- 5mm from the post central gyrus, except for one participant who revealed displaced or reorganized somatotopic organization. Such reorganization has been documented in children with HCP in response to tactile stimulation.15

Note that two source locations, both left and right hemispheric locations, are demonstrated at each time point. This is to distinguish the source location between the right hand affected participants (n=6) and the left hand affected participants (n=2). Source location is contralateral to stimulated hand. In addition, localized group peaks are displayed on the glass brain in Figure 14 demonstrating distinct group beta-band reactivity in the contralateral hemisphere to stimulation.
Table 10. Sam-localized beta ERD coordinates on the group average image at baseline, post CIMT and six months post CIMT for both the right hand affected (n=6) and the left hand affected (n=2) participants. Source localization is separated into left and right hand affected to show specific region of interest (Left or Right BA3). *Denotes location +/- 5 mm from the post central gyrus. †Individual locations revealed L post central gyrus, however only one participant showed somatotopic reorganization of L Inferior Parietal Lobule, BA40.
**Figure 14.** SAM image of tactile stimulation localization of beta (15-30Hz) ERD on the group average image for the right hand affected participants (n=6) for both the (a) affected and the (b) unaffected hand. * denotes left postcentral Gyrus ** denotes right postcentral Gyrus Stimulation localization is contralateral to stimulated hand. Left hand affected participant not shown.
**CIMT effects on sensory beta-band event related desynchronization (ERD)**

Table 11 below summarizes all group averaged mean integrated % change in power for the beta band ERD as well as corresponding ERD onset/offset, latency duration and maximum peak for the at baseline and post CIMT for the affected and unaffected hand.

**Beta ERD power quantified for comparison before and after CIMT effects**

Using the generated tactile stimulation time-frequency (TFR) plots, a clear beta band suppression (ERD) was identified for the group average following tactile stimulus presentation for both the affected and unaffected hand. However, beta rebound was not consistent across time points and affected/unaffected hand (only 2 of 8 participants had a clear beta rebound). Thus only beta suppression was evaluated.

To quantify differences in the magnitude of beta ERD, the source power (% change in power) was integrated over the chosen time course to obtain the area under the curve, using 17 millisecond time windows. Furthermore, latency comparisons were also made using ERD onset and offset times (defined as the overall ERD duration in response to tactile stimulation). An example of a time course of beta suppression and rebound of the left postcentral gyrus of a right hand affected participant is shown in Figure 15b, defining the onset and offset of ERD suppression at baseline.
Affected hand

Using a paired t-test, beta-band ERD integrated % change in power (area under the curve) was compared from baseline to post CIMT. ERD power of the affected hand decreased from baseline (-4726.9 ± 4146.2) to post CIMT (-3065.1 ± 2992.7) shown in Figure 16. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. Comparing CIMT-induced changes of alpha ERD power of the affected hand revealed no significant intervention group effects involving alpha ERD power from baseline to post CIMT for the affected hand, t(7) = 1.85, p=0.11.
Unaffected Hand

Using a paired t-test, beta-band ERD integrated power (area under the curve) was compared from baseline to post CIMT. ERD power of the unaffected hand increased from baseline (-3665.5 ± 2818.6) to post CIMT -4218.7± 4527.9) shown in Figure 17. There was one outlier (participant 3), however, the data were normally distributed, as assessed by the boxplot and Shapiro-Wilk's test (p>0.05), respectively. Inspection of their value did not reveal them to be extreme and they were kept in the analysis. However, comparing of CIMT-induced changes of beta ERD power of the unaffected hand revealed no significant intervention group effects involving alpha ERD power from baseline to CIMT, t(7)=0.37, p=0.72.
Comparing beta ERD minimum/maximum peak, onset/offset and latency duration

**Affected hand**

**Affected hand - Minimum peak**

The minimum peak of the beta-band ERD was compared from baseline to post CIMT. Minimum peak decreased from baseline (-19.9 ± 12.3) to post CIMT (-16.2 ± 12.1) in response to tactile stimulation to the affected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p > 0.05), respectively. A paired t-test revealed no significant change in peak latency duration of the alpha-band suppression for the affected hand following CIMT, $t(7) = 1.78$, $p = 0.12$.

**Affected hand – ERD onset**

The ERD onset of the beta-band was compared from baseline to post CIMT. The ERD onset latency was consistent from baseline (0.06 ± 0.2) to post CIMT (0.1 ± 0.1) in response to tactile stimulation of the affected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p > 0.05), respectively. A paired t-test revealed no significant change in ERD onset latency for the affected hand following CIMT.
intervention, \( t(7) = 0.72, p=0.50 \).

**Affected hand – ERD offset**

Furthermore, ERD offset latency remained consistent from baseline \((0.6 \pm 0.3)\) in comparison to post CIMT \((0.6 \pm 0.2)\). There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test \((p>0.05)\), respectively. *A paired t-test revealed no significant change in ERD offset latency for the affected hand following CIMT, \( t(7) = 0.03, p=0.98 \).*

**Affected hand – ERD peak latency duration**

The group peak latency duration (onset to offset) of the beta-band ERD was also compared from baseline to post CIMT. Peak latency remained consistent from baseline \((0.6 \pm 0.3)\) to post CIMT \((0.5 \pm 0.2)\) in response to tactile stimulation to the affected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test \((p>0.05)\), respectively. *A paired t-test revealed no significant change in peak latency duration of the beta-band suppression for the affected hand following CIMT, \( t(7) = -0.57, p=0.59 \).*

**Unaffected hand**

**Unaffected hand - Minimum peak**

The minimum peak of the beta-band ERD was compared from baseline to post CIMT. Minimum peak was consistent from baseline \((-19.1 \pm 10.0)\) to post CIMT \((-18.4 \pm 13.7)\) in response to tactile stimulation to the unaffected hand. Inspection of their value did not reveal them to be extreme and they were kept in the analysis, as assessed by a boxplot and Shapiro-Wilk's test \((p>0.05)\), respectively. *A paired t-test revealed no significant change in minimum peak of the alpha-band suppression for the unaffected hand following CIMT, \( t(7) = 0.15, p=0.88 \).*

**Unaffected hand – ERD onset**

The ERD onset of the beta-band was compared from baseline to post CIMT. The ERD onset latency was initiated slightly later at post CIMT \((0.09 \pm 0.1)\) in comparison to baseline \((0.04 \pm 0.1)\) in response to tactile stimulation of the unaffected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test \((p>0.05)\), respectively. *A paired t-test revealed no significant change in ERD onset latency for the unaffected hand following CIMT intervention, \( t(7) = 1.14, p=0.29 \).*
**Unaffected hand – ERD offset**

Furthermore, ERD offset latency was ended later at post CIMT (0.6 ± 0.2) compared to baseline (0.4 ± 0.2) in response to tactile stimulation of the unaffected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed no significant change in ERD offset latency for the unaffected hand following CIMT, t(7)= 2.35, p=0.051.*

**Unaffected hand – ERD peak latency duration**

The group peak latency duration (onset to offset) of the beta-band ERD was also compared from baseline to post CIMT. Peak latency was longer at post CIMT (0.5 ± 0.3) compared to baseline (0.3 ± 0.3) in response to tactile stimulation to the unaffected hand. There were no outliers and the data were normally distributed, as assessed by a boxplot and Shapiro-Wilk's test (p>0.05), respectively. *A paired t-test revealed no significant change in peak latency duration of the beta-band suppression for the unaffected hand following CIMT, t(7)= 1.47, p=0.18.*

**Beta band suppression reactivity at 6 months post CIMT**

6 months post CIMT effects were also investigated to evaluate any potential long-term impact (compared to baseline and post CIMT respectively) using a repeated measures ANOVA. Overall, CIMT intervention did not elicit statistically significant changes for ERD beta power, minimum/maximum peak, onset/offset or latency duration for both the affected hand and unaffected with values remaining fairly consistent from baseline to post CIMT to six-month post CIMT. Therefore, a post hoc analysis was not applied. Table 11 summarizes all group averaged mean integrated power for beta band ERD as well as corresponding onset, offset and latency duration for both the unaffected hand and affected hand at all 3 timepoints. Furthermore, grand-average time course of alpha suppression (8-13Hz) for the (a) affected hand and (b) unaffected hand are shown in Figure 18.
Table 11. Summary of mean group averaged mean integrated power for beta band ERD as well as corresponding ERD onset, offset and latency duration for both the affected and unaffected hand. Paired t test compare mean values from baseline to post CIMT. Repeated measures ANOVA, with Mauchly's test of sphericity, compare significance over time points, baseline, post CIMT and six month post CIMT. * Greenhouse-Geisser correction applied when Mauchly's test of sphericity was violated.

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<th>Affected Hand (n=8)</th>
<th></th>
<th>Unaffected Hand (n=8)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Integrated ERD power</td>
<td>Minimum peak</td>
<td>Latency onset</td>
<td>Latency offset</td>
</tr>
<tr>
<td>Baseline</td>
<td>-4726.9 (4146.2)</td>
<td>-19.9 (12.3)</td>
<td>0.1 (0.17)</td>
<td>0.6 (0.3)</td>
</tr>
<tr>
<td>1 month</td>
<td>-3065.1 (2992.7)</td>
<td>-16.2 (12.1)</td>
<td>0.1 (0.1)</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>6 month</td>
<td>-3022.1 (3610.49)</td>
<td>-16.7 (14.8)</td>
<td>0.2 (0.2)</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td></td>
<td>ANOVA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F = 1.98, p = 0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F = 2.14, p = 0.07</td>
<td></td>
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<tr>
<td></td>
<td>F = 1.09, p = 0.34</td>
<td></td>
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<tr>
<td></td>
<td>F = 0.61, p = 0.34</td>
<td></td>
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</tr>
</tbody>
</table>

|                | Integrated ERD power| Minimum peak   | Latency onset         | Latency offset | Latency duration |
|                | -3665.5 (2818.6)    | -19.1 (10.0)   | 0.04 (0.1)            | 0.4 (0.2)      | 0.4 (0.3)        |
| 1 month        | -4218.7 (4527.9)    | -18.4 (13.7)   | 0.1 (0.1)             | 0.6 (0.2)      | 0.5 (0.3)        |
| 6 month        | -4476.76 (4224.53)  | -21.0 (14.62)  | -0.14 (0.18)          | 0.58 (0.34)    | 0.60 (0.38)      |
|                | ANOVA               |                |                       |                |
|                | F = 1.87, p = 0.84  |                |                       |                |
|                | F = 1.24, p = 0.08  |                |                       |                |
|                | F = 1.09, p = 0.34  |                |                       |                |
|                | F = 0.58, p = 0.34  |                |                       |                |

p-value: t(7) = 1.85, p = 0.11

p-value: t(7) = 1.09, p = 0.14

p-value: F = 1.17, p = 0.05

p-value: t(7) = 2.35, p = 0.02

p-value: F = 1.53, p = 0.025
Figure 18. Grand average time course of beta ERD (suppression) in the contralateral post central gryus BA3 at all 3 timepoints (baseline, post CIMT and six month post CIMT) for the (a) affected hand and (b) unaffected (n= 8). Tactile stimulus onset is at 0s. Error bars reflect standard mean error.
5.4 Relationship of motor and sensory CIMT effects

A Pearson’s correlation was run to assess the relationship between each clinical sensory measure change score (post CIMT – baseline) and QUEST change score (post CIMT-baseline) for the affected hand. Furthermore, a Pearson’s correlation was run to assess the relationship between the MEG SEF sensory measures change score (amplitude and latency) and QUEST change score. Correlation results are shown below:

Tactile discrimination and QUEST score

There was moderate positive correlation between two-point discrimination change score and QUEST change score, r(10) = 0.5. This relationship statically explained 28% of the variability in population. However, the relationship was not statically significant (p=0.11) and thus the null hypothesis was not rejected. The analysis showed the relationship to be linear with both variables normally distributed as assessed by Shapiro-Wilk test (p>0.05). However there was one outlier (participant 4) (Figure 19).

![Figure 19](image)

Figure 19. Correlation analysis between QUEST difference scores and 2-point discrimination difference scores.

Tactile registration and QUEST score

To explore the relationship between these two variables using a Pearson correlation, means rather than medians were used for tactile registration. There was moderate negative correlation between tactile registration change score and QUEST change score, r(10) = -0.4. This
relationship statically explained 20% of the variability in population. However, the relationship was not statically significant (p=0.20) and thus the null hypothesis was not rejected. The analysis showed the relationship to be linear, however the tactile registration variable was not normally distributed, as assessed by Shapiro-Wilk test (p=0.01). However, a Pearson’s correlation was run since the test is robust to deviations from normality (Figure 20).

![Figure 20](image)

Figure 20. Correlation analysis between QUEST difference scores and tactile registration difference scores.

**Stereognosis and QUEST score**

To explore the relationship between these two variables using a Pearson correlation, means rather than medians were used for stereognosis. There was moderate correlation between stereognosis change score and QUEST change score, r(10) = 0.3. This relationship statically explained 10% of the variability in population. Therefore, the relationship was not statically significant (p=0.37) and the null hypothesis was not rejected. The analysis showed the relationship to be linear, however, the stereognosis variable was not normally distributed, assessed by Shapiro-Wilk test (p=0.004) However, Pearson’s correlation was run since the test is robust to deviations form normality (Figure 21).
Proprioception and QUEST score

There was small correlation between proprioceptive error degree change score and QUEST change score, $r(9) = 0.3$. This relationship statically explained 8% of the variability in population. Therefore, the relationship was not statically significant ($p=0.47$) and the null hypothesis was not rejected. The analysis showed the relationship to be linear with both variables normally distributed, as assessed by Shapiro-Wilk test ($p>0.05$), with one outlier. Outlier was not removed as additional correlation analysis with the outlier removed revealed same result, no significance (Figure 22).

Figure 21. Correlation analysis between QUEST difference scores and stereognosis difference scores.

Figure 22. Correlation analysis between QUEST difference scores and proprioception angle error difference change scores.
Kinesthesia and QUEST score

There was small positive correlation between kinesthesia change score and QUEST change score, $r(9) = 0.2$. This relationship statically explained 4% of the variability in population. Therefore, the relationship was not statically significant ($p=0.62$) and the null hypothesis was not rejected. The analysis showed the relationship to be linear with both variables, normally distributed as assessed by Shapiro-Wilk test ($p>0.05$) with no outliers (Figure 23).

![Figure 23. Correlation analysis between QUEST difference scores and kinesthesia change difference scores.](image)

SEF amplitude and QUEST score

There was no correlation between SEF amplitude change score and QUEST change score, $r(8) = 0.002$. Therefore, the relationship was not statically significant ($p=0.96$) and thus the null hypothesis was not rejected. The analysis showed the relationship to be linear with both variables normally distributed as assessed by Shapiro-Wilk test ($p>0.05$) with no outliers (Figure 24).
**SEF latency and QUEST score**

A moderate negative correlation between SEF peak latency change score and QUEST change score, \( r(8) = -0.3 \) was identified. This relationship statically explained 10% of the variability in population. However, *the relationship was not statistically significant (p=0.46) and thus the null hypothesis was not rejected.* The analysis showed the relationship to be linear with both variables normally distributed, as assessed by Shapiro-Wilk test (p>0.05) and with no outliers (Figure 25).

**Figure 24.** Correlation analysis between QUEST difference scores and SEF amplitude difference scores.

**Figure 25.** Correlation analysis between QUEST difference scores and SEF latency change scores.
CHAPTER 6: Discussion

Individuals with hemiplegic cerebral palsy (HCP) experience impaired unilateral upper limb motor and sensory function. While therapies such as CIMT have focused on the enhancement of motor function, changes in sensory function have been under-investigated. Within the context of exploring CIMT-driven sensory changes in children with HCP, the CIMT program was enhanced to optimize the sensory experience and maximize the potential to elicit sensory change. To date, the integration of targeted and graded sensory activities into a CIMT protocol is novel. The present study used both clinical and MEG sensory measures to evaluate if sensory changes occurred immediately and six months following a sensory-enhanced CIMT program, to examine the mechanistic sensory role of improved hand/arm function following CIMT. However, despite efforts to enhance sensory training, sensory change at both a functional and neuronal level was not identified in this study. This suggests that sensation may be less remedial to CIMT intervention than enhanced upper limb motor function and hand usage. The following paragraphs will first discuss and interpret each of the individual results. After discussing the results, other potential explanations of the study’s main finding will be proposed in greater detail, which will include the following: i) the contribution of the underlying neuropathology (MVA versus aPVI lesion location), ii) high baseline sensory function, and iii) methodological challenges.

6.1 Enhancement of the CIMT program

In order to achieve precision and efficacy of cortical processing, stimulation in the form of repetitive movement and sensory experiences during early developing years is important. Taub and colleagues have demonstrated that repetitive activities coupled with restraint of the unaffected hand, appears to exert its effects through neuroplasticity in helping children with HCP improve motor function of their affected hand.101, 124 The amount of plasticity in the nervous system has been linked with the extent of the activity in the synapse.102 This means that increased function can arise by way of strengthening connecting synapses between specific neurons. However, if activation of these neurons are reduced or weakened, they may consequently be removed from this circuit or, “pruned away”. However, if used, they have the ability to become integrated into the circuitry of the brain.103 Much like the repetitive motor activities used to enhance motor development using CIMT, the enhancement of sensory activities could also provide benefit in sensory development and be associated with enhanced manual
function in children with HCP. The opportunity to receive appropriate sensory input using meaningful and appropriate activities may improve the ability of the central nervous system to process and integrate sensory input.\textsuperscript{104,105} It is well known that the planning and execution of proper hand function relies on grip strength, in-hand manipulation, and tool use.\textsuperscript{84} Therefore, the underlying upper extremity sensation associated with all these actions are also required for appropriate hand function.\textsuperscript{84} When severe sensory deficits exist, individuals tend to neglect the affected limb and as a result it can result in a decline in upper limb function.\textsuperscript{85} In the context of exploring sensory change following CIMT in children with HCP, the CIMT program continued to focus on motor activities but was enhanced to optimize both the sensory experience as well as facilitate change in sensory function. These sensory activities catered to various sensory modalities (e.g. tactile, proprioceptive and stereognosis). The integration of the sensory activities into a CIMT protocol was novel and to date, no other study has done this. However, our results have shown that even with this enhancement, we were not able to identify significant sensory improvement using both clinical and MEG sensory measures.

6.2 Interpretation of clinical sensory results

Previous CIMT studies have investigated changes in 2-point discrimination and stereognosis after CIMT as secondary objectives, and revealed no change following intervention.\textsuperscript{12,13} In agreement with their results, our study demonstrated no statistically significant change post CIMT for both these modalities. Our study is the first to evaluate proprioceptive and kinesthetic changes after CIMT in children with HCP. However, our sensory enhanced CIMT intervention also did not elicit statistically significant changes in proprioception and kinesthesia. Interestingly, out of all five sensory modalities, only proprioception and kinesthesia revealed trends towards improvement. The proprioceptive magnitude error demonstrated a small decrease from baseline to post CIMT that was maintained at 6 months post CIMT, but the change was not statistically significant. In addition, kinesthetic accuracy showed a small increase from baseline to post CIMT and was maintained at 6 months post CIMT. It has been previously established that proprioception and kinesthesia have a strong interaction with motor control.\textsuperscript{106} Proprioceptive signals from mechanoreceptors of the joints, muscles, tendons, and skin are important for the neural control of movement.\textsuperscript{107} Damage to proprioceptive and kinesthetic afferents may affect muscle tone and impair limb movement in relation to its position in time and space.\textsuperscript{108} Unlike sensory modalities such as tactile discrimination where, 2-point discrimination can be tested in the absence of limb and body movement, proprioception requires
movement. Given that CIMT involves significant motor training, motor activities can indirectly contribute to proprioceptive and kinesthetic training, bolstering their function. In turn, this increase in training of these two sensory modalities could be key factors underlying the mechanisms behind the improvement of motor function after CIMT. In fact, the MEG case study by Sutcliffe and colleagues revealed an increase in contralateral movement evoked field activation of the somatosensory cortex. It was suggested that the observed increase in movement-evoked activation reflects peripheral feedback to the sensorimotor cortex which is required to generate perceptual awareness of arm movement and that CIMT may improve hand function via ‘a mechanism that enhances sensory input by way of the somatosensory cortex’. However, in the current study we did not observe any significant changes in clinical sensory measures following CIMT.

6.3 Interpretation of MEG results

MEG provides the advantage of both high temporal (timing) and spatial (location) resolution with details of cortical somatosensory processing activity in the order of milliseconds after tactile stimulation. As part of our study’s primary objective, both SEF amplitude and latency were studied as an indicator of increased synaptic somatosensory processing in response to tactile stimulation after CIMT. Compared to the contralateral hemisphere, there were no identifiable SEF responses in the S1 region ipsilateral to the stimulated hand in the group and individual data. This outlines that sensory processing in response to activation of the affected hand remained in the contralateral hemisphere. This contralateral response pattern to somatosensory stimulus is consistent with previously documented observations in both tactile and median nerve stimulation in both MEG and EEG studies (in normal and HCP subjects).

The enhancement of synaptic coupling induced by CIMT intervention could reduce synaptic transmission time as well as increase the number of synapses. In turn, this would result in stronger excitation of postsynaptic neurons and could lead to an increase in SEF amplitude and latency. In Juenger’s study, they demonstrated a reduction in latency and an increase in peak amplitude of the N20 component (20ms after tactile stimulation onset) following CIMT in the affected hemisphere (contralateral to the stimulated affected hand). However, our study’s results did not elicit similar changes in SEF amplitude and latency. Our population sample demonstrated no statistically significant change in SEF ‘P50’ amplitude or latency from baseline to post CIMT.
Juenger et al’s study investigated changes in somatosensory processing post CIMT utilizing a tactile stimulation paradigm. Their results demonstrated a reduction in latency and an increase in peak amplitude of the N20 component (20ms after tactile stimulation onset) following CIMT in the contralateral affected hemisphere. However, our study’s results did not elicit similar changes in SEF amplitude and/or latency. It is important to note that various differences in methodology may contribute to these different results. In our study we evaluated tactile responses at 50ms (range 35 to 70ms) after tactile stimulation (P50). A N20 component in our population was not identified, despite a similar application of pneumatic stimulation. The N20 has only been established as a reliable component in median nerve stimulation in individuals with HCP and does not reflect a pneumatic tactile response. An argument can also be made that a response based on finger location can elicit different processing. While Juenger et al’s study applied tactile stimulation to the thumb and 5th digit, the present study stimulated only the index finger. Stimulation of two fingers as opposed to one may provide an increase in cortical spread across the S1 cortex, allowing for a more detectable response to stimulation. In addition, a difference in age range between the two studies was observed. While Juenger et al’s cohort included older children and young adults ranging from ages 11-31 years old, our study included only children aged 6-13. Therefore, our results could be influenced by including younger children with variable levels of cortical and functional development. This could have caused more SEF latency and amplitude variability within our cohort and would make small changes harder to detect in comparison to older individuals. Moreover, younger children may have different attentional abilities and thus may process sensory stimuli differently. For example, younger children may either process the sensory stimulus, or may learn to ignore it after the first 50 or so stimulations. In addition, a difference in subject lesion type may have also contributed to the various differences in study results. Juenger et al included both unilateral periventricular lesions with ipsilateral projections to the affected hand and MCA infarctions with crossed corticospinal projections, whereas 90% of our population sample had a unilateral periventricular lesion (differences in lesion types are discussed in further detail below).

MEG also provides us with the opportunity to evaluate spontaneous (‘induced’) cortical oscillations and their modulation to tactile stimulation. Spontaneous oscillations are not related to the stimuli and contribute to important background sensory processing activity. Induced oscillations after stimulation are not ‘phased-locked’ to stimulus and thus are not affected by averaging signals since they are not cancelled out due to random phase relation to the tactile
stimuli. Thus, oscillations as opposed to evoked responses reflect different but complementary neuronal sensory processes and mechanisms. As a secondary objective, reactivity of alpha and beta oscillations in response to tactile stimulation before and after CIMT was evaluated with an exploratory approach. In our study, localized alpha and beta oscillatory activity was shown for both the affected hand and unaffected hand, specifically within the contralateral post central gyrus or neighbouring areas (+/- 5mm from the post central gyrus). Most participants showed clear alpha and beta ERD activity and weak ERS activity, which is similar to Pihko et al’s study after median nerve stimulation. Our study is the first to evaluate the modulation of oscillatory activity within the alpha and beta band after CIMT in children with HCP. However, in conjunction with the insignificant CIMT induced SEF changes, investigation of oscillation reactivity (integrated ERD power or ERD latency duration) did not elicit any significant change after CIMT of the affected hemisphere post CIMT as well as six month post CIMT. Since only one study has investigated alpha and beta oscillations in children with HCP, further knowledge in this population may be required before interpreting therapeutic effects using oscillatory data.

6.4 Interpretation of secondary objectives

Unaffected hand

As a secondary objective, we also explored change in the unaffected hand following CIMT intervention. CIMT intervention did not elicit statistically significant changes in all five modalities when comparing time points for the unaffected hand: two-point discrimination, tactile registration, stereognosis, proprioception and kinesthesia. To our knowledge, no previous study has assessed clinical sensory changes in the unaffected hand following CIMT. Furthermore, differences in SEF P50 amplitude and latency as well as alpha and beta oscillatory measures, of the unaffected hand over all three time points were not detected. These results provide evidence that there were no negative consequences of CIMT on the sensory function of the unaffected hand.

QUEST and sensory outcome correlation interpretations

The inherent and supported link existing between sensory and motor systems supports the idea that increases observed in either system could be coupled with improvement in the other following therapy. Specifically, if motor function is improved following CIMT, then sensory should also improve. Therefore, the present study’s secondary objective was to identify if a motor-sensory relationship after CIMT exists. In a study by Laible, better outcome in motor
function in stroke participants following CIMT revealed greater increases in functional MRI S1 cortex activation. To date, our study is the first to evaluate the relationship between motor and clinical and MEG sensory improvement after CIMT intervention in children with HCP. There was a range of motor change following the CIMT intervention with half of our participants demonstrating a minimally important clinical change on the QUEST, but no statistically significant averaged changes. Our results demonstrated no significant correlation between QUEST score change and clinical sensory score change for all measures, two-point discrimination, tactile registration, stereognosis, proprioception and kinesthesia from baseline to post CIMT. In addition, the relationship between change in QUEST scores and MEG SEF amplitude and latency were also evaluated, revealing no significant correlation. Therefore, even in children who improved motor function post CIMT we did not find an improvement in sensory function or processing.

6.5 Potential explanations of main findings

After investigating sensory function following CIMT, it can be collectively demonstrated that clinical and MEG sensory measures (SEF and alpha oscillations) did not show a significant short and long term improvement in sensory function or processing, even with the optimization of sensory function within the intervention. However, given previous studies which have shown sensory improvements following CIMT in adults with MCA stroke as well as those that show increases in sensory cortical processing in children with HCP following CIMT, it is important to consider other potential explanations of this main finding including: i) the contribution of the underlying neuropathology, ii) high baseline sensory function, and iii) methodological challenges.

6.5.1 Neuropathology pattern differences

*Unilateral middle cerebral artery (MCA) infarction versus asymmetrical periventricular injury (aPVI)*

Two of the most common neuropathology patterns associated with HCP and accounting for the majority of lesion types include a unilateral middle cerebral artery (MCA) infarction and an asymmetrical periventricular injury (aPVI) often secondary to a presumed venous infarction (aPVI). Our eligibility criteria allowed for the inclusion of both MCA and aPVI injury lesion sub-types, however, the majority of recruited participants had an aPVI injury (9 of 10). This has the potential to impact sensory change following CIMT in two ways. Firstly, MCA and aPVI
have distinct lesion locations. MCA injuries occur in the cortex and involve a focal arterial stroke of the middle cerebral artery. They represent an injury predominantly to the gray matter involving the M1S1 regions where there is a predominance of nerve cell bodies. An aPVI involves a unilateral periventricular infarction is subcortical due to an intraventricular hemorrhage which consequently heavily implicating axons, which include white matter loss and ventricular dilatation at the lesion site. Lesion location may influence the extent of sensory plasticity based on the specific structural components predominantly affected (e.g. nerve cell body versus axon).

Nerve cell bodies with multiple dendrites/dendritic spines have enhanced opportunities for synaptic plasticity and synaptogenesis compared to axons. Evidence in the literature suggests that gray matter is sensitive to change and can be modified through development or repetitive training. For example, adults with acquired MCA stroke show significant gray matter changes in both sensory and motor areas following CIMT, accompanied by improvements in upper limb function. Furthermore, musicians have demonstrated experience-dependent plasticity with distinct increases in gray matter volume, as well as cortical thickness in auditory cortices. Increased years of musical practice are consistently shown to boost these effects. Preclinical work in animal models has also supported the idea that induced cortical lesions can lead to more recovery compared to subcortical lesions. For example, motor skill learning has been shown to promote gray matter changes by persistent and continued increases of synaptogenesis and dendritic spine formation. Thus, it can be postulated that the subcortical nature of the injury pattern in our study subjects, with predominately white matter injury, may have limited the ability to induce synaptogenesis and hence limited change in sensory function/processing. Recently, Kuhnke and colleagues suggested that patients with congenital hemiparesis (specifically with unilateral periventricular lesion) with reorganized ipsilateral projections to the paretic hand, showed slower gains in speed after CIMT in comparison to those with preserved contralateral projections to the paretic hand (specifically with an MCA infraction). This study focused on differences in cortical projections contributing to varying degrees in motor recovery. However, it can be extrapolated further by differences in observed lesion types. Therefore, increased sensory as well as motor plasticity based on lesion location and cortical matter injury can be an important biomarker that has yet to be investigated in further detail.
6.5.2 Sensory ceiling effects due to differences in lesion location

While the degree of motor deficits between aPVI and MCA are comparable, there is evidence in our clinical literature that sensory deficits are different between the two groups. Studies have demonstrated that HCP children with an aPVI lesion have higher baseline sensory function compared to those with an MCA insult. In addition, when comparing both lesion types, a significant reduction in functional connectivity in the lesioned S2 was observed for the MCA group. Similarly, when comparing baseline sensory capabilities of the affected and unaffected hand in our sample (additional analysis), lower clinical scores for the affected hand were only observed for the 2-point discrimination test. Therefore, the study group of individuals with predominantly aPVI lesion type had high baseline sensory scores. Sensory ceiling effects with a high baseline sensory level may impair the ability to detect changes in sensory function following CIMT.

6.5.3 Limitations

Methodological issues may have contributed to our study results. The sensory measures utilized were well established in the literature as valid and reliable but they have not been used extensively as evaluative measures and may have lacked responsiveness to measure small but clinically important change. It should be noted that the clinical tests such as the 2-point discrimination, stereognosis and tactile registration (monofilaments) have been tested for moderate to high inter-rater reliability, intra-rater reliability and test-retest reliability and thus have been readily used in research and practice. Previous studies have often used these measures to discriminate deficits between children with HCP and TDC. Functional assessments such as the QUEST and the Melbourne have been validated to detect changes after therapeutic intervention whereas sensory measures have not. Therefore, the clinical sensory measures that were used have established discriminative properties but have not been proven as an evaluative tool since established responsiveness and knowledge on minimally important clinical change has not yet been determined.

Our research group postulated that change in proprioception and awareness of where the hand and arm are in space was a critically important aspect of sensory change to drive improvements in motor function. We had challenges with the proprioceptive testing parameter in that we measured change by asking the participants to move the goniometer device into both
Supination and pronation. Supination is a more challenging motor movement compared to pronation in HCP and therefore enhanced the confounding between sensory and motor function reflected in this combined task. Future use of this particular paradigm should revise the task to have the subject move into pronation exclusively. This would minimize any motor challenge by allowing the child to complete an easier motor movement, which in turn will help to measure proprioceptive function more accurately. Imaging studies including MEG have relied heavily on tactile stimulation, however, developing an MEG proprioceptive measure may better focus our evaluation of changes in sensory processing on this specific modality.

Aside from methodological challenges, there are some other limitations that are important to address when interpreting our study’s results. The sample size was small, potentially limiting power, and the predominance of a subcortical aPVI injury type limits generalizability of these results to aPVI subgroup rather than expanding to include the MCA group.

6.6 Future Directions

Given the importance of sensory function, further studies are warranted and should consider recruiting a targeted group of children with HCP secondary to MCA infarct. A larger sample size, should target a balance of both MCA and PVI injury types and thus, if sensory function does show change, having both lesion types will help to determine if it is a contributing biomarker of CIMT change. Children with moderate to severe upper limb sensory function in conjunction to motor impairments should be recruited to avoid ceiling effects, ensuring that a cut-point for decreased sensory function is met prior to enrollment. This would have important implications, in that children with a more severe deficit would exhibit a larger observed change. Furthermore the contribution of proprioception to motor planning and control is of particular importance and the development of a MEG proprioceptive task should be considered. This study highlights the need to develop better evaluative tools for sensory assessment as well as further understand how different brain lesions may affect sensory processing to in turn understand how these may impact sensory improvement following CIMT in children with HCP. Collectively, such considerations will lead to the further investigation of CIMTs impact on sensory function and its potential contribution to motor function.
CHAPTER 7: Relevance to Rehabilitation

The present thesis is being completed within the Rehabilitation Science Institute, and it is important to address the present study within the context of rehabilitation. From a rehabilitation perspective CIMT has well established evidence for enhancing the use and manual motor performance of the hemiplegic hand. However, sensory function changes with CIMT have not been well studied and are important as motor and sensory function are closely linked. This thesis did not find evidence for a change in sensory function and processing with CIMT in children with hemiplegic cerebral palsy. It is also important to note that the majority of children had a subcortical injury and this may have impacted on their ability to enhance sensory function even when changes in motor function were seen. Furthermore the results of this study suggest that clinical and imaging biomarkers (e.g. sensory threshold and location of the lesion) may impact the child’s ability to respond highlighting the need for clinicians to assess baseline sensory function and also be aware of the neuropathology sub-type. This has the potential to maximize individualized effectiveness of therapy and guide clinical recommendations for children/youth and families regarding the potential for sensory recovery.

CHAPTER 8: Conclusion

In summary, we did not find evidence to support change in sensory function and neural processing following a sensory enhanced CIMT protocol in children with HCP, who predominantly (80% of the study sample) had a subcortical aPVI. Potential interpretations include lower synaptogenesis ability for a subcortical axonal injury, and a high baseline level of sensory function with a possible ceiling effect. Overall the present study did not support the initial hypothesis of improved sensory function and processing in children with HCP following CIMT. Despite the absence of significant changes in clinical and MEG sensory function after CIMT, this study adds to the literature by (1) being the first study to assess sensory function using MEG neuroimaging and clinical sensory measures as a primary objective and (2) revealing a possible potential of proprioceptive and kinesthetic changes after CIMT.
CHAPTER 9: References


12. Sakzewski L, Ziviani J, Abbott DF. Randomized trial of constraint-induced movement...


24. Jamali S, Ross B. Precise mapping of the somatotopic hand area using neuromagnetic


50. Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW. Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with


Makeig S, Debener S, Onton J, Delorme A. Mining event-related brain dynamics.


CHAPTER 10: Manuscript

Investigating Sensory Plasticity in Hemiplegic Cerebral Palsy following Constraint Induced Movement Therapy

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Abstract

Children with hemiplegic cerebral palsy (HCP) experience upper limb somatosensory and motor deficits. While constraint-induced movement therapy (CIMT) is effective in improving manual motor function in individuals with HCP, its impact on somatosensory function remains under-investigated. The present study evaluates the effectiveness of CIMT on somatosensory perception and related brain responses in children with HCP using neuroimaging and clinical diagnostic tools. Ten children with HCP attended a three-week CIMT intervention with the inclusion of a somatosensory component to optimize potential somatosensory change. Magnetoencephalography (MEG) and clinical somatosensory assessments were completed at baseline (one week prior CIMT) and one month post baseline, post CIMT (+/- 1 week). CIMT did not result in significant changes in clinical somatosensory modalities or MEG measures of somatosensory processing of the affected hand. This is the first study to investigate the effect of CIMT on somatosensory function utilizing both clinical and neural processing somatosensory measures.

Keywords: constraint-induced movement therapy, hemiplegic cerebral palsy, sensory function, magnetoencephalography
Introduction

Children with hemiplegic cerebral palsy (HCP) experience motor and somatosensory impairments that impact their hemiplegic hand/arm functioning. Constraint-induced movement therapy (CIMT) has been shown to improve manual motor ability in children with HCP, as evidenced from randomized control trials,\(^1,2\) by forcing the use of the affected limb through immobilization of the unaffected limb, and paired with intensive motor training.\(^3\) The neural mechanism behind this improvement remains under investigation, with evidence for rebalancing of the sensorimotor networks between the two hemispheres\(^4\) as well as increased activation of the affected motor cortex (M1).\(^5-7\) Current research has largely focused on motor change (both at a clinical and neural level), leaving the impact on improving somatosensory function with CIMT under-investigated.

Somatosensory input is an essential component of motor function and control. Deficits in neuromotor function have profound effects on somatosensory awareness and responsiveness. Conversely, decreased somatosensory feedback can limit production of fine motor movements. Children with HCP have hemiplegic limb somatosensory deficits in areas of tactile discrimination/registration, proprioception, and stereognosis.\(^8-12\) To date, only two studies have explored the effect of CIMT on tactile discrimination and stereognosis as secondary objectives, finding no improvement.\(^13,14\) Changes in proprioception and kinesthesia have yet to be evaluated and may play an important role in CIMT.

Neuroimaging studies involving magnetoencephalography (MEG) and electroencephalography (EEG) have demonstrated somatosensory deficits and somatotopic map disorganization of the contralateral primary somatosensory cortex (S1) in HCP. Recorded MEG waveforms can provide valuable information about the strength and timing of neural activation in response to tactile stimulation measured by somatosensory evoked fields (SEFs). Furthermore, cortical responses can also be characterized by oscillatory activity at the alpha (8-13Hz) and beta (15-30Hz) frequency range following stimulation.\(^15\) Collectively, the role of SEFs and neural oscillatory synchrony in response to tactile stimulation can provide complementary understanding of the
rhythmic brain activity and the role it plays in sensory processing. For example, children with HCP show evoked responses of longer latencies and lower amplitudes as well as abnormal morphology of the SEFs. Two previous MEG studies have specifically addressed somatosensory changes following CIMT at a neural level. A case study revealed changes in proprioceptive responses in the contralateral (affected) S1 following CIMT after completing a standardized motor task. Juenger et al investigated the S1 after CIMT using a somatosensory specific task in individuals (10-30 years old) with congenital HCP with either a unilateral periventricular white matter lesion or infarction in the middle cerebral artery territory. In their study, an increase in S1 activation in the ‘early-SEF’ at N20 (20ms after stimulation onset) in response to pneumatic tactile stimulation after CIMT training was observed in children with both contralateral and ipsilateral corticospinal projections, while a reduction in latency was observed in individuals with contralateral projections. SEF activation following pneumatic stimulation at P50 (50 ms after stimulation onset) has been shown to be a more reliable indicator of somatosensory processing than N20, which is commonly used in electrical nerve stimulation.

A study evaluating clinical somatosensory outcomes in children with HCP simultaneously paired with an advanced neuroimaging technique (MEG) capable of evaluating changes in somatosensory processing at 50ms will aid in further understanding the effect of CIMT on somatosensory function. The primary objective of the current study is to evaluate functional changes in somatosensory ability observed in the affected hand of children with HCP treated with CIMT utilizing clinical and MEG somatosensory measures (SEFs and alpha/beta oscillations).

**Methods**

**Participants**

Participants were recruited from Holland Bloorview Kids Rehabilitation Hospital (HBKRH). Recruitment criteria included age of 5-12 years, diagnosis of HCP as a result of a vascular cortical and/or subcortical injury. Additionally, participants were screened on their ability to understand and
perform each task, as well as on tolerability to remain still for up to 60 minutes. Any previous participation in a CIMT camp within 9-months of study entry or Botulinum toxin upper limb injections within 6-months of study entry were exclusion criteria from the recruitment process. All participants provided informed consent and the study was approved by the research ethics boards from both research sites (HBKRH for recruitment and clinical assessments and The Hospital for Sick Children, SK for MEG/MRI assessments).

Study Design

The study design was a repeated measures case series with outcomes obtained at baseline and post CIMT (one month post baseline).

CIMT intervention

A 3-week modified CIMT intervention was administered. The first week required the participants to wear a non-removable below-elbow cast on their unaffected limb within their home/community full-time (24 hours per day) thus forcing the use of their affected limb. This was followed by a 2-week CIMT day-camp (called “Hand2Hand” developed at HBKRH), where a removable cast was worn part-time for the majority of the camp day during the first week, and for 1 hour per day during the second week. Children worked with occupational therapists in a group setting for 4 hours a day, 5 days per week (40 hours total). The intervention concentrated on unilateral and bilateral motor/somatosensory activities in the first and second week respectively. Somatosensory activities were integrated within the CIMT protocol to enhance the somatosensory component of the CIMT camp and optimize potential change in somatosensory function. Such activities focused on tactile, stereognosis and proprioceptive modalities (Table 1). Activity modifications were progressively scaled to ensure a level of challenge based on individual ability.
Clinical Evaluation

The following somatosensory evaluations were performed while obstructing the affected hand with an opaque curtain or blindfolded at baseline and post CIMT intervention (one month post baseline).

(1) Tactile registration of the index finger was measured using the 5-item Semmes-Weinstein Monofilament kit, which was applied three times, with one or more correct responses out of three taken as an affirmative response\(^8,29\) (scores 0–4, where 4 = normal, and 0 = no sensation).

(2) 2-point discrimination (2PD) test was measured by applying the Disk-Criminator spaced exactly 5 mm apart, to the thumb, index, and middle finger, 5 times each (total score out of 15).

(3) The stereognosis test evaluated tactile identification of familiar objects. Of 12 objects, the evaluator randomly selected 6 objects to be identified where 3 were from similar pairs (e.g. pencil/pen) and 3 were non-similar pairs (e.g. key/clothespin). The score was the number of correct responses out of 6.

(4) Proprioception was assessed using a goniometer protocol previously used on participants with CP\(^11\), where participants completed a series of 10 proprioceptive-matching trials (blindfolded), in which the affected hand was passively extended to target angles. Participants then actively replicated the target position. Difference magnitude (degrees) of error was recorded for each trial to the nearest degree.

(5) Kinesthesia was measured using the same goniometer device by direct passive rotation of the control rod. Participants reported movement direction immediately after movement was applied. Performance accuracy was scored out of 10 trials.

In addition, the Quality of Upper Extremity Skills Test (QUEST) was used to measure unilateral quality of hand movements.\(^30\) A change of 5 points on the QUEST is considered a minimal clinically important response.
**MEG Assessment and Analysis**

The MEG protocol and analysis are detailed in the Supplementary Information (Appendix A). MEG cortical responses to tactile stimulation are characterized in the time domain to study somatosensory event-related fields (SEFs) or in the time-frequency domain to study oscillatory activity at the alpha (8-13Hz) and beta (15-30Hz) frequency range.

*Somatosensory evoked fields (SEFs)*: A time window of 0.5 second preceding and 0.5 seconds following stimulus onset (time zero) was used to compute weights using a bandpass of 1-50 Hz. SEFs were then characterized by a prominent positive peak around 50ms (P50) post-stimulus onset. As the SEF component generated in the lesioned hemisphere may be delayed or distorted, a larger time window of 35-70 ms was used for P50, if present. The peak amplitude and corresponding peak latencies were logged.

*Oscillations*: Alpha and beta modulations to tactile stimulation reflect the reactivity of the ongoing cortical activity to sensory input. This is measured by the signal power change over time of a specific frequency band (alpha band, 7-13Hz and beta band, 15-30Hz). Latency and duration of alpha and beta frequency event-related synchronization, ERS and desynchronization, ERD, as well as minimum and maximum power change peak were measured.

**Statistical Analysis**

All statistical analyses were performed using IBM’s Statistical Product and Service Solutions (SPSS) software (version 21). Parametric paired sample t-tests or a non-parametric Wilcoxon signed-rank test were used to evaluate clinical somatosensory changes from baseline to post CIMT for the affected hand. Bonferroni correction was set to p<0.01 for the 5 clinical somatosensory measures. Furthermore, paired parametric t-tests were used to evaluate MEG SEF (amplitude and latency) and alpha/beta changes (integrated percent power change ERS/ERS onset, offset, minimum/maximum peak) from baseline to post CIMT. To determine if the data was normally distributed, the Shapiro-Wilk test was applied to parametric comparisons.
Results

Participants

Ten children diagnosed with HCP (8 males and 2 females; mean age: 7 years ± 2.4; age range 5-12 years; 7 right hand affected and 3 left hand affected) were recruited. Demographic and clinical descriptions are summarized in Table 2. All 10 participants completed two clinical assessments, however, 2 participants did not complete the imaging assessments due to the presence of epileptiform background activity (which obscured somatosensory responses) and/or not wanting to enter the MEG scanner. Baseline clinical sensory results can be found in Table 3.

Clinical outcomes

In addition to baseline clinical sensory results, Table 3 outlines change in the clinical somatosensory results for the affected hand. No significant changes were seen in clinical somatosensory function following the CIMT intervention. There were no outliers and the data was normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p>0.05), respectively. QUEST averaged group scores for the affected hand revealed no significant difference from baseline (50.9 ± 21.5) to post CIMT (56.3 ± 22.1, p=0.08). However, 5/10 participants improved QUEST scores by a clinically relevant improvement of at least five points.

Neuroimaging outcomes

The SEF P50 component and alpha and beta oscillatory modulations of the somatosensory evoked magnetic fields were identified in the affected hand within the contralateral post central gyrus.

Somatosensory Evoked Field (SEFs)

The P50 component was the only distinct component across all 10 participants and thus was the only reliable component to evaluate somatosensory processing following stimulation. Later peaks such as P100 (100 ms following stimulation) were not consistent across all participants (present in 2
out of 8 participants). CIMT intervention did not elicit statistically significant changes in SEF P50 amplitude (nanoAmperes, nAm) nor latency (seconds, s) for the affected hand, and amplitude and latency values remained relatively consistent between baseline and one-month post-CIMT scans (Figure 1, Table 4). There were no outliers and the data were normally distributed, as assessed by boxplot and Shapiro-Wilk's test (p>0.05), respectively. No identifiable SEF or oscillatory responses were present in the primary sensory (S1) region ipsilateral to the stimulated hand and thus only the contralateral side was examined.

**Induced Oscillations (alpha and beta)**

Power time-course plots revealed that the typical suppression of alpha (7-13 Hz) and beta (15-30Hz) oscillations induced by each stimulus was present at both time points (Figure 2). Alpha and beta rhythm rebound (overshoot) was less consistent across time points. Thus, only alpha and beta suppression were evaluated. One participant 10 (left hand affected) did not demonstrate a typical group alpha-band reactivity in the contralateral hemisphere in response to stimulation and was consequently removed from analysis. Beta suppression (ERD) was evaluated for all 8 participants (6 right hand and 2 left hand affected) at baseline and post CIMT. CIMT intervention did not elicit statistically significant changes in alpha or beta-band ERD and percent power change (i.e. area under the curve), ERD minimum peak, onset/offset, latency or duration for the affected hand (Table 5). Alpha-band ERD latency onset was normally distributed with no outliers. However, the other outcomes had outliers when comparing data from baseline to post CIMT and all were normally distributed except for one (ERD offset latency). ERD power of the affected hand had two outliers (participant 1 and 4), minimum peak of the alpha-band suppression, had one outlier (participant 1), group peak latency duration (onset to offset) of the alpha-band suppression had two outliers (participants 4 and 9), and ERD offset latency had one outlier (participant 9). Inspection of the value of the outliers did not reveal them to be extreme and they were kept in the analyses.
Discussion

Individuals with HCP experience impaired unilateral upper limb motor and somatosensory function. While therapies such as CIMT have focused on the enhancement of motor function, changes in somatosensory function have been under-investigated. The present study used both clinical and MEG somatosensory measures to evaluate if somatosensory changes occurred immediately following a somatosensory-enhanced CIMT program. Within the context of exploring CIMT-driven somatosensory changes in children with HCP, the CIMT program was enhanced to optimize the somatosensory experience and maximize the potential to elicit somatosensory change. To date, the integration of targeted and graded somatosensory activities into a CIMT protocol is novel. Despite efforts to enhance somatosensory training, no change in somatosensory ability was found at either a functional or neuronal level. This suggests that haptic or tactile sensation may be less remedial to CIMT intervention than enhanced upper limb motor function and hand usage.

Given previous studies which have shown somatosensory improvements following CIMT in adults with MCA stroke as well as those that show increases in somatosensory cortical processing in children with HCP following CIMT,\textsuperscript{23,31} it is important to consider a number of potential explanations of our current findings.

Two of the most common neuropathology patterns associated with HCP and accounting for the majority of lesion types include a unilateral middle cerebral artery (MCA) infarction and an asymmetrical periventricular injury (aPVI) often secondary to a presumed venous infarction.\textsuperscript{32} Our eligibility criteria allowed for the inclusion of both MCA and subcortical aPVI injury lesion types, however, the majority of recruited participants had an aPVI injury (8 of 10). This has the potential to impact somatosensory change following CIMT, as MCA injuries occur in the cortex and represent an injury predominantly to the gray matter where there is a predominance of nerve cell bodies, whereas aPVI lesions are subcortical, consequently heavily implicating axons and white matter at the lesion site.\textsuperscript{33} Lesion location may influence the extent of somatosensory plasticity based on the specific structural components predominantly affected (e.g. nerve cell body versus axon). Nerve cell bodies
with multiple dendrites/dendritic spines have enhanced opportunities for synaptic plasticity and synaptogenesis compared to axons. Evidence in the literature suggests that gray matter is sensitive to functional change and can be modified through development or repetitive training. For example, adults with acquired MCA stroke show significant gray matter changes in both somatosensory and motor areas following CIMT, accompanied by improvements in upper limb function. Furthermore, musicians have demonstrated experience-dependent plasticity with distinct increases in gray matter volume, as well as cortical thickness in auditory cortices. Preclinical work in animal models has also supported the idea that induced cortical lesions can lead to more functional recovery compared to subcortical lesions. For example, motor skill learning has been shown to promote gray matter changes by persistent and continued increases of synaptogenesis and dendritic spine formation. In preclinical work Roof et al., found that lesions involving subcortical white matter in rodents exhibited less recovery compared to lesions restricted to the cortex. Therefore, the subcortical nature of the injury pattern in our study participants may have limited the ability to induce synaptogenesis and hence limited change in somatosensory function/processing.

Juenger et al’s study investigated changes in somatosensory processing post CIMT in adults with HCP utilizing a tactile stimulation paradigm. Their results demonstrated a reduction in latency and an increase in peak amplitude of the N20 component (20ms after tactile stimulation onset) following CIMT in the contralateral affected hemisphere. However, our study’s results did not elicit similar changes in SEF amplitude and/or latency. Differences in results may be attributed to subject’s lesion type, (which included unilateral periventricular lesions with ipsilateral projections to the affected hand as well as MCA infarctions with preserved crossed corticospinal projections) whereas 80% of our study’s sample was unilateral subcortical aPVI injury lesion types. Age differences may have also contributed varying results where our sample were younger in comparison to Juenger et al’s older age range, 11-30 years. In addition to varying lesion type and age, results can also be attributed to the various differences in study methodology. Despite a similar application of pneumatic stimulation, the N20 component used in Juenger et al’s study was not identified in our population.
The N20 peak component has only been established as a reliable component in the median nerve stimulation of individuals with HCP and has not been established to reflect a pneumatic tactile response. In contrast, a P50 has been identified to reflect a pneumatic tactile response and was therefore chosen as a reliable somatosensory component for this study.\textsuperscript{20, 39-40}

While the degree of motor deficits between aPVI and MCA are comparable, there is evidence in our clinical literature that somatosensory deficits are different between the two groups.\textsuperscript{41} Studies have demonstrated that HCP children with an aPVI lesion have higher baseline somatosensory function compared to those with an MCA insult.\textsuperscript{42} In addition, when comparing both lesion types, a significant reduction in functional connectivity in the lesioned S2 was observed for the MCA group.\textsuperscript{41, 42} Therefore, somatosensory ceiling effects with a high baseline somatosensory level in individuals with an aPVI injury may impair the ability to detect changes in somatosensory function following CIMT.

Finally, methodological issues may have contributed to our study results. The sample size was small, potentially limiting power. The somatosensory measures utilized were well established in the literature as valid and reliable, but they have not been used extensively as evaluative measures and may have lacked sensitivity to a small but clinically important change. We have postulated that change in proprioception and awareness of where the hand and arm are in space is a critically important aspect of somatosensory change to drive improvements in motor function. In the current study, the proprioceptive testing protocol may have been limited by the fact that we measured change by asking the participants to move the goniometer device into both supination and pronation.\textsuperscript{11} Clinically, supination is a more challenging motor movement compared to pronation in HCP and changes in proprioception may have been more accurately measured by having the child exclusively move the device into pronation.

In summary, we did not find evidence to support change in somatosensory function and somatosensory neural processing following a somatosensory enhanced CIMT protocol in children with HCP, who predominantly had a subcortical injury pattern. This might suggest a limited ability of
CIMT to induce change in somatosensory function, or a failure of the SEF measures to detect such changes. However, reduced synaptogenesis for a subcortical axonal injury, and/or a high baseline level of somatosensory function resulting in a ceiling effect in the specific group of children tested may have been a contributing factor. Given the importance of somatosensation in rehabilitation of motor skills, further studies are warranted to test this hypotheses, for example, recruiting children with HCP secondary to MCA infarcts, in addition to screening for decreased somatosensory function prior to enrollment.

Acknowledgements
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Author Contributions
DF, DC and SM contributed to the study design and were responsible for the overall study. Clinical data measures and analysis was conducted by SD and LS. Authors SM, SD, CJ and SB contributed to neuroimaging data acquisition and analyses. SD wrote the manuscript with critical input from all authors.

Declaration of Conflicting Interests
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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authors and no endorsement by the Ontario Brain Institute is intended or should be inferred.

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**Ethical Approval**

Research ethics approval was obtained from the University of Toronto Research Ethics Boards, Holland Bloorview Research Ethics Board and the Hospital for Sick Children Research Ethics Board. Informed consent and assent were obtained.
References


Table 1: Description of one sensory activity example integrated into constraint-induced movement therapy camp. A full list of activities can be found in the ‘A practical guide to implementing Constraint therapy and Bimanual training’s at [www.hollandbloorview.ca].

<table>
<thead>
<tr>
<th>Sensory activities protocol</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory Grasp</strong></td>
<td><strong>Grade Down:</strong></td>
</tr>
<tr>
<td><em>(Target: Stereognosis)</em></td>
<td>• Therapist moves the object with the child’s hand if the child is unable to grasp</td>
</tr>
<tr>
<td>Desired sensory response/movement:</td>
<td>• Therapist places the object in child’s hand to facilitate grasp</td>
</tr>
<tr>
<td>Stereognosis</td>
<td>• Therapist provides a visual aid for reference (i.e. picture of the same set of objects to be identified)</td>
</tr>
<tr>
<td>Child starts in sitting and vision is occluded (i.e. can use a blindfold, ask to close his/her eyes, or use a curtained box).</td>
<td>• Therapist limits the number of objects presented</td>
</tr>
<tr>
<td>Therapist presents a number of common items and asks the child to name the items through touch</td>
<td>• Therapist gives objects with very different characteristics (i.e. size, shape, texture)</td>
</tr>
<tr>
<td></td>
<td>• More time is allowed to name the objects</td>
</tr>
<tr>
<td></td>
<td><strong>Grade Up:</strong></td>
</tr>
<tr>
<td></td>
<td>• Child reaches behind the curtain and finds the objects</td>
</tr>
<tr>
<td></td>
<td>• Child move the object within his/her own hand</td>
</tr>
<tr>
<td></td>
<td>• No visual aids are provided</td>
</tr>
<tr>
<td></td>
<td>• Therapist increases the number of objects presented</td>
</tr>
<tr>
<td></td>
<td>• Therapist provides objects with very subtle differences</td>
</tr>
<tr>
<td></td>
<td>• Therapist places the objects within a medium (i.e. place the objects in a bin of sand, uncooked beans)</td>
</tr>
<tr>
<td></td>
<td>• A timed component is put in place</td>
</tr>
</tbody>
</table>
Table 2: Participant Demographics.

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Sex</th>
<th>Age</th>
<th>Affected Hand</th>
<th>Injury Pattern</th>
<th>GMFCS Level</th>
<th>MACS Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>12</td>
<td>Left</td>
<td>MCA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>9</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>6</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI *</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7</td>
<td>Right</td>
<td>aPVI *</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>5</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>7</td>
<td>Right</td>
<td>aPVI</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>5</td>
<td>Right</td>
<td>LLS</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>9</td>
<td>Left</td>
<td>aPVI</td>
<td>I</td>
<td>II</td>
</tr>
</tbody>
</table>

Abbreviations: aPVI, Asymmetric periventricular injury; LLS, Lateral lenticulostriate infarction; MCA, Middle cerebral artery; GMFCS, Gross motor function classification system; MACS, Manual ability classification system. *Denotes participants who did not complete the neuroimaging component of the study.
Table 3: Mean/median clinical sensory scores at baseline of the affected and unaffected hand and post constraint-induced movement therapy scores of the affected hand. A Paired t-test or Wilcoxon signed-rank test was used to compare mean or median values respectively from baseline to post CIMT of the affected hand (Bonferroni correction p< 0.01).

<table>
<thead>
<tr>
<th></th>
<th>2PD (out of 15)</th>
<th>Tactile Registration (out of 4)</th>
<th>Stereognosis (out of 6)</th>
<th>Kinesthesia (% accuracy)</th>
<th>Proprioception (angle error difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=10 mean (SD)</td>
<td>n=10 median (range)</td>
<td>n=10 median (range)</td>
<td>n=9 mean (SD)</td>
<td>n=9 mean (SD)</td>
</tr>
<tr>
<td>Unaffected Baseline</td>
<td>13.3 (2.9)</td>
<td>3.0 (2-4)</td>
<td>6.0 (3-6)</td>
<td>80.0 (21.8)</td>
<td>12.2° (5.3)</td>
</tr>
<tr>
<td>AFFECTED Baseline</td>
<td>9.8 (4.1)</td>
<td>3.0 (1-4)</td>
<td>3.0 (0-6)</td>
<td>61.7 (27.6)</td>
<td>16.9° (8.4)</td>
</tr>
<tr>
<td>AFFECTED Post CIMT</td>
<td>10.3 (3.7)</td>
<td>3.0 (2-4)</td>
<td>3.0 (0-6)</td>
<td>70.0 (21.8)</td>
<td>12.3° (7.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>t(9)=1.00, p=0.34</td>
<td>z=-0.45, p=0.66</td>
<td>z=-0.58, p=0.56</td>
<td>t(8)=1.03, p=0.33</td>
<td>t(8)= -2.61, p=0.03</td>
</tr>
</tbody>
</table>
Table 4: Summary of mean MEG P50 amplitude and latency values at baseline and post constraint-induced movement therapy (CIMT) for the affected hand, n=8. Parametric t-test assessed significance between baseline and post CIMT time points.

<table>
<thead>
<tr>
<th></th>
<th>SEF amplitude (nAm)</th>
<th>SEF latency (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=8 mean (SD)</td>
<td>n=8 mean (SD)</td>
</tr>
<tr>
<td>Baseline</td>
<td>14.4 (5.2)</td>
<td>0.04 (0.005)</td>
</tr>
<tr>
<td>1 month</td>
<td>14.6 (6.7)</td>
<td>0.04 (0.004)</td>
</tr>
<tr>
<td>p-value</td>
<td>t(7)=0.14, p=0.90</td>
<td>t(7)= -1.28, p=0.24</td>
</tr>
</tbody>
</table>

Abbreviations: P50, first prominent peak identified; SEF, somatosensory evoked fields.
Table 5: Summary of mean group averaged mean integrated power for alpha and beta band event-related desynchronization (ERD) as well as corresponding ERD onset, offset and latency duration for both the affected hand. Paired t test compared mean values from baseline to post constraint-induced movement therapy.

<table>
<thead>
<tr>
<th></th>
<th>Integrated ERD power</th>
<th>Minimum peak</th>
<th>Latency onset</th>
<th>Latency Offset</th>
<th>Latency duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha (7-13Hz)</strong>&lt;br&gt;n=7&lt;br&gt;mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-7634.4 (5955.9)</td>
<td>-25.7 (19.2)</td>
<td>-0.2 (0.1)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>1 month</td>
<td>-5593.8 (4013.0)</td>
<td>-22.7 (13.4)</td>
<td>-0.002 (0.3)</td>
<td>0.5 (0.4)</td>
<td>0.7 (0.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>t(6)=1.04, p=0.34</td>
<td>t(6)=0.51, p=0.63</td>
<td>t(6)=-1.88, p=0.31</td>
<td>t(6)=-1.46, p=0.2</td>
<td>t(6)=-0.63, p=0.55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Integrated ERD power</th>
<th>Minimum peak</th>
<th>Latency onset</th>
<th>Latency Offset</th>
<th>Latency duration</th>
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<tbody>
<tr>
<td><strong>Beta (15-30Hz)</strong>&lt;br&gt;n=8&lt;br&gt;mean (SD)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>-4726.9 (4146.2)</td>
<td>-19.9 (12.3)</td>
<td>0.1 (0.17)</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
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<tr>
<td>1 month</td>
<td>-3065.1 (2992.7)</td>
<td>-16.2 (12.1)</td>
<td>0.1 (0.1)</td>
<td>0.6 (0.1)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>t(7)=1.85, p=0.11</td>
<td>t(7)=1.78, p=0.12</td>
<td>t(7)=0.72, p=0.50</td>
<td>t(7)=0.03, p=0.98</td>
<td>t(7)=-0.57, p=0.59</td>
</tr>
</tbody>
</table>
Figure 1: Grand averaged somatosensory evoked fields (SEF) waveform at baseline (black line) and post constraint-induced movement therapy, CIMT (dark red line) of the affected hand, P50 (first prominent peak identified, 50 milliseconds after stimulation). SEF waveforms are observed for the source localized contralateral to the stimulated affected hand. P50 SEF amplitude and peak latency at baseline and post CIMT remain the same (no significant changes) for the affected hand.
Figure 2. For visualization, a wideband time-frequency representation plot (TFR) of virtual sensors shows both alpha and beta modulations extracted from the affected post central gyrus (n=8) at a) baseline and b) post constraint-induced movement therapy (CIMT). Note: specific frequency range TFR plots were generated for alpha and beta oscillatory activity change analysis. Beta modulation (15-30 Hz) reveals a strong suppression (blue) followed by a weak rebound (red) (dashed box). Alpha modulation reveals a strong suppression (blue) followed by a weak rebound (red) (solid black box). Tactile stimulus onset is presented with a vertical dashed line. Grand average time course of alpha (blue) and beta (green) event-related desynchronization (ERD) in the contralateral post central gyrus at c) baseline, d) post CIMT of the affected hand. Alpha and beta event-related synchronization (ERS) are not reflected on the time courses due to weak rebound. Tactile stimulus onset is at 0s. Error bars reflect standard mean error.
Appendix A

Supplementary Information: Neuroimaging Data Acquisition and Protocol

**MEG:** Brain signals were recorded in a magnetically shielded room using a 151-channel, whole-head MEG system (CTF, VSM MedTech, Ltd.) at a sampling rate of 600 samples/second (bandpass 0-150Hz). Participants were positioned supine, with arms resting on either side while watching a movie to reduce head and eye movements. Three fiducial landmarks were placed on the nasion, left and right pre-auricular points in order to continuously monitor the participant’s head position relative to the sensor array throughout the scan. A custom, pneumatically driven tactile stimulation device designed to deliver pulses of non-painful stimuli (synonymous to a “tap”) via inflatable plastic membranes (1cm diameter discs, 4D-Neuroimaging, San Diego, CA), were attached to the left and right index fingers. Electromyography electrodes were also placed on each forearm to monitor unnecessary arm movements. Participants were instructed to remain as still as possible as the tactile stimulation device “tapped” (with 30 psi pressure) the index finger on their affected hand, unaffected hand, then both simultaneously. Rapid pulses were generated once every 1-1.5 seconds under computer control, effectively collecting approximately 400 trials.

**MRI:** Spatial patterns of the magnetic fields are used to localize the sources of the activity within the brain. These source locations are superimposed on the participants MRI. High-resolution structural brain images were obtained once in the first scanning session (CIMT baseline), in a 3T Siemens Trio scanner while the child simply watched an age-appropriate movie for the duration of the scan. Standard structural 1mm isotropic T1-weighted images were obtained using a magnetization prepared gradient-echo sequence (MPRAGE) with parallel acquisition technique (GRAPPA) for improved acquisition speed.

**Source Localization (SEF and oscillations):** Continuous MEG data was segmented into 2-second trials, from 1 seconds preceding and 1 second following each tactile event (affected hand only and
unaffected hand only). Trials containing large eye, or limb movements were removed prior to analysis, and conservatively corrected for head motions deviating greater than 1 cm from the previous event. Datasets were then averaged to each event type, and beamformer algorithms were applied using a specialized source localization MATLAB toolbox, BrainWave (http://cheynelab.utoronto.ca/brainwave). Images were analyzed in normalized (MNI) space using 4 mm volumetric resolution. Scalar event-related beamformer (ERB) algorithm was applied to reveal SEFs. Furthermore, source locations for specific narrow band oscillations, such as alpha (7-13 Hz) and beta (15-30 Hz), were analyzed using whole-brain pseudo-t image analyses of the Synthetic Aperture Magnetometry (SAM) algorithm. Group averages were scanned for maximum peaks for power changes. Coordinates for the postcentral gyrus, preferably the Brodmann area 3 (BA3), were identified for both SEF and oscillatory activity by locating the highest peak activation following tactile stimulation. Talairach coordinates, +/- 5 mm from the postcentral gyrus were accepted.

**Alpha and beta oscillation analysis:** The reactivity of somatosensory oscillations in the alpha and beta band was analyzed using a time-frequency representation plot (TFR) generated from each SAM image. Data was bandpass filtered into frequency bands of interest, alpha (7-13Hz) or beta (15-30Hz), with a Morlet wavelet step size of 7 cycles. Power was converted to percent change relative to the pre-stimulus baseline. This integrated percent power is transiently modulated after stimulation reflected by suppression (area below the curve) and rebound (area above the curve), which have been termed event-related synchronization (ERS) and desynchronization (ERD) respectively. Integrated percent power change for ERS and ERD of the alpha and beta oscillations was measured by using the power time-courses across subject-specific time windows. Latency and duration (onset and offset of ERD and ERS activity) as well as ERS and ERD minimum and maximum peak were also logged.
APPENDICES
Appendix A: Sensory activities protocol

Table 1: Description of CIMT sensory activities which can be found in the ‘A practical guide to implementing Constraint therapy and Bimanual training’ at [Insert website – online version will be available soon]. Manual was created by occupational therapists Sophie Lam-Damji, Linda Fay and Yvonne Ng at Holland Bloorview Kids Rehabilitation Hospital.

<table>
<thead>
<tr>
<th>Sensory activities protocol</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory Grasp</td>
<td></td>
</tr>
<tr>
<td>Desired sensory response/movement: Stereognosis</td>
<td>Grade Down</td>
</tr>
</tbody>
</table>
| Child starts in sitting and vision is occluded (i.e. can use a blindfold, ask to close his/her eyes, or use a curtained box). Therapist presents a number of common items and asks the child to name the items through touch | • Therapist moves the object within the child’s hand if the child is unable to grasp  
• Therapist places the object in the child’s hand to facilitate grasp  
• Therapist provides a visual aid for reference (i.e. picture of the same set of objects to be identified)  
• Therapist limits the number of objects presented  
• Therapist gives descriptors of the objects to cue the child  
• Therapist provides objects with very different characteristics (i.e. size, shape, texture)  
• More time is allowed to name the objects |
| Grade Up                    |                |
| • Child reaches behind the curtain and finds the objects  
• Child moves the object within his/her own hand  
• No visual aids are provided  
• Therapist increases the number of objects presented  
• Therapist provides objects with very subtle differences  
• Therapist places the objects within a medium (i.e. place the objects in a bin of sand, uncooked beans)  
• A timed component is put in place |
<table>
<thead>
<tr>
<th>Sensory Reach</th>
<th>Grade Down</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Desired sensory response/movement:</strong> Proprioception</td>
<td><strong>Therapist provides kinesthetic feedback of location of target through passive assist followed by asking the child to mimic the movement</strong></td>
</tr>
<tr>
<td>Child begins standing comfortably in front of “Pin the tail on donkey” game mounted on wall. Child is then blind folded, and takes turns with a partner to accurately target tail placement.</td>
<td><strong>Therapist provides auditory clues/feedback to assist with targeting (i.e. “getting warmer”, ring bell/rattle as getting closer to target)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Child wears weighted cuff or sound bracelet in order to increase feedback of where arm is in space</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Target size is increased</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Therapist decreases grasp demands i.e. vary shape/thickness of tail, secure tail for child in hand with velcro wrap</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Child is allowed increased response time</strong></td>
</tr>
<tr>
<td><strong>Grade Down</strong></td>
<td><strong>Therapist chooses progressively more difficult games (i.e. with a decrease response time, timed component, more targets, smaller targets, busier backgrounds, crossing midline, targeting using a larger range of movement)</strong></td>
</tr>
<tr>
<td><strong>Therapist chooses progressively more difficult games (i.e. with a decrease response time, timed component, more targets, smaller targets, busier backgrounds, crossing midline, targeting using a larger range of movement)</strong></td>
<td><strong>Child only uses the affected hand for playing</strong></td>
</tr>
<tr>
<td><strong>Grade Up</strong></td>
<td><strong>Child plays with a partner</strong></td>
</tr>
</tbody>
</table>

**Computer gaming**

**Desired sensory response/movement:** Proprioception, arm extension/reach

Child plays Kinect or Wii games to encourage use of the affected arm for targeting.

Rehabilitation based virtual reality are available, allowing therapists to customize parameters to grade the activity. Examples used include SeeMe and Jintronix

## Appendix B: 2-week CIMT Camp Schedule

<table>
<thead>
<tr>
<th>Time</th>
<th>Mon July 7</th>
<th>Tue July 8</th>
<th>Wed July 9</th>
<th>Thu July 10</th>
<th>Fri July 11</th>
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<tbody>
<tr>
<td>8:30am</td>
<td>Welcome and Ice Breakers</td>
<td>Sensory Circuits</td>
<td>Gross Motor</td>
<td>Snack Prep</td>
<td>Lunch</td>
</tr>
<tr>
<td>9:00am</td>
<td>Sensory Circuits</td>
<td>Gross Motor</td>
<td>Magic</td>
<td>Lunch</td>
<td>Virtual Reality Games/Virtual Reality <em>included proprioceptive activities</em></td>
</tr>
<tr>
<td>9:15am</td>
<td>Gross Motor</td>
<td>Snack</td>
<td>Magic</td>
<td>Lunch</td>
<td>Virtual Reality Games/Virtual Reality <em>included proprioceptive activities</em></td>
</tr>
<tr>
<td>9:30am</td>
<td>Snack</td>
<td>Magic</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Virtual Reality Games/Virtual Reality <em>included proprioceptive activities</em></td>
</tr>
<tr>
<td>9:45am</td>
<td>Craft/Cast Removal</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
<td>Lunch</td>
</tr>
<tr>
<td>10:00am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>10:15am</td>
<td>Outdoor Activities</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>10:30am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>10:45am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>11:00am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>11:15am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>11:30am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>11:45am</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>12:00pm</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>12:15pm</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
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<tr>
<td>12:30pm</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
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<tr>
<td>12:45pm</td>
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<td>Lunch</td>
<td>Lunch</td>
<td>Lunch</td>
<td>Outdoor Activities</td>
</tr>
<tr>
<td>1:00pm</td>
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<td>Lunch</td>
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<td>Time</td>
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<td>Wed Jul 16</td>
<td>Thur Jul 17</td>
<td>Fri Jul 18</td>
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<td>Swimming</td>
<td>ADL</td>
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<tr>
<td>9:30am</td>
<td>Sensory Circuits</td>
<td>Sensory Circuits</td>
<td>Kitchen/Cupcakes</td>
<td></td>
<td>Sensory Circuits</td>
</tr>
<tr>
<td>9:45am</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00am</td>
<td>Gross Motor</td>
<td>Gross Motor</td>
<td>Sensory Circuits</td>
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<td>ADL</td>
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<tr>
<td>10:15am</td>
<td></td>
<td></td>
<td></td>
<td>Gross Motor (10:15-11am)</td>
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</tr>
<tr>
<td>10:30am</td>
<td></td>
<td></td>
<td></td>
<td>10:30-12pm parent Social Work/Networking</td>
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</tr>
<tr>
<td>10:45am</td>
<td>Snack</td>
<td>Snack</td>
<td></td>
<td>Snack</td>
<td></td>
</tr>
<tr>
<td>11:00am</td>
<td>Magic</td>
<td>Social Work</td>
<td>Magic</td>
<td>Cupcake Decoration</td>
<td></td>
</tr>
<tr>
<td>11:15am</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:30am</td>
<td>Pizza Lunch</td>
<td></td>
<td>Lunch</td>
<td></td>
<td>Lunch</td>
</tr>
<tr>
<td>11:45am</td>
<td></td>
<td></td>
<td>Lunch</td>
<td></td>
<td>Lunch</td>
</tr>
<tr>
<td>12:00pm</td>
<td></td>
<td></td>
<td>Lunch</td>
<td></td>
<td>Lunch</td>
</tr>
<tr>
<td>12:15pm</td>
<td>Unilateral Games/Virtual Reality *included proprioceptive activities</td>
<td></td>
<td>Unilateral Games/Virtual Reality (Linda) *included proprioceptive activities</td>
<td></td>
<td>Closing</td>
</tr>
<tr>
<td>12:30pm</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>12:45pm</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:00pm</td>
<td></td>
<td></td>
<td></td>
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</table>
Appendix C: Determination of latency range for p50

Individual waveforms for somatosensory evoked fields (SEF) at baseline. Tactile stimulus was applied at 0s. Using the averaged sensor plots, the first peak and trough after stimulus was represented as the first SEF component, P50. This approach was taken to determine a latency range for P50 activation in response to stimulation.

**Affected Hemisphere**

01_02_RH - Latency: 37.3 ms
02_02_LH - Latency: 44.3 ms
03_02_RH - Latency: 50 ms
04_02_RH - Latency: 47.3 ms
07_02_RH - Latency: 41.4 ms
08_02_RH - Latency: 44.7 ms
09_02_RH - Latency: 60.5 ms
10_02_LH - Latency: 60.5 ms

**Unaffected Hemisphere**

01_02_LH - Latency: 41.8 ms
02_02_RH - Latency: 46.5 ms
03_02_LH - Latency: 50 ms
04_02_LH - Latency: 46.7 ms
07_02_LH - Latency: 49.9 ms
08_02_LH - Latency: 49.9 ms
09_02_LH - Latency: 37.9 ms
10_02_RH - Latency: 41.4 ms
## APPENDIX D: Somatosensory Evoked Fields (SEFs)

### AFFECTED HAND

<table>
<thead>
<tr>
<th>Subject</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Magnitude</th>
<th>Brain Location</th>
<th>Moment (50)</th>
<th>Latency (50)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>-30</td>
<td>-33</td>
<td>44</td>
<td>4.14</td>
<td>L Postcentral Gyrus BA3</td>
<td>20.29</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>-21</td>
<td>54</td>
<td>2.52</td>
<td>R Precentral Gyrus BA4*</td>
<td>10.69</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>-34</td>
<td>-17</td>
<td>51</td>
<td>3.35</td>
<td>L Precentral Gyrus BA4*</td>
<td>22.61</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>-18</td>
<td>-25</td>
<td>47</td>
<td>0.93</td>
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<td>0.05</td>
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<tr>
<td>7</td>
<td>-34</td>
<td>-14</td>
<td>36</td>
<td>1.37</td>
<td>L Precentral Gyrus BA4*</td>
<td>8.51</td>
<td>0.05</td>
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<tr>
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<td>-42</td>
<td>-18</td>
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<tr>
<td>9</td>
<td>-30</td>
<td>-18</td>
<td>25</td>
<td>2.18</td>
<td>L Insula, BA13*</td>
<td>14.9</td>
<td>0.04</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>6</td>
<td>35</td>
<td>2.78</td>
<td>R Sub-Gyral†</td>
<td>23.3</td>
<td>0.04</td>
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</table>

### BASELINE

<table>
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<tr>
<th>Subject</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Magnitude</th>
<th>Brain Location</th>
<th>Moment (50)</th>
<th>Latency (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-26</td>
<td>-13</td>
<td>58</td>
<td>2.84</td>
<td>L Precentral gyrus*</td>
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<tr>
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<td>46</td>
<td>-13</td>
<td>43</td>
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<td>-34</td>
<td>-21</td>
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<td>4</td>
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<td>-25</td>
<td>44</td>
<td>1.22</td>
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<td>7.50</td>
<td>0.05</td>
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<td>-18</td>
<td>-21</td>
<td>51</td>
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<tr>
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<td>-13</td>
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<td>0.66</td>
<td>L Precentral gyrus BA4*</td>
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<td>0.05</td>
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<tr>
<td>9</td>
<td>-14</td>
<td>-29</td>
<td>36</td>
<td>3.03</td>
<td>L Cingulate Gyrus, BA31*</td>
<td>15.26</td>
<td>0.04</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>6</td>
<td>35</td>
<td>3.04</td>
<td>R Sub-Gyral†</td>
<td>23.17</td>
<td>0.04</td>
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</table>

### POST CIMT

<table>
<thead>
<tr>
<th>Subject</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Magnitude</th>
<th>Brain Location</th>
<th>Moment (50)</th>
<th>Latency (50)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>-29</td>
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### SIX MONTH

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Table A. Subject specific source location with corresponding Talairach coordinates in the affected hemisphere at all 3 time points (baseline, post CIMT and six month post CIMT), including magnitude for peak identification. *Denotes location is +/- 5 mm from post central gyrus. Mean MEG P50 amplitude (nAm) and latency (s) values at baseline, post CIMT and six month post CIMT for the affected hand. † Represents reorganization in response to tactile stimulation.
Table B. Subject specific source location with corresponding Talairach coordinates in the unaffected hemisphere at all 3 time points (baseline, post CIMT and six month post CIMT), including magnitude for peak identification. *Denotes location is +/- 5 mm from post central gyrus. Mean MEG P50 amplitude (nAm) and latency (s) values at baseline, post CIMT and six month post CIMT for the unaffected hand. †Represents reorganization in response to tactile stimulation.

### UNAFFECTED HAND

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### SIX MONTH

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