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The Neurological Abnormalities of the Brain and Spinal Cord in Individuals with Cerebral Palsy

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THE NEUROLOGICAL ABNORMALITIES OF THE BRAIN AND SPINAL CORD IN INDIVIDUALS WITH CEREBRAL PALSY

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Cerebral palsy (CP) results from an insult to the developing brain, and it is one of the most common neurodevelopmental disorders in the United States. The insult produces a cascade of activity-dependent plastic changes within the neurophysiology and structure of the brain and spinal cord that ultimately leads to sensorimotor and mobility impairments that may increase in severity throughout the lifespan. Despite this phenomenon, there are a lack of neuroimaging studies in adults with CP, generating a knowledge gap in determining how brain and spinal cord activity and structure may be altered throughout the transition into adulthood. Furthermore, the specific microstructural changes in the spinal cord and the relationship between how the brain and spinal cord interact to produce these impairments remains poorly understood. We sought to address these knowledge gaps by employing a series of studies utilizing a combination of magnetoencephalography (MEG), MRI, and genetic methodologies during a variety of simple sensorimotor tasks. Overall, we uncovered aberrant sensorimotor cortical activity in both children and adults with CP in comparison to their healthy peers. Furthermore, we demonstrated specific structural deficiencies within the somatosensory cortex and the upper spinal cord of adults with CP, and these alterations were related to the aberrant sensorimotor cortical activity. Finally, we found that a polymorphism at the gene coding for brain derived neurotrophic factor (BDNF) contributed to more significant aberrancies in cortical activity in individuals with CP. Ultimately, these findings provide support for the notion that aberrant activity within the brain of individuals with CP, which is exacerbated by a polymorphism at the *BDNF* gene, results in neuroplastic changes

along the spinal cord that may ultimately contribute to the clinical sensorimotor impairments seen within this population.

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LIST OF ABBREVIATIONS

AC	Adult Controls
AD	Axial Diffusivity
AHA	Assisting Hand Assessment
ALS	Amyotrophic Lateral Sclerosis
aMT	active Motor Threshold
ASD	Autism Spectrum Disorder
AU	Arbitrary Units
BDNF	Brain Derived Neurotrophic Factor
BESA	Brain Electrical Source Analysis
CI	Confidence Interval
CIMT	Constraint Induced Movement Therapy
CMCT	Central Motor Conduction Time
CNS	Central Nervous System
CP	Cerebral Palsy
CS	Conditioning Stimulus
CSA	Cross Sectional Area
CSP	Cortical Silent Period
CST	Corticospinal tract
DICS	Dynamic Imaging of Coherent Sources
DLPFC	Dorsolateral Prefrontal Cortex

DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EDACS	Eating and Drinking Ability Classification System
EEG	Electroencephalography
EMG	Electromyography
ERD	Event-related desynchronization
ERS	Event-Related Synchronization
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
fNIRS	functional Near-Infrared Spectroscopy
GABA	Gamma Amino-Butyric Acid
GM	Gray Matter
GMFCS	Gross Motor Function Classification System
HC	Healthy Controls
ICF	International Classification of Functioning
ISI	Interstimulus Interval
IVH	Intraventricular Hemorrhage
JTTHF	Jebsen Taylor Test of Hand Functioning
LICI	Long Interval Intracortical Inhibition
MACS	Manual Ability Classification System
MD	Mean diffusivity

MEG	Magnetoencephalography
MEP	Motor-Evoked Potential
MRGS	Motor-Related Gamma Synchronization
MRI	Magnetic Resonance Imaging
MTR	Magnetic Transfer Ratio
MUUL	Manual Assessment of Upper Limb Function
NMDA	N -methyl- D -aspartate
NT	Neurotypicals
PBT	Projection Based Thickness
PCR	Polymerase Chain Reaction
PD	Parkinson's Disease
PET	Positron Emission Tomography
PMBR	Post Movement Beta Rebound
PMC	Premotor Cortex
ppTMS	paired pulse Transcranial Magnetic Stimulation
PVL	Periventricular Leukomalacia
RD	Radial Diffusivity
rMT	resting Motor Threshold
ROI	Region of Interest
rTMS	repetitive Transcranial Magnetic Stimulation
SICI	Short Interval Intracortical Inhibition

sLORETA	standardized Low Resolution brain Electromagnetic Tomography
SMA	Supplementary Motor Area
SNR	Signal to Noise Ratio
SSP	Signal Space Projection
TMS	Transcranial Magnetic Stimulation
TS	Test Stimulus
WM	White Matter

INTRODUCTION

Cerebral palsy (CP) refers to a group of neurodevelopmental disorders that result from an insult to the developing brain. Nearly 3 out of every 1,000 children are diagnosed with the disorder, making it the most common nonprogressive developmental disorder in the United States. Although motor and mobility impairments are inherent to the disorder, a large number of studies have documented impairments in tactile discrimination, stereognosis, and proprioception[1-8]. Thus, sensory and perceptual deficits have been added into the definition of CP. Despite CP commonly being considered a childhood disorder, a large number of these individuals survive well into adulthood, and many of the impairments actually worsen with age. In fact, many individuals with CP that were previously able to walk independently lose this ability at some point in their adult lives[9-14]. Despite this phenomenon, much of the literature has primarily focused on children with CP, despite the fact that specialized care is difficult to find for adults with CP.

Important in the comprehensive understanding of the disorder is uncovering the neurophysiological and structural underpinnings of the sensorimotor and mobility deficits that are seen within this population. Magnetoencephalography (MEG) is a neuroimaging device that measures the minute magnetic fields that are generated by the underlying neuronal populations. MEG has both high temporal and spatial resolution, which makes it a viable mechanism for studying the activity within the sensorimotor cortices. Previous neuroimaging studies using both MEG and electroencephalography (EEG) have identified that prior to movement onset there is a sharp decrease in power within the beta band (15-30Hz) which lasts throughout the entire movement [15-19]. This beta event-related desynchronization (ERD) has been linked with movement planning, as it begins prior to movement onset, begins earlier for simpler movements, and its magnitude is related to response certainty [19-29]. An increase in power within the beta range then occurs after movement termination, termed the post movement beta rebound (PMBR)[15,17,21-24,18,19].

The PMBR is thought to be tied to afferent sensory feedback to the sensorimotor cortices [30,31], movement termination [32-34], or feedforward from the internal model and movement certainty[35,36]. Within the upper gamma band, there is a transient increase in power that begins just before movement onset and lasts about 200 ms, and this response is thought to play a role in movement execution[37-39,19].

Previous studies have identified that these oscillatory responses surrounding movement planning, execution, and termination are aberrant in children with CP, and these aberrant responses are connected with clinical deficits of sensorimotor functioning. While performing both lower and upper extremity tasks, the beta-event related desynchronization (ERD) has been shown to be stronger in children with CP[40,41], indicating increased difficulty in planning motor actions. Additionally, the gamma ERS was decreased in amplitude in the children with CP[41], likely adversely affecting the execution of the motor action. Movement-related oscillatory activity associated with upper extremity motor actions has also been studied in CP, in which the gamma ERS and PMBR were both weaker during the arrow version of the Eriksen Flanker task[42].

Several studies have also assessed the somatosensory cortical activity in individuals with CP. The somatosensory cortical oscillatory activity within the theta/alpha (4-14Hz) and beta (8-34Hz) range is aberrant following tactile and electrical stimulation of the foot and hands[43-47]. The aberrant functioning within the somatosensory cortices of children with CP has also been connected with mobility and ankle plantarflexor strength in children with CP[44,47] Furthermore, children with CP tend to hyper-gate paired somatosensory stimulations of the foot[48]. In addition to the altered induced activity, numerous studies have demonstrated that the phase-locked somatosensory-evoked cortical activity is decreased in magnitude, and sometimes latent, in children with CP[49,50,43,7,51,52]. Overall, these findings demonstrate that there are clear neurophysiological correlates within the brain that correspond to the aberrant sensorimotor functioning that affects the quality of life in these individuals. However, the brain alone is not solely responsible for producing motor actions and

processing sensations. In order for sensations to be processed and motor actions to be produced, the neural activity inherently has to be transmitted through the spinal cord.

Far less investigation has been put into how the spinal cord may contribute to aberrant sensorimotor functioning within individuals with CP. Nevertheless, several studies have demonstrated that an insult to the developing brain may result in activity-dependent neuroplastic changes within the spinal cord. For example, in response to a unilateral insult, reorganization of the corticospinal tracts may occur such that motor actions from the more affected side of the body are processed by the non-affected, ipsilateral hemisphere [53,54]. Furthermore, corticospinal terminations may also become dorsalized, such that they are competing for real estate within the dorsal horn of the spinal cord where the sensory neurons typically reside[55,56]. These structural changes within the spinal cord are a direct result of changes that are occurring in the brain. Yet, the specific microstructural changes that are occurring in the spinal cord have not been investigated. This knowledge is critical to understanding the neurological impairments in CP from a broader perspective, as the spinal cord may be a significant contributor to the sensorimotor deficits seen within this population. Furthermore, the results from functional brain imaging studies in individuals with CP are difficult to interpret without a concrete understanding of how the spinal cord may be contributing.

An ongoing and challenging issue within this population is understanding the underlying factors contributing to the large amount of heterogeneity of outcomes following therapeutic interventions. Some individuals respond very well to therapy, while others do not seem to respond at all. Potentially, the individuals that do not respond well to therapy have less capacity for neuroplastic change. This would result in limited capacity for brain-related functional and structural changes following therapy, creating difficulty in making significant improvements in mobility, strength, and sensorimotor functioning. Recently, there has been interest in investigating the impact that the protein brain-derived neurotrophic factor (BDNF) and the gene that codes for it may have on neuroplastic change. Several motor learning studies have confirmed that BDNF is highly

involved in the brain in regulating neuroplastic change[57-59]. However, brain imaging and transcranial magnetic stimulation (TMS) studies have illustrated that healthy individuals that have a single nucleotide polymorphism (approximately 30% of the general population) at one or both alleles of the *BDNF* gene have decreased retention, less reorganization in their sensorimotor cortices, and less change in motor-evoked potentials after learning a new motor skill[60,61]. Thus, it is possible that the individuals with CP that do not respond well to therapy have the polymorphism at the *BDNF* gene, exacerbating their sensorimotor impairments and decreasing their ability to achieve positive changes following therapy.

Overall, the goal of this dissertation was to expand on the knowledge base of the underlying cortical and spinal cord neurophysiological and structural abnormalities that contribute to the impaired sensorimotor functioning in both children and adults with CP. The first main objective was to utilize MEG to assess the dynamics of the sensorimotor cortical activity during the transition from adolescence to adulthood, as well as understand how these changes may be linked with underlying structural changes in the cortex. We hypothesized that the somatosensory evoked cortical activity would be reduced in magnitude and also display an aberrant trajectory throughout the transition from adolescence to adulthood in the individuals with CP. Moreover, we hypothesized that individuals with CP would have aberrant GABAergic inhibitory functioning as represented by the hyper-gating of paired pulse stimulations. Finally, we hypothesized that the altered somatosensory cortical activity would be directly related to cortical thickness within the region of the somatosensory cortex generating the response.

The second objective of this dissertation was to determine how the spinal cord microstructure may be affected in adults with CP and how this may be related to changes in motor-related oscillatory activity within the brain. We hypothesized that alterations in cervical-thoracic spinal cord microstructure within adults with CP would be reflected by decreases in gray and white matter, as well as changes in the integrity of the corticospinal and cuneatus tracts, reflected by reduced fractional anisotropy (FA) and magnetization transfer ratio (MTR). We also hypothesized

that these microstructural changes within the spinal cord would be related to a weaker beta ERD and PMBR within the sensorimotor cortices.

The last objective of this dissertation was to assess whether a polymorphism at the *BDNF* gene plays a role in the altered brain activity seen within individuals with CP. We hypothesized that somatosensory cortical activity would be more aberrant in the individuals with CP that had the *BDNF* polymorphism compared with the individuals with CP that did not have the polymorphism. The following chapters within this dissertation highlight the specific methods and paradigms used to uncover these objectives, with the overall goal of providing knowledge that may enhance the understanding of the underlying neurological impairments in individuals with CP.

CHAPTER 1: LITERATURE REVIEW

Magnetoencephalography

Instrumentation and Physiological Bases of Recorded Signal

Magnetoencephalography (MEG) is a functional brain imaging device with high temporal (<1ms) and spatial (<5mm) resolution, optimal for measuring both evoked and induced neuronal population activity. MEG systems utilize sensors that consist of superconducting quantum interference devices (SQUIDs) that are coupled to sensor coils (i.e. pick up coils and compensation coils) which allow for the detection of the minute magnetic fields emanating from the brain. The sensor coils detect the magnetic field and squeeze it through the SQUIDs, which then convert the magnetic signal into a voltage signal that can be amplified and be read by modern electronic systems. Modern MEG systems typically contain 200 to over 300 sensors that are bathed in liquid helium within a dewar in order to maintain a superconducting temperature, allowing for electromagnetic flow with no resistance [62].

Two types of MEG sensors exist; magnetometers are comprised solely of a pick-up coil, allowing for direct measurement of the magnetic field and making them more sensitive to sources that are further away. The second type of sensor is a gradiometer, which consists of both a pick up and compensation coil and measures the gradient of the magnetic field between the two coils. Essentially, magnetic fields that are further away are more homogeneous, and thus there will be no net magnetic field measured between the pick-up and compensation coil, making gradiometers more optimal for measuring closer sources without picking up environmental noise from further away sources. Gradiometers can either be axial, which detect radial magnetic fields from around the rim of the sensor, or planar, which detect tangential magnetic fields directly under the sensor [62,63].

MEG systems are typically housed within rooms that provide passive shielding from magnetic sources stemming from outside the room. Passive shielding of external magnetic fields is

maintained by plates consisting of nickel, iron, and aluminum that surround the room. Active shielding can also be employed to enhance this protection by applying a compensatory magnetic field which cancels out external magnetic fields and, therefore, enhances the detection of true neural signal by the MEG sensors.

MEG sensors measure magnetic fields primarily generated from neuronal currents of pyramidal neurons, based on the right hand rule of magnetism, and it is approximated that ~15,000 neurons must be synchronously active in order for a measurable signal to be detected via MEG. However, action potentials are mediated by fast-acting sodium and potassium voltage gated ion channels, making them extremely transient (lasting 1-2ms), and so it is widely accepted that action potentials do not account for the majority of the signal measured with MEG. Post synaptic potentials, on the other hand, are mediated by distinct neurotransmitters, ligand gated channels, and secondary messenger systems, and thus they occur on a much longer time scale (hundreds of milliseconds), creating a longer temporal interval for overlap of signal to occur. Consequently, the main source of MEG signal is likely attributed to primary (intracellular) neuronal currents generated by excitatory and inhibitory post synaptic potentials, in addition to a minor contribution from action potentials[62].

Acquisition and Analysis

In order to maximize the strength of the above described neuromagnetic signal during acquisition, it is necessary that the positioning of the subject's head within the MEG is as close to the sensor array as possible, as the strength of magnetic fields falls off as a square of the distance from the current source. MEG experiments typically comprise a large number of trials where a stimulus or event is repeatedly presented. The signal to noise ratio (SNR) in a single trial is relatively low due to environmental, instrumental, and physiological noise. Therefore, it is necessary to average a large number of trials to increase the SNR, and this can be done in the time domain, frequency domain, or time-frequency domain. After data is acquired, neuromagnetic

responses are often partitioned into epochs, and thorough preprocessing of the signals typically occurs as a first step in the data analysis pipeline [63].

Preprocessing of the neuromagnetic signal is performed in an effort to assure that the data being analyzed is of the neural origin of interest. Removal of both physiological and non-physiological artifacts is a necessary first step, and a common method employed for removing these artifacts is signal space projection [64]. Additionally, thresholding of amplitude and gradient values across trials can be used to remove unclean trials from the data, and other common procedures in preprocessing include application of low pass filters and removal of noisy channels.

After preprocessing, neuromagnetic signals at the sensor level are averaged, as mentioned above. Time domain averaging is the averaging of each data point across all trials and across the entire epoch, resulting in one epoch of data per participant, and it can be utilized to measure evoked activity within the neuromagnetic signal [63]. Evoked activity is phase locked to an event or stimulus, and it typically reflects the brain's initial response to a stimulus. However, MEG is also an optimal methodology to study induced activity, and time-frequency domain averaging is a viable approach to uncover both evoked and induced activity.

In time-frequency domain averaging, the neuromagnetic signal is partitioned into its spectral components, often through complex demodulation, and activity within pre-defined resolutions of time and frequency are summed together to reveal induced activity, which can then be visually depicted with time frequency components (TFCs). Induced activity, or oscillatory activity, is not always phase locked to an event, and it is a reflection of the rhythmic activity of neuronal populations. The oscillatory activity can be divided into canonical frequency bands, which are loosely defined as delta (~1-4Hz), theta (4-8Hz), alpha (~8-14Hz), beta (~14-30Hz), and gamma (>30Hz), and activity within these different frequency bands is a reflection of the distinct role they play in different brain areas and across modalities. For example, the motor cortex tends to oscillate at the beta frequency, and several responses surrounding movement are explicit to this range.

Spontaneous, or baseline, oscillatory activity is the rhythmic activity of neuronal populations when the brain is at rest. Stimulus or event induced responses, however, are often measured relative to baseline activity, in order to get an index of how the brain is active in response to, or before, the stimulus or event of interest. Increases in neural power from baseline are termed synchronizations, while decreases in neural power from baseline are termed desynchronizations. However, it is important to be aware that a desynchronization does not reflect a decrease in brain activity; rather, it is a decrease in the number of neurons oscillating at that frequency, or perhaps the neurons that were oscillating at the frequency are no longer synchronous, and thus a "decrease in power" still reflects brain activity. A synchronization, on the other hand, reflects an increase in the amount of neurons oscillating at that frequency, or neurons that were already oscillating at that frequency are now doing so more synchronously.

Time-frequency clusters that are statistically different in activity from baseline can subsequently be carried from "sensor space" to "source space." A problem common to all MEG research is that data that is acquired at the sensor level can come from an infinite number of sources from within the brain, and this will differ based on an individual's brain structure as well as how far away the subject's head was during acquisition. Prior to source localization of neural activity, MEG data is co-registered to individual MRI data. Head position indicator coils, responsible for tracking and correcting for head movements throughout the MEG acquisition, are used to couple the MEG coordinate system to the head coordinate system. The head coordinate system is aligned to the MRI coordinate system by aligning landmarks (e.g. nasion, periauricular points) placed on the participant prior to recording with those landmarks on their MRI [62]. Finally, MEG data can be properly mapped onto an individual's MRI data so that sensor level data can be source localized. Subsequently, the individual's MRI is transformed into a standardized coordinate system, so that brain activity can be compared at a group level. Additionally, a head model is defined in order to account for differential conductivity patterns across tissue volumes, and the most commonly employed head model for MEG research is the spherical head model [65].

Two main problems exist during source localization of brain activity. The forward problem is determining the distribution of activity in the sensors that would occur based on brain activity in a given region, and this problem can be solved using mathematics. The second problem is identifying where in the brain the sensor level activity is coming from, which is termed the inverse problem and, while it cannot be solved perfectly, several methods of source space localization provide viable mechanisms for appropriately estimating solutions to the inverse problem. The two main approaches to solve the inverse problem consist of a dipole approach and an imaging approach. The dipole approach aims to determine the location of brain activity from the data, in which a dipole fit that most closely elicits the actual sensor level data is the solution. Imaging methods, on the other hand, determine a solution from a predefined source model [63]. For example, beamforming utilizes a spatial filtering system, in which brain activity from one voxel is passed and activity from all other voxels is filtered out. The forward solution (i.e. individual sensor weightings for each voxel) is then used to algorithmically calculate brain activity within each voxel. Imaging methods may be preferred to the dipole approach, as they can take into account neural activity stemming from multiple sources.

After deriving source space brain activity, neural time courses can be extracted from peak voxels across group level averages, and these can be utilized to identify the temporal progression of brain activity across the epoch. Additionally, these can be utilized to assess differences in strength or latency of oscillatory responses between populations. Of course, many other analyses of the data can be performed after source localization, and novel methodologies are continuously emerging and driving the field of MEG research forward. Below is a review of MEG literature surrounding just one of the modalities that has been extensively studied using MEG: sensorimotor oscillatory activity.

Motor-related oscillatory activity

Numerous investigations have utilized MEG and electroencephalography (EEG) in order to study neural oscillatory responses surrounding movement planning, execution, and termination [66,15,24,67,27,19]. A decrease in neural power in the beta range (~15-30 Hz), termed beta event-related desynchronization (ERD), begins several hundred milliseconds prior to movement onset and persists until shortly after movement termination. The beta ERD has been shown in numerous motor-related brain regions, including the pre and post central gyri, the premotor cortex, the supplementary motor area, posterior parietal areas, and the cerebellum [15,17,24,18], and it is closely linked to movement planning. Subsequently, beginning right before movement onset there is a brief synchronization of neural activity within the gamma range, termed gamma event-related synchronization (ERS) or motor-related gamma synchrony (MRGS). Finally, beginning soon after movement offset, and lasting several hundreds of milliseconds to seconds afterwards, an increase in neural power from baseline occurs in the beta and, and this is termed the post movement beta rebound (PMBR) [37,17,68,24,27,19]. Each of these responses plays a unique role in motor activity as well as the cognitive components of motor planning and execution.

The beta ERD is widely accepted as an oscillatory response related to the planning of motor actions. It begins several hundred milliseconds before movement onset, persists throughout the ongoing movement until dissipating shortly after movement offset, and it is elicited not only through voluntary movements, but also through passive movements, imagined movements, and action observation [30,69,70,39]. Exemplifying its role in action selection, the strength of the beta ERD scales as a function of movement wherein the amplitude of the response is greater (i.e. a greater reduction in beta power from baseline) for movements with greater certainty, when there are fewer or less ambiguous movement cues [71,27,72,28]. The beta ERD typically is present bilaterally in the premotor cortices, but it is stronger in the contralateral hemisphere and more lateralized when laterality cues for an upcoming movement are provided [73]. Additionally, during the execution phase

of this oscillatory response, the beta ERD is increased in amplitude in the left dorsolateral prefrontal cortex (DLPFC) and right parietal cortices during more complex movements compared with simple movements. These regions are also more functionally connected during this time period, indicating they also contribute significantly to the motor selection process [21].

The beta ERD has also been shown to be modulated by circadian rhythms. Both the beta ERD, as well as baseline (spontaneous) beta activity, increase in strength throughout the course of the day in numerous motor-related brain regions, suggesting that the circadian cycle has a direct effect on the beta ERD [18]. The concomitant increase in the beta ERD and spontaneous activity throughout the day suggests a relationship between these two variables, and later studies confirmed that as spontaneous beta activity increases, the strength of the beta ERD also increases [22,74]. This created the notion that, potentially, an absolute level of beta desynchronization is required for the initiation of movement.

The beta ERD elicited during an upper extremity motor task has also been shown to scale linearly with age, wherein the strength of the response, as well as the spontaneous beta activity, are each higher in healthy older individuals bilaterally in the precentral cortices [22,75], and this increase in beta ERD magnitude is associated with increased time to complete a motor task. However, in children and adolescents, the beta ERD during the planning stage of a lower extremity task has been shown to decrease in strength with age, while during the execution stage it increased in strength with age [26]. Furthermore, a study using a similar age range has shown that the beta ERD seems to be relatively stable across the developmental period surrounding the pubertal stage of development [74]. These results suggest that the scaling of the beta ERD with age may be dependent on the task, the age range being analyzed, and the different stages of the response.

Finally, both spontaneous beta, as well as the beta ERD, increase in strength with increased endogenous gamma amino-butyric acid (GABA) and with the administration of a GABA agonist [76,77]. Thus, an increase in GABA levels may contribute to elevated spontaneous beta, which in turn increases the strength of the ERD required for movement, leading to decreases in motor

performance [22]. Overall, these results suggest that the beta ERD is a motor-related oscillatory response tightly coupled with movement planning and action selection that scales with age, and alterations in its power and spontaneous activity may directly influence motor execution and motor performance.

MRGS is elicited temporally closer to movement onset than the beta ERD, and it is present right before active, but not passive, movement onsets and dissipates quickly [78,79,67,80]. Unlike the beta ERD, this response is not sustained throughout the entirety of movements, and thus it is thought to play a critical role in the execution of movement, potentially via disinhibition [37].

The MRGS response is localized tightly to the contralateral primary motor cortex and is not present in the other cortical motor regions in which motor-related beta oscillations persist (i.e. postcentral gyrus, posterior parietal areas, supplementary motor area (SMA), etc..), although there is evidence that MRGS is found within the subthalamic nucleus and globus pallidus of the basal ganglia [71,81]. The motor-related gamma seen in the cortex has a phase lag from that in the basal ganglia, and this idea supports the notion that the MRGS response may be more generalized to a state of arousal/movement disinhibition in the motor cortex, driven by brainstem nuclei activity propagation through the thalamus [82]. However, one electrocorticographic study showed that a prosthetic arm could be controlled by a machine learning algorithm able to distinguish specific movements based on MRGS, providing evidence that MRGS may have specificity for different movements, indicating a more specialized role in motor execution [83]. Additionally, gamma peak frequency is higher in upper limbs compared with lower limbs, is highly consistent within individuals over time, and is consistent between mototopic regions representing movement of homologous muscles between hemispheres, further supporting the idea for a more specified role of motor gamma [37]. Finally, it is possible that generation of MRGS may be related to GABAergic mechanisms, as higher peak frequency of gamma band activity is directly correlated with GABA concentration within the primary motor cortex [68]. Although, other work has presented a lack of

gamma band modulation upon administration of a GABA-A agonist [76], and so this requires further investigation.

The PMBR occurs temporally after the beta ERD and MRGS, and it is tightly locked to movement offset of both voluntary and passive movements [17,24,15,84], but the functional relevance of the PMBR remains controversial. Currently, there are three different ideas surrounding its relevance. The first idea is that the PMBR is simply a rebound of neural activity that reverts the motor system back to its resting state following the perturbation from the beta ERD [66,85,86]. However, in contradiction to this idea, the PMBR does not systematically change in amplitude throughout the course of the day in all of the brain areas that the beta ERD does [18], which would be expected if the PMBR was to function simply as a rebound. The second idea is that the PMBR reflects sensory feedback to the motor system, and this is supported by the fact that deafferentation eliminates the PMBR [31,87]. However, the PMBR likely is not solely a reflection of ongoing sensory feedback, as it is only elicited after the final movement in a sequence [88]. Finally, the PMBR has also been suggested to reflect active termination of movements [84,30,17,33], as its amplitude changes under different conditions in which movement termination parameters are adjusted. Additionally, at least one study has shown increased strength of the PMBR may be related to increased GABA concentration [68], which could provide additional support for this hypothesis, except there is controversy as to the modulatory effects of GABA on PMBR strength [76,77]. Considering all evidence, it is likely that the PMBR takes part in multiple functions, both in movement termination and sensory afferent feedback (and potentially for reverting the motor system back to its resting state).

Somatosensory-related oscillatory activity

Induced somatosensory activity can be elicited within the postcentral gyrus upon tactile or electrical peripheral nerve stimulation. In healthy individuals, broadband synchronization of neural activity occurs in response to single pulse electrical stimulation of the tibial [48] and median nerves

[89,90]. Alternatively, tactile stimulation of the tibial nerve primarily elicits synchronization in the theta/alpha bands in healthy individuals [44], and tactile stimulation of the hands has shown to elicit synchronization within the theta/alpha band and a desynchronization within the upper beta band [46].

When paired pulse electrical stimulations are applied, the induced response to the second stimulus is attenuated. This phenomenon, termed sensory gating, likely reflects the filtering of redundant information, and it can be seen across numerous sensory modalities [91]. Sensory gating has been shown to be aberrant across a number of patient populations, including CP, schizophrenia, HIV-infected patients, and even healthy older adults, and this likely indicates aberrant inhibitory GABAergic mechanisms [92,48,89,90]. Increased sensory gating has also been associated with better performance on somatosensory tasks [93], indicating that appropriate gating is critical to the healthy functioning of the somatosensory system and likely contributes to efficient sensorimotor integration.

Transcranial Magnetic Stimulation

Device and Physiological mechanisms

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation mechanism that has proven useful in both research and clinical settings. It operates by transmitting a magnetic pulse from a stimulation coil that generates an electrical current within the brain, thereby inducing neural activity. The TMS device itself typically consists of a stimulation coil that holds a capacitor and copper wiring; when the capacitor releases charge, an electrical current flows through the copper wiring [94]. Subsequently, a magnetic field is produced perpendicular to the plane of the coil, which then flows through the subject's scalp and skull unimpeded, stimulating axons and generating an electrical current that runs parallel to the cortical surface of the brain [95,96]. TMS magnetic field strength is typically around 1 – 2.5 Tesla (T), which is enough to depolarize neurons and elicit action potentials. However, as magnetic field intensity falls off as the square of the distance from

the source, the current induced directly from the stimulation typically reaches ~2cm deep into the brain. However, dozens of different coil designs exist, and generally there is a depth-focality trade off, wherein coils able to reach deeper areas tend to be less focal. Thus, deeper structures are not able to be stimulated directly by TMS with most coil designs [97].

Nevertheless, TMS offers a viable mechanism to study various aspects of cortical physiology. Variable effects on the underlying neurophysiology occur based upon the simulation paradigm used, offering a wide range of possibilities in research. The main stimulation paradigms utilized consist of single pulse, paired pulse, and repetitive TMS. Single pulse TMS is primarily utilized to assess the excitability of different cortical structures [98,99]. When a single TMS pulse is delivered to the motor cortex, a series of descending volleys is transmitted down the spinal cord and to the periphery. These descending volleys are separated by short intervals (~1.5 ms) and are reflective of distinct neuronal events occurring in the cortex. The first volley that reaches the spinal cord is the result of direct activation of pyramidal neurons in the corticospinal tract, and this is termed the direct wave (D-wave). Subsequently, pyramidal neurons are activated indirectly through monosynaptic connections via excitatory interneurons, and these waves are termed indirect waves (I-waves), which are more susceptible to being affected by cortical injury [100]. The I-waves and D-waves can be recorded from the spinal cord, and physiological delays in timing can be exploited to study different mechanisms within the cortex [101]. However, these waves tend to summate at the spinal cord, and thus when measuring motor-evoked potentials (MEP) using electromyography (EMG), a single wave is apparent.

It is worthwhile to note that several physical and physiological factors contribute to variability within EMG recordings from TMS. Firstly, and most intuitively, the intensity at which a pulse is generated, which is based on the capacitance voltage from the actual coil, will influence the response from the cortex or the periphery, wherein stronger intensities will elicit greater amplitude MEPs. The shape of the pulse, however, also has an impact on the response; pulses can either be monophasic, biphasic, or polyphasic, but this typically differs between TMS devices and

is usually not able to be adjusted. These different pulses can differentially modulate descending I and D-waves [102], and typically higher motor thresholds (MT) and lower MEPs are elicited by monophasic pulses [103]. Furthermore, the type of activation these pulses generate is highly dependent on the orientation of the coil when the stimulus is applied.

The orientation of the coil can modulate direction of the induced current, which cells are being depolarized, which location on the cell is being depolarized, and even the likelihood of inducing particular descending volleys. For example, monophasic pulses are more likely to be modulated by coil orientation than biphasic pulses, with a posterior-anterior orientation eliciting greater MEPs [103]. Thus, coil direction should be taken into consideration when designing experiments, especially when using monophasic pulses. In addition to physical factors, several physiological factors, such as tissue structure, menstrual cycles, corticospinal fluid, circadian rhythm, and hormone levels can all influence output from TMS.

Methodology

One of the most commonly employed uses for single pulse TMS is motor thresholding, which provides a general measure of motor cortex excitability as well as a baseline for stimulation intensity to be used in other paradigms. Stimulation intensities used for paired pulse and repetitive TMS (ppTMS and rTMS, respectively) often are applied at intensities of a given percentage of the subject's MT. Motor thresholding can be done either when the target muscle is at rest or in a contracted state. Active motor thresholds (aMT) are almost always lower than resting motor thresholds (rMT), because the excitability of corticospinal neurons is increased during muscle contraction [104].

To find the MT of a subject, the researcher initially maps out the motor cortex by sending single pulses of varying intensity along the expanse of the precentral gyrus and records MEPs from a given muscle with EMG. Once a hotspot (i.e. the region in the motor cortex which elicits the largest response from the muscle being recorded) is localized, the MT is determined by the smallest

stimulation intensity that elicits a motor response from the muscle. Different parameters can be selected for determining the MT, but protocols usually define a rMT as the minimal intensity that elicits an MEP greater than 50 microvolts (or 200 microvolts for active aMT) in at least five out of ten consecutive trials [94]. The rMT varies between muscles, which is dependent on the size of representative area within the cortex as well as size of the muscle. For example, rMT tends to be smaller in hand muscles compared to arm and leg muscles [105]. In addition to the MT, the latency and size of the MEPs themselves can provide information on the integrity of white matter tracts and thickness of myelin sheaths.

Single pulse TMS has many other applications in addition to motor thresholding. Increasing stimulation intensity and tracking the output allows the researcher to create an input/output (I/O) curve to assess the activity of neurons with varying levels of excitability, and it can also be informative of CST integrity [106]. Another use is the assessment of the cortical silent period (CSP). Briefly, after an MEP, the tar *N* -methyl- D -aspartate get muscle, as well as the homologous muscle on the ipsilateral side, exhibit a period of a few hundred milliseconds in which the EMG activity is suppressed. The CSP on the contralateral muscle is thought to be mediated initially by spinal hyperpolarization and then by cortical inhibitory mechanisms [107], while the CSP on the ipsilateral muscle is thought to be mediated by transcallosal inhibition [108]. Central motor conduction time (CMCT) can also be evaluated to determine the conduction time from the pyramidal neurons in the motor cortex to the motor neuron pool in the spinal cord. Typically, this is done by subtracting the latency of peripheral nerve stimulation from the latency of an MEP, and it is yet another viable mechanism for extracting information about the integrity of the CST.

Although one of the simpler TMS protocols, single pulse allows researchers to extract extensive amounts of information that can be applicable to the monitoring, early detection, and outcome of diseases and neurodegenerative disorders. For example, lesion severity has been evaluated by assessing changes in MT and I/O curves [106]. Furthermore, patients with Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) have been shown to have shortening of the

CSP [106,109], and patients with ALS also demonstrate increased rMT. Neurocognitive disorders also show aberrant patterns of cortical excitability; both reduced CSP and MT have been reported in Alzheimer's [110]. In regard to aging, maturational changes in I/O curves, CSP, and MT have all been noted, which allows single pulse TMS to serve as a monitoring tool for development with the potential of early identification of neurodevelopmental disorders.

Finally, single pulse TMS can be used to interrupt normal cognitive processes and assess the impact of this interference on task performance. One study, for example, found that providing strong visual cues regarding an object enhanced grasping ability of that particular object, but applying single pulse TMS to the intraparietal sulcus shortly after visual object presentation impaired motor planning and task performance [111]. Thus, it could be concluded from this study that the intraparietal sulcus is critical for integrating visual cues into proper motor planning, exemplifying the capability for TMS to uncover the neural correlates during particular tasks.

Paired pulse TMS refers to the application of two pulses in succinct temporal intervals which induce distinct excitatory and inhibitory effects within corticocortical circuits. The first pulse in the pair is termed the conditioning stimulus (CS), and the second pulse is termed the test stimulus (TS). Altering the inter-stimulus interval (ISI) between the CS and TS, as well as altering the intensity of the pulses, creates variability in the physiological processes and activation of distinct circuits. Thus, numerous different inhibitory and excitatory circuits can be studied within various ppTMS paradigms. While interhemispheric and interregional paired pulse paradigms are utilized in some studies, the most commonly employed paradigms are those in which both of the pulses are sent into the same cortical location.

When the ISI is between 1 - 7ms, and the CS is applied below motor threshold and the TS applied supra threshold, the conditioned TS is reduced in amplitude in comparison with an unconditioned TS. This is a mechanism termed short interval intracortical inhibition (SICI), and it is likely initially a result of axonal hyperpolarization. Pharmacological studies, however, have demonstrated that the latter portion of SICI is modulated by postsynaptic GABA type A receptors

(GABA-A) [112]; the administration of lorazepam, an agonist of GABA-A, increased SICI but did not have an effect on the amplitude of MEPs, indicating that SICI is a result of the activation of distinct circuits. In contrast to SICI, when the CS and TS are sent from approximately 8 – 30 ms apart, the conditioned TS is increased in amplitude in comparison to the unconditioned TS, a process termed intracortical facilitation. Though the physiological process behind this mechanism is less understood, ICF is thought to be the result of glutamatergic processes.

Long interval intracortical inhibition (LICI) is induced when the CS and TS are sent from 50 – 200 ms apart and are each suprathreshold. While LICI has the same effect as SICI, these two mechanisms are modulated by the activation of distinct circuits. The time-course of the metabotropic action of inhibitory post synaptic potentials elicited by GABA type B (GABA-B) receptors is consistent with the time-course of LICI [113], and pharmacological studies have further confirmed that the postsynaptic action of GABA-B receptors is responsible for LICI [114]. In addition to the commonly used paradigms described, numerous other paired pulse paradigms exist, including short interval intracortical facilitation, short interval afferent inhibition, and interhemispheric inhibition [96], and these paradigms have each been utilized to investigate excitatory and inhibitory circuits in various movement and psychiatric disorders.

In many movement disorders, such as PD, ALS, dystonia, myoclonus, chorea, and hemiparetic CP, SICI is reduced [115,96,116], and healthy older individuals show reduced SICI in comparison with younger healthy individuals, indicative of altered GABAergic mechanisms [117]. Alternatively, PD and ataxia show increases in LICI [115]. The CSP is also reduced in CP, PD, and ALS. While the exact functional role of these mechanisms are unknown, it is thought that these contribute to the facilitation of intended movements and inhibition of unwanted movements, and aberrancies of these mechanisms likely contributes to the motor impairments present across these populations. Potentially, the use of rTMS to normalize these mechanisms and restore balanced inhibitory and excitatory circuits could lead to improved sensorimotor functioning.

Repetitive TMS is a form of stimulation that results in facilitative or suppressive effects on cortical excitability that last beyond the stimulus train. The effects induced by rTMS are driven by neuroplastic change, and these can last up to several weeks, which can prove to be extremely useful as a therapeutic approach to treating an assortment of clinical populations. Generally, stimulating at lower frequencies (1Hz and below) continuously for an extended period of time will suppress cortical excitability, while intermittent, higher frequency stimulation (>5Hz) will induce increased excitability [118].

Numerous investigations have utilized rTMS in various ways to induce differential physiological effects. One of these paradigms involves inducing virtual lesions by applying high frequency TMS during a task to delineate neurological correlates of behavior. For example, it was shown that inducing a virtual lesion by applying 10Hz stimulation in bursts to the occipital cortices diminished the ability for blind individuals to read braille [119,120]. Alternatively, high frequency, intermittent rTMS applied offline can be used to increase cortical excitability. For instance, high frequency, intermittent rTMS applied over the DLPFC may be as effective as commercial drugs in the treatment of depression [121].

Repetitive TMS may also be used offline to induce suppressive effects on cortical excitability. Unlike high frequency rTMS, low frequency rTMS is typically applied continuously (i.e. not in trains), and the suppressive effects of low frequency rTMS are likely regulated by GABA and *N* -methyl- D -aspartate (NMDA). Finally, it is worthwhile to note that intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTMS) are becoming increasingly popular rTMS protocols for increasing and suppressing cortical excitability, respectively [122,123]. These protocols may have effects that last longer, and iTBS has even been shown to decrease spasticity in individuals with multiple sclerosis [124].

Cerebral Palsy

Classification and Prevalence of Cerebral Palsy

Cerebral palsy (CP) refers to a general class of movement disorders that result from an insult to the developing brain [125]. Recently, the definition of CP was updated to include sensory and perception deficits, cognitive impairments, and behavioral deficits, as functional disturbances in visual perception, somatosensation, auditory deficits, and cognition deficits are each common in individuals with CP [125]. Numerous studies documenting the prevalence of CP have consistently observed that approximately 2-4 out of 1,000 children are diagnosed with CP. Multiple large cohort studies of nearly 150,000 eight year old children found a prevalence of CP of 3.1 – 3.3 per 1,000 [126,127], and this number substantially increases for infants that are born very preterm [128]. Furthermore, there is a higher prevalence of CP among males than females and a higher prevalence of African-American children living with CP compared with non-hispanic white children [126,127].

Additionally, co-occurring autism and epilepsy are more common in CP than in the general population. Autism spectrum disorder (ASD) was found to have a prevalence of between 7 - 8% in individuals with CP, much higher than the prevalence in the general population, which is around 1%. Epilepsy was found as a comorbidity with CP at a prevalence of 35-40%, which is also much higher than in the general population [126,127]. The relationship between ASD, epilepsy and CP depends on functional severity of the CP; co-occurring ASD is more likely in CP when individuals have better mobility, whereas co-occurring epilepsy is more likely among individuals with more severe mobility issues [126,127].

CP is a very heterogeneous disorder with numerous types, levels of severity, presentation, and deficits. Four main subtypes of CP exist: spastic, ataxic, athetoid, and mixed. Spastic CP is defined primarily by abnormal muscle contraction and hypertonia, related to lesions in the corticospinal tract (CST) or motor cortex, which can impair the ability of neurons to transmit gamma aminobutyric acid (GABA), leading to hyperexcitability of the spinal cord and muscle

stiffness [129]. Often, spastic CP is related to white matter damage—periventricular leukomalacia (PVL) or intraventricular hemorrhage (IVH)— within the CNS, but it can also be a result of cortical or subcortical lesions. Spastic CP is by far the most common type of CP, with around 70% of all cases classified as such, and it can be further broken down by topographical presentation. Spastic hemiplegia refers to unilateral spasticity, diplegia refers to bilateral spasticity wherein the legs are more affected than arms, and spastic quadriplegia refers to upper and lower limbs both being significantly affected [129].

Ataxic CP, on the other hand, is found within only 5-10% of total cases of CP. It is most often associated with damage to the cerebellum, which causes difficulties with coordination as well as tremor, making tasks difficult to complete [129]. Athetoid, or dyskinetic, CP is associated with lesions within the basal ganglia and, in particular, the substantia nigra. Athetoid CP can be further subdivided into choreo-athetoid and dystonic-athetoid. The former is characterized by sudden involuntary movements, while the latter is characterized by long rotational muscular contractions of the torso or limbs.

Severity of functional deficits varies depending on type of CP. For example, spastic CP typically presents less severe deficits than athetoid CP. Numerous functional classification systems have been created to create more standardized language between providers and to further partition functional deficits. Gross motor functioning can be categorized based on the gross motor function classification system (GMFCS) [130]. This system divides gross motor dysfunction severity into five levels (I – V). Generally, GMFCS levels I and II refer to individuals that are able to ambulate independently, GMFCS level III pertains to individuals that require assistive devices (crutches, walkers, assistive orthotics) (Figure 1), and GMFCS levels IV and V refer to individuals that have little to no ambulatory ability and often require powered mobility devices.

The Manual Ability Classification System (MACS) is an upper extremity equivalent to the GMFCS for children and adolescents [131]. It is also scored from I – V, ranging from very little difficulty in handling objects (level I) to almost complete inability to handle any objects (level V).

Further classification systems include the communication function classification system (CFCS)[132], which is a five level classification system of everyday communication, as well as the Eating and Drinking Ability Classification System (EDACS)[133]. Each of these systems have high reliability and are complementary to the GMFCS and MACS.

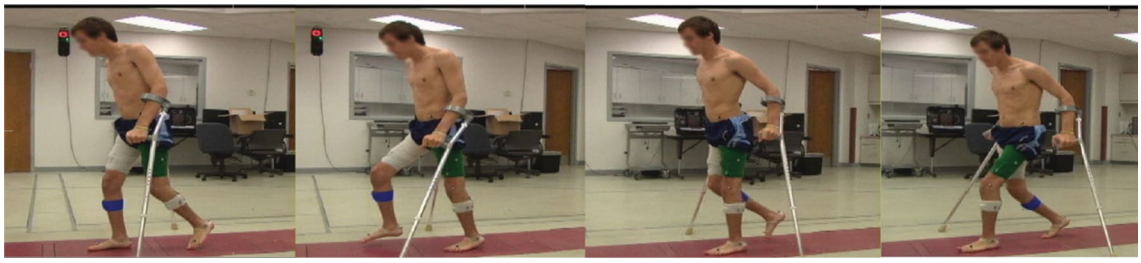

Figure 1: GMFCS Exemplary mobility for a youth with CP that has a GMFCS level of III. Individuals with a GMFCS I have notable mobility deficiencies that limit their ability to walk long distances, while children with GMFCS III have more severe deficiencies and need an assistive device to walk (e.g., forearm crutches, wheeled walker). Individuals with GMFCS level IV use power mobility.

Clinical Deficits in CP

Deficits in motor abilities are an inherent element of cerebral palsy. Increased muscle tone, hyperexcitable reflexes, spasticity, hypertonia, and joint contractures are all contributors of decreased motor abilities [134]. Additionally, disuse of muscles in CP leads to decreases in sarcomeres in parallel and in series, resulting in overall decreases in volume, physiological and anatomical cross sectional area, and length of muscles, especially in the lower limbs [134-136]. Decreases in maximal torque generated by dorsiflexors, and to an even greater extent, plantarflexors, is significantly reduced in children and adolescents with hemiplegic and diplegic CP [135,137], likely a result of decreased muscle volume. However, specific tension, which is the maximal torque able to be generated in relation to the anatomical cross sectional area of the muscle, is also reduced in the lower extremity muscles of children with CP [135]. Furthermore, neuromuscular activation, which is the ratio between the maximal output from a muscle during voluntary contraction and the maximal M-wave elicited through electrical stimulation, is also significantly lower in the gastrocnemius and the tibialis anterior [137]. Hence, muscle weakness is not only attributed to smaller volume of muscles

but also with decreased ability to fully activate the muscle or recruit larger motor neurons with higher thresholds. Finally, coactivation of agonist and antagonist muscles, as well as abnormal sequential contractions of muscles, are present in CP, illustrating hyperexcitability that leads to abnormal muscles other than prime movers being activated prematurely during sequential movements [135,138].

These problems in the musculoskeletal system have downstream effects in motor execution. Deficits in motor execution are apparent in individuals with all types and topographies of CP across a wide range of clinical tasks, such as box and blocks, assisting hand assessment (AHA), Jebsen Taylor Test of Hand Functioning (JBTTHF), and the Melbourne assessment of unilateral upper limb function (MUUL) [6,139,140]. However, numerous studies have documented that motor planning, which temporally precedes motor execution, is also impaired in CP and may contribute to motor execution problems. For example, in TD individuals, selecting a comfortable starting hand position for a task is sacrificed for selecting a position that may be uncomfortable but results in correct execution. This is referred to as end posture comfort effect [141]. Individuals with CP, however, more often select a comfortable hand starting position even if it results in task failure. This has been documented in numerous studies wherein participants with CP were unable to effectively rotate a six-sided knob 180 degrees due to improper initial grip positioning [142,143].

Additionally, individuals with hemiplegic CP have been shown to have deficits in anticipatory force scaling during a variety of tasks for different sized objects, although they are able to accommodate for this deficit with practice, or through the use of the less affected hand in individuals with hemiplegia [144-146]. Additionally, pinch grip tasks tend to be performed more sequentially in children with CP, with longer phases comprising the movement [144,145]. Interestingly, numerous studies have shown that individuals with left hemispheric damage (right hemiplegia) may be more impaired with motor planning than individuals with left hemiplegia [147,142,148]. However, this is a controversial topic, as Kirkpatrick et al., 2013 showed no differences in motor planning based on lesion side, and this study used a much larger sample size [149].

Deficits in motor planning have often been attributed to deficits in motor imagery, which allows for the development of an internal representation of how an action should be performed. One innovative method employed for assessing motor imagery is by evaluating reaction time differences between imagining medial and lateral rotations of the hand. In the study mentioned above by Craje et al, 2010, pictures of hands at different angles were presented to individuals with CP, and they were instructed to decide whether it was the left or right hand by either mentally rotating it medially or laterally. As medial rotations are biomechanically easier to perform than lateral rotations, shorter reaction times presumably would indicate that motor imagery is being utilized. If there are no reaction time differences, it is presumed that the participant used an alternative, such as visual imagery—which would indicate imagining the hand being rotated from a third person perspective as opposed to first person—to complete the task [150]. Individuals with CP failed to display differences in reaction times between these conditions, suggesting that a lack of utilizing motor imagery exists within the population [143]. Subsequently, this could impact the ability to form an internal model and contribute to the deficits in motor planning.

Numerous studies have also documented clinical somatosensory deficits within individuals with CP, as well as how these may adversely impact motor functioning. Many individuals with CP exhibit sensory hyper responsivity, in which aberrant physical, and sometimes emotional, reactions occur in response to stimuli that are not adverse, as well as hypersensitivity, which consists of the increased peripheral nervous system response to external stimuli [2]. The ability to discriminate between two tactile stimuli that are close to each other, typically measured via the two point discrimination test, as well as the ability to discriminate between objects without vision (stereognosis) are each impaired in individuals with CP [139,4]. Additional deficits in texture discrimination have also been documented in individuals with spastic hemiplegic, diplegic, and dystonic CP [4], and adolescents and adults with CP show decreased tactile sensitivity [151].

Impairments in these various somatosensory modalities contribute to aberrant motor functioning. Auld et al., 2012 assessed how tactile registration, which is the initial recognition of a

stimulus, tactile perception, which is the awareness of what the stimulus is and where it is located, and tactile textural discrimination are related to unimanual and bimanual motor functioning [6]. Each of the clinical tests used for tactile registration and spatial tactile perception were significant predictors of performance on the AHA, MUUL, and JTTHF [6]. However, tactile discrimination was not a significant predictor of motor functioning. Nevertheless, this illustrates the idea that aberrant somatosensory registration and perception adversely affect motor functioning.

Furthermore, proprioceptive abilities are hindered in CP. Proprioception is a necessary sensation in order to appropriately respond to the environment during locomotion, and this can be tested by assessing whether an individual can return a limb to a designated position without vision. Numerous studies have demonstrated that both children and adults with CP are impaired in their ability to accurately perceive the position of both upper and lower extremities [152-154] in addition to having significant balance deficits that contribute to abnormal gait and motor dysfunction [154]. Interestingly, individuals with right hemispheric damage have decreased proprioceptive abilities in comparison to those with left hemispheric damage [152]. Utilizing proprioceptive feedback from one arm to direct the limb position of the opposite arm requires interhemispheric information transfer and, thus, is more difficult than when using information from the same arm to direct limb position. When individuals with hemiplegic CP use their unaffected arm as a reference for positioning of the more affected arm, they are able to maintain their proprioceptive abilities. However, when the affected arm is used a reference, individuals are significantly less capable of perceiving their limb position [152].

While proprioception is a likely contributor of deficits in locomotion and motor impairments, it has been shown to improve following therapeutic intervention as well as motor learning, even when proprioception is not directly being targeted by the intervention [152,155].

3.3 Structural Neuroimaging in CP

The use of MRI has been commonly employed to assess how insults to the developing brain, which can include inflammation and the release of cytokines, oxidative stress, infection, and hypoxic-ischemia, can result in various abnormalities in brain structure and, subsequently, brain functioning and functional deficits [156-158]. Approximately 85 – 90% of individuals with CP have abnormal findings within their MRI, and this is especially true for those whom have spastic CP. Individuals with ataxic CP, however, are less likely to present abnormal MRI findings [157]. Remarkably, around 10% of individuals with CP have completely normal MRIs with no aberrant findings, yet some individuals with normal MRIs have severe functional deficits, indicating that there is a potential genetic factor in this subpopulation [159]. Thus, the link between structure and function within the CNS is not completely clear.

Among the various abnormal findings from MRIs in individuals with CP, white matter damage of immaturity is by far the most common, and it is especially prevalent in individuals born very prematurely [157]. Following this, basal ganglia lesions, cortical/subcortical lesions, malformations, infarcts, and miscellaneous lesions are all among the abnormal structural findings on MRIs in CP [157].

Timing in which an insult to the brain occurs has a large impact on the type of damage that follows and the severity of functional impairments. The first and second trimesters of development, when neural cells are proliferating and migrating, is a critical period for development of gross brain structure. An insult during this time period often results in malformations (i.e. lissencephaly, polymicrogyria, schizencephaly, cortical dysplasia, etc.) [159]. During the early part of the third trimester, dendritic growth, synaptogenesis, and myelination occurs, and disruption of this process will primarily result in white matter damage, usually resulting in spastic CP [157]. Insults occurring during the latter part of the third trimester typically result in gray matter lesions, either within the cortex or subcortical areas, such as the basal ganglia, which usually results in athetoid CP.

Insult timing can also have an effect on the severity of functional symptoms of CP. Typically, individuals with insults occurring during the perinatal or neonatal period have more severe impairments than individuals with insults that occur during the prenatal period [158]. This can be exemplified by the generalization that, typically, those with athetoid CP (from an insult during the later third trimester) have more severe functional deficits in comparison with those that have spastic CP (an insult that likely occurred during the early part of the third trimester).

Finally, timing of insult and the subsequent type of damage that occurs can strongly influence the amount of comorbidities present in individuals with CP. While basal ganglia lesions often result in athetoid CP and severe motor dysfunction, these lesions are also associated with less pronounced cognitive deficits [160]. Brain maldevelopment, on the contrary, is the most common cause of CP associated with co-occurring cognitive disorder [158], and cortical and subcortical lesions are the most common damage associated with individuals with five or more co-occurring impairments (cognitive disorder, hearing and visual impairments, etc…)[158]. Periventricular white matter damage typically results in the fewest co-occurring impairments in children with CP, although severe PVL can result in severe spastic CP, cerebral visual impairment [161], and significant enlargement of their ventricles [162].

In summary, various types of insults to the developing brain can occur and, depending on the timing of these insults, specific types of brain damage will occur. Different types of brain damage then result in different types of CP and distinct functional impairments and severities, as well as varying types of co-occurring impairments.

Diffusion tensor imaging (DTI) is an extension of conventional MRI which measures the diffusion of water molecules to assess the integrity, structure, and damage of axons and white matter tracts. White matter tracts that are commonly studied using DTI include the CST, thalamocortical and corticothalamic tracts, spinothalamic tract, and corticocortical tracts. Among the most common outcome measures of DTI are fractional anisotropy (FA), mean diffusivity (MD),

axial diffusivity (AD), and radial diffusivity (RD), and each of these provides unique information pertaining to the structure of white matter and axons.

In brevity, FA describes the overall integrity of white matter tracts, wherein lower values indicate more loss of uniformity in axonal organization [163]. AD refers more directly to axonal loss, wherein higher values are indicative of greater axonal damage [164,165]. MD is reflective of both the intracellular and extracellular diffusion of water, wherein higher values indicate increased extracellular water diffusion. Higher values of MD are thought to be a result of gliosis that occurs in response to neuronal damage [163]. Finally, RD reflects the diffusion of water molecules perpendicular to axons, and higher values are thought to indicate greater demyelination [164,165]. These measures all make DTI a viable tool for detecting abnormal structure in the brain that may not be seen with conventional MRI. DTI provides a mechanism for further interrogating structural damage in individuals with CP even when they present normal findings on conventional MRI.

Son, et al., 2007 effectively demonstrated that white matter damage can be seen using DTI on individuals with CP whom exhibited completely normal conventional MRIs [166]. Among the numerous studies that have used DTI to examine white matter abnormalities in individuals with CP, it has been consistently found that FA values tend to be reduced and MD values tend to be increased within the CST and ThC [51,167,168]. The reduced FA values are indicative of an overall loss of structural organization in white matter tracts, and it is likely that the increased MD values are a result of gliosis that occurs in response to neuronal damage. The aberrant FA and MD values are also related to overall mobility in CP; MD values in motor tracts are positively correlated with GMFCS level, indicating that individuals with CP with higher extracellular diffusion tend to have more severe impairments, and FA values in both sensory and motor tracts are negatively associated with GMFCS levels, indicating that greater loss of uniformity in white matter structure tends to occur in individuals with more severe mobility impairment [169].

Several studies have further illustrated that both CST and cTh tract integrity is associated with manual functioning in individuals with CP [170,171], and ThC white matter injury is associated

with sensory and motor impairments [168]. The fact that the thalamocortical projections, which are typically involved in relaying sensory information to the brain, are related to motor functioning, exemplifies the notion that motor system deficits may at least partially be attributed to deficits in somatosensation.

It is important to note that white matter tracts are not unmalleable; following botulinum injections and physical therapy, FA values within the CST show increases in those with CP [167]. This is critical information, as it indicates that therapeutic interventions can directly alter neuronal pathways and potentially restore function to pathways that exhibit aberrant structure.

In addition to measuring the integrity and uniformity of white matter tracts, the amount of asymmetry in the size of the CST is another methodological approach useful in relating brain structure to sensorimotor function. Asymmetry can either be measured using DTI or through the cross sectional area of the cerebral peduncles, and increased asymmetry in the CST is associated with decreased stereognosis and both bimanual and unimanual hand function in individuals with unilateral CP [172,173,140].

Asymmetry has also been proposed to potentially have an effect on the way an individual will respond to therapeutic intervention. A considerable amount of variability exists within the therapeutic outcomes that are seen within CP, with some individuals responding very well and others being clear non-responders. There have been many attempts in determining the bases for this discrepancy, but attempts thus far have been unsuccessful. Neither integrity nor asymmetry of the corticospinal tracts have been consistently shown to predict improvements in functioning following therapy [140,170].

It has also been predicted that the projection pattern of an individual's motor system has an impact on outcomes seen following constraint induced movement therapy (CIMT), which is an effective, commonly used intervention aimed to enhance functionality of an affected limb by constraining the use of the unaffected or less affected limb [174]. One study used DTI to show that select cohorts of individuals with CP whom have ipsilateral projection patterns do not benefit as

greatly from constraint induced movement therapy (CIMT) as those with contralateral projections [175,176], as change in amplitude of MEPs elicited using TMS were dependent on projection pattern. However, other groups have found that CIMT is beneficial to functional outcomes of CIMT no matter the projection type an individual with CP exhibits [177]. Similarly, improvement in functioning after bimanual therapy has been shown to be independent of CST connectivity patterns [178]. Thus, whether projection type does influence therapeutic outcomes remains controversial, and more work is required to determine additional factors that predict therapeutic outcomes.

As visual, cognitive, auditory, and numerous other impairments also exist within CP, it is likely that responsiveness to therapy is dependent on an assortment of factors. This is a research area that requires further investigation in order for more individualized therapies to be produced to benefit all individuals within such a multifaceted disorder.

Functional Neuroimaging in CP

Numerous studies have taken advantage of technological advancements in brain imaging to study the neurological nexus of the various impairments present in CP. Magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) have been the most commonly employed methodologies, but some studies have also utilized positron emission tomography (PET) and functional near-infrared spectroscopy (fNIRS). Importantly, the published literature on the oscillatory dynamics surrounding sensorimotor functioning have primarily been investigated in children and adolescents with CP, leaving a large knowledge gap pertaining to this activity in adult populations with CP.

Numerous studies have investigated the motor system in CP using MEG, and it has been found that oscillatory dynamics during movement planning and execution in children and adolescents with CP are altered. Children with CP exhibit increased strength (i.e. a greater reduction in power) of both the beta and alpha ERD in motor regions such as the primary motor cortex (M1), the premotor cortex (PMC), and the SMA during a leg target matching task [41,40]. Interestingly,

during the same task, the beta and alpha ERD are weaker (less reduction in power) in visual processing areas compared with TD individuals. The stronger power of alpha and beta oscillations in the motor areas and the weaker power in visual areas are each associated with greater motor performance errors and slower reaction times, indicating that these altered oscillatory dynamics lead to difficulties in motor planning and execution as well as visuomotor integration [40]. Furthermore, the gamma ERS is weaker in individuals with CP, which may be a result of the aberrant beta ERD and contribute to deficits in motor execution [41].

As described previously, clinical impairments in proprioception and somatosensation are also highly prevalent in CP [1,52,6,2], and it has been found that these individuals exhibit altered brain activity within the postcentral gyrus that may correspond to these impairments. It has been illustrated that individuals with spastic CP have decreased magnitude of evoked responses within the somatosensory cortices in comparison to their typically developing (TD) peers [49,50,43,7,51]. In another study, four participants with CP that underwent 10 weeks of body weight supported treadmill training exhibited decreased somatosensory evoked responses after training, potentially due to the foot region of the somatosensory cortex becoming more finely tuned. Importantly, this highlights the idea that the sensorimotor cortices in individuals with CP is capable of undergoing neuroplastic change.

In addition to measuring the evoked responses within the somatosensory cortices, follow up studies have looked into the oscillatory dynamics in the somatosensory cortex. In response to tactile stimulation of the foot, individuals with CP show a desynchronization within the alpha/theta frequency range while their TD peers show a synchronization [44]. Furthermore, the amount of synchronization elicited was directly related to gait velocity and ankle plantarflexion force and negatively associated with motor errors [44]. In response to tactile stimulation of the hand, children with CP show similar alpha/theta synchronization compared with TD individuals. However, within the beta range, TD individuals show a desynchronization of neural activity whereas children with CP show a synchronization [46]. Finally, children with CP tend to gate somatosensory information

much more than their TD peers, potentially occurring as compensation for extra noise that exists within the damaged thalamocortical tracts [48].

When presented with somatosensory stimuli, several brain regions within the motor system are activated. This activity may either reflect direct input from afferent tracts that terminate in motor areas, and/or input directly from the somatosensory cortex. Functional MRI has shown that activity in these motor regions is reduced during tactile discrimination tasks in CP [179]. Importantly, this could indicate that the somatosensory cortices are not adequately sending information to motor regions. This in turn could impair sensorimotor integration and contribute to movement planning and execution difficulties.

In addition to aberrant processing of afferent information, the cortical areas representing the digits in individuals with CP are closer in proximity than in TD individuals, and closer proximity of digit representation in the cortex is related to more severe sensory deficits [52,180]. Impaired hand functioning throughout development and a lack of environmental exploration likely contributes to this phenomenon, which again reiterates the dependence that the somatosensory and motor systems have with each other [180].

TMS in CP

TMS provides a methodological approach to assess CST projection type, inhibitory/excitatory mechanisms, and therapeutic intervention in CP that complement the findings from neuroimaging studies. In individuals with CP, a series of latent MEPs are sometimes elicited by TMS which are of longer latency than typical MEPs, ranging from 35 – 225ms [181]. As this increased latency reaches up to ten fold the latency of normal MEPs, it is highly unlikely that this is simply due to decreased conduction velocity. Rather, it has been suggested that increased spinal cord excitability could account for these long-latency responses.

Vry et al, 2008 used TMS to examine the CSP and CMCT in children with spastic diplegic CP [182]. The CMCTs were almost identical between the patient and control group, whereas the MEPs

were lower and the CSP was shortened in the individuals with CP. Motor evoked potentials have also been shown to be decreased in adults with CP [183]. These results indicate that structural damage in CP likely results in an overall loss of axonal projections rather than demyelination along the entire corticospinal tract, as one would expect conduction times to be slowed if the latter were the case. The decreased MEPs are likely a result of damaged excitatory pathways, whereas the decreased CSP indicates inhibitory and excitatory dysregulation in CP. This reduced inhibition could either be due to an overall loss of GABAergic inhibitory neurons in the cortex or less activity within these neurons due to lack of facilitatory drive from damaged thalamocortical tracts. This decrease in inhibitory input is likely the primary contributor to the increased excitability in the spinal cord.

In line with these findings, rTMS has been employed to target the lack of inhibitory drive along the CST. Inhibitory rTMS intervention over the intact hemisphere in hemiplegic CP showed increased MEPs, CSPs, and sensorimotor performance on clinical tests after a 6 week period. Additionally, Hoffman reflex (H-reflex) H/M wave ratio was significantly reduced[184]. It is likely that, by reducing excitability within the intact hemisphere, transcallosal inhibition was reduced which enabled increased excitability within the damaged hemisphere. Additionally, high frequency excitatory rTMS intervention in individuals with spastic diplegic CP has been shown to effectively reduce spasticity and improve motor function [185-187]. The notion is that increasing excitability in the motor cortex increases GABAergic inhibition along the CST, and this results in reduced spinal cord excitability and in turn reduced spasticity.

Thus, TMS has provided evidence that certain parameters of inhibitory mechanisms within CP are aberrant and has provided an opportunity to alter these through the use of rTMS. However, it is unknown how these parameters are related to outcome measures from functional neuroimaging (e.g. oscillatory activity), which could provide more precise information that could guide decisions on parameters to use during rTMS and other treatment interventions for individuals with CP.

Spinal Cord Excitability in CP

In support of the TMS findings that have suggested that decreasing spinal cord excitability improves motor functioning and spasticity, spinal cord excitability has been assessed directly in CP using the Hoffmann-reflex (H-reflex). The H-reflex is physiologically similar to the stretch reflex, wherein changes in muscle spindle length activate sensory Ia neurons, which synapse onto alpha motor neurons at the spinal cord, in turn causing a muscle contraction.

Eliciting the H-reflex involves direct stimulation of the nerve, thus bypassing the muscle spindle activity [188]. Typically, H-reflex recruitment curves are obtained by gradually increasing electrical stimulation intensity of a target nerve from low to high and measuring the EMG response from a given muscle. As sensory neurons have lower activation thresholds than motor neurons, lower intensities of stimulation initially activate only sensory neurons. Sensory Ia fibers transmit the stimulation afferently toward the spinal cord, where monosynaptic connections with the alpha motor neuron pool occur and elicit an "H-wave" within the muscle. As the stimulation intensity rises, more sensory neurons are activated and the H-wave gets larger. Eventually, the higher threshold alpha motor neurons get recruited and elicit an "M-wave" temporally preceding the H-wave, as the M-wave does not transmit through the spinal cord but inputs directly to the muscle. As stimulation intensity rises even further, motor neurons eventually start sending signals antidromically which interferes with the H-wave and causes it to reduce in amplitude, while subsequently the M-wave is getting larger due to more motor neurons being recruited. The antidromic activation of motor neurons also excites the motor neuron pool at the spinal cord and sends a third wave back toward the muscle; this is referred to as the F-wave which temporally comes in-between the M-wave and H-wave. Eventually, the H-wave disappears as the antidromic signals completely interfere with it, and the M-wave will reach a maximum threshold once all of the motor neurons within the motor neuron pool are excited. The H/M wave ratio can then be calculated as the ratio between the maximum H-wave and the maximum M-wave. This is the ratio

of the number of motor neurons activated by sensory stimulation compared with the total number of motor neurons, and thus a higher ratio indicates increased spinal cord motor neuron pool excitability.

H-reflexes exhibit a tonic depression in amplitude during gait from ages 6 -13 years during normal development, but the amplitude does not change during normal standing throughout development [189]. Additionally, a rhythmic modulation of H-reflex amplitude occurs during gait, in which the amplitude is higher during the stance phase compared with the swing phase [190] Functionally, this may be in order to reduce soleus activation, which is largely activated through reflexes [191]. In patients with spinal cord injury, this rhythmic modulation during gait is aberrant, but in patients with CP, rhythmic modulation remains intact. Contrastingly, the tonic depression of H-reflex throughout development is impaired in patients with CP, alongside an overall increased amplitude of H-reflex during gait and at rest [192,193]. This indicates that tonic depression likely occurs within the cortex, whereas the rhythmic modulation during gait likely is controlled by spinal mechanisms. Both treadmill training and rTMS have been shown to be effective methods for reducing the H-reflex amplitude in the soleus and improving gait parameters in CP [192,194,184].

Thus, H-reflexes are normally suppressed during gait in comparison with normal standing, but this is impaired in CP. The absence of tonic depression that occurs in CP is likely due to aberrant development and drive from the motor cortex, which results in maldevelopment or malfunction of cortical and spinal inhibitory interneurons [192]. It was found that both presynaptic Ia inhibition and post-activation depression are decreased in adults with CP, whereas propriospinally-mediated Group II facilitation is increased [195,193]. Overall, these results indicate that the spinal cord exhibits increased excitability and decreased inhibition in individuals with CP, which may lead to the co-contractions of agonist and antagonistic muscles that contribute to abnormal gait patterns.

GABA expression in CP

Aberrant inhibitory processes in CP, such as the decreased length of the CSP and SICI, likely stem from a reduction in GABAergic cortical activity [182,185]. However, increased GABA-A receptor binding potential has been demonstrated in the precentral cortices in individuals with spastic and hemiplegic CP [196], and this was related to decreased functional connectivity in ThC and corticocortical tracts as well as reduced FA [196,197]. Thus, it seems counterintuitive that there is decreased GABAergic cortical inhibition but increased GABAergic receptor expression in CP. However, as mentioned above, the GABAergic interneurons may either be dysfunctional or not receive input from the damaged ThC tracts [182]. In this case, increased receptor expression would not lead to an increase in GABAergic circuitry activity. In fact, the increased receptor expression could even be a compensatory mechanism for the lack of input from the thalamocortical tracts, supported by the fact that decreased functional connectivity in between the thalamus and precentral cortices is associated with increased receptor expression. Nevertheless, it is possible that increased inhibition in the cortex is present during development of the CST in individuals with CP but reduced later on.

In support of this notion, it has been shown that increased GABAergic activity during development subsequently leads to a vast array of adverse effects on the CNS. Increased inhibition may result in abnormal migration of neurons during development, potentially affecting the functional linking of the motor and sensory cortices [198,199]. Additionally, oligodendrocytes are a prime target for GABAergic interneurons, and, as these are responsible for myelination within the CNS, increased inhibition of these cells may lead to white matter damage and CST development [200]. Increased inhibition has also been shown to decrease the size of receptive fields, potentially altering the ability of the motor cortex to receive proper input from sensory cortices [201]. Increased GABAergic activity may thus decrease the ability of the motor cortex to undergo activity-dependent plasticity by inhibiting sensory feedback and motor cortex reorganization [202].

Overall, increased GABAergic receptor expression and binding potential leads to aberrant inhibitory processes within the central nervous system, and this likely results in alterations in connectivity, myelination patterns, sensorimotor integration and decreased plasticity within the CNS during development. Thus, the increased GABAergic receptor expression may have led to increased inhibition during development, but lack of input from ThC tracts or receptor dysfunction could explain the lack of cortical inhibition in individuals with CP later in life.

Neuroplasticity and Reorganization in CP

During typical development, infants have both ipsilateral and contralateral projections from their motor cortices to the periphery. Throughout the course of normal development, the ipsilateral projections get pruned, leaving contralateral projections from the motor cortices that control the opposite side of the body [203]. TMS has shown that cortical excitability and amplitude of MEPs each significantly decrease in the ipsilateral hemisphere from 3 to 18 months after birth, reflective of this pruning [38]. However, when unilateral damage occurs to the primary motor cortex, the neurons innervating the affected side of the body seek new connections, and this often results in plastic change that enables the motor cortex in the ipsilateral hemisphere to take over control of the affected side [54,53]. This ipsilateral reorganization most likely occurs as a re-crossing of fibers after the pyramidal decussation [54].

It is thought that one of the mechanisms by which the ipsilateral reorganization occurs is through the release of denervation factors at the spinal cord upon unilateral damage, which in turn results in the sprouting of axon collaterals from the unaffected hemisphere that cross back over to the paretic side after the pyramidal decussation [54]. Alternatively, the ipsilateral projections present during development may be maintained in response to significant unilateral damage. Thus, the motor cortex seems to inherently have a viable compensatory mechanism for reorganizing itself in response to unilateral damage. This reorganization, however, does not occur in all individuals that

have a unilateral brain lesion, as it is much more likely to occur in individuals with larger lesions and lesions which occur earlier in development [54,53].

In individuals with hemiplegic CP who have ipsilateral motor control over their affected side, sensory and motor functioning tends to be poorer [53,204,205], especially when the lesion occurs later in development. Those who have earlier lesions that result in ipsilateral reorganization, however, are more likely to have preserved hand functioning, because it allows for more time for the connections with subcortical networks to be established [205]. Potentially, applying a paradigm such as rTMS could increase the activity within the affected hemisphere and preserve the contralateral projections, but this probably would need to be done early in development, before the ipsilateral projections are established (i.e. before the first two years of life) [205].

Using TMS, Staudt et al., 2002, found that individuals with small lesions only show MEPs elicited from the affected hand when the affected hemisphere is stimulated (no ipsilateral reorganization). For those with large lesions, MEPs in the affected hand can only be elicited upon stimulation of the unaffected hemisphere (complete ipsilateral reorganization), and for those with intermediate lesions, MEPs are elicited in the affected hand upon stimulation of both hemispheres (partial reorganization). The same pattern follows for activated regions shown using fMRI during a motor task [54]. Additionally, smaller axons within contralateral tracts from the damaged hemisphere are associated with larger axonal diameter in the ipsilateral projections from the undamaged hemisphere [205]. Thus, there seems to be a grating of ipsilateral (contralesional) reorganization of the motor cortex resulting from the extent of the initial lesion. This could also help to explain why individuals with ipsilateral (contralesional) reorganization of the motor system tend to have poorer motor functioning, as they may have greater sizes of lesion to begin with [204].

The somatosensory system, in contrast to the motor system, has only contralateral connections during development, and numerous studies using TMS, MEG, and fMRI have determined that ipsilateral reorganization does not occur in the somatosensory cortices, even in the event of unilateral damage [46,206,207]. While ipsilateral activation of the somatosensory cortices does

occur in response to peripheral stimulation, these responses are of longer latency than from contralateral stimulation, indicating that they are likely coming from transcallosal activity rather than from ipsilateral reorganization of the somatosensory cortices [204]. In fact, the ThC projections to the somatosensory cortices are able to curve around the lesioned area and still terminate in the contralateral hemisphere [206]. When the motor system reorganizes, but the somatosensory system does not, this leads to a hemispheric disassociation between the somatosensory and motor representation of the affected side of the body. When this disassociation between somatosensory and motor representation occur, sensory and motor abilities are not associated with each other as they are when both modalities are represented in the same hemisphere [204].

Animal models have also been utilized to further study the influence that activity dependent reorganization of the CST has on motor functioning and the connection with spinal cord circuits. By inactivating the motor cortex of kittens unilaterally through administration of musimol, a GABAergic medication, between postnatal weeks 5 and 7, ipsilateral connections are maintained and CST projections terminate in more dorsal areas of the spinal cord, similar to what happens in unilateral CP [55]. However, by inactivating the other motor cortex later in development, between weeks 7 and 11, ipsilateral projections become pruned, contralateral projections become less dorsalized, and hand functioning in the affected hand improves. Importantly, this study showed that by inactivating the non-affected motor cortex, this allows for restoration of projections from the affected cortex, corroborating the idea that activity-dependent plasticity in the CST is still viable later in development, and the developed projection patterns are not completely non-malleable [55]. Another study by the same group demonstrated that CIMT can restore projection patterns in a kitten model, but it is most affective when combined with early reach training [56]. Additionally, the development of cholinergic interneurons is also dependent on an active CST, and reductions in the total number of these cells can result in aberrant motor functioning [208].

Thus, activity dependent plasticity plays a crucial role in the development of the sensorimotor system. Yet, these tracts remain malleable within the first few years of life, which

may provide a window of opportunity to restore normal organization, and rTMS paradigms aimed at increasing cortical excitability described above may be more effective early in development.

International Classification of Functioning and CP Treatment Outcomes

The International Classification of Functioning (ICF) is a model for the classification of all aspects of health, functioning, an disability. Unlike its predecessor, the International Classification of Impairments, Disabilities, and Handicaps, which focused on the disease state of an individual, the ICF places a more integrative role and incorporates a broader perspective of health. Its aims are to create a universal classification and coding system pertaining to the multifaceted aspects of functioning and health of an individual as well as the change in health status over time. It also aims to identify the factors that contribute as either facilitators or barriers of health and function, while using neutral terms in order to avoid marginalization. Perhaps most importantly, the ICF not only assesses the body structure and function of an individual in a disease state; rather, it incorporates environmental and personal factors, as well as activity ability and participation, in order to get the broader scope of overall health status. Thus, the ICF has immense applications, and applying it to a multifaceted disorder such as CP provides a unique and valuable mechanism for clinical decision making.

When an individual is diagnosed with CP, there is a spectrum of functional deficits, comorbidities, and trajectories of the disorder that could occur, making the treatment of CP inherently complex. Identifying type, etiology, presentation, and degree of functional impairment can help in this regard, but identifying the environmental factors and personal values that contribute to their health status and trajectory will further assist in the prevention of secondary mental or physical impairments as well as their overall wellbeing [209]. For example, an individual with CP may have little motivation for enduring physical therapy, unless it is focused on improving an aspect of functioning that is of personal value. Alternatively, the individual may have only mild

functional impairment, but their current home environment is unfit to handle an individual with a disability. Each of these issues would be considered barriers to the patient's overall health status.

The amount of personal values and environmental factors that inevitably affect an individual with CP is extensive, and while not every factor is able to be directly addressed, the overall goal is to minimize the discrepancy between an individual's capacity (i.e. their potential) and their performance (i.e. their actual level of functioning). This includes, among other things, addressing environmental factors that may be hindering their performance and enlarging this discrepancy, or addressing personal factors that may be modulating their motivation. Furthermore, by addressing these factors, treatment strategies can be individualized and not necessarily as focused on "normalizing" the person but rather provide the tools to enable them to be successful in the areas of life that are important to them. In an optimal situation, interventions that induce improvement in one domain would have beneficial effects in other domains of health.

In line with the ICF, a recent systematic review of systematic reviews evaluated the efficacy of a number of therapies aimed at the body structure and function level, the activity and participation level, and the environment level, as well as the lateral effects the interventions may have on the non-targeted domains [210]. The overall effort of the review was to help guide decision making for clinicians and provide a common reference for efficacy of interventions. The authors used the GRADE system, as well as the evidence alert traffic light system, to gage the efficacy of the interventions, based not only on how much evidence existed for that intervention, but also on the quality of the evidence and the impact the intervention may have on the individual. The traffic light system provides a simplified recommendation on whether to do the intervention (green light), probably do it (yellow light), or not do it (red light). The GRADE system provides a measure of the strength of recommendation based on an evaluation of the amount and the quality of evidence for that particular intervention. Thus, a green light therapy can either imply that the intervention has sufficient evidence of beneficial effects in CP, or that it has limited evidence but is highly

effective in other populations and may be critical to avoid serious injury or death in CP (i.e. anticonvulsants to prevent seizures).

Out of 131 interventions, 16% were considered to be green light therapies. Among these included bimanual intensive therapy and CIMT for improving motor functioning and self-care, selective dorsal rhizotomy for improving gait kinematics and reducing spasticity, anticonvulsants for treating seizures, botulinum injections for reducing spasticity, and casting for improving ankle range of motion. Concerningly, all of the green light interventions were aimed at either the body structure and function or activities levels, whereas none of the interventions that aimed at improving participation or environment were completely successful. Additionally, none of the interventions determined to be a green light therapy for body structure and function had downstream effects on activities, and no green light activities based interventions had any beneficial effects on body structure and function. Thus, not only are interventions aimed at participation and environment severely lacking, but there is a paucity of interventions that have carryover effects to different levels of the ICF.

Importantly, Thomason et al., 2014 wrote a response to the above described review of interventions that presented numerous methodological concerns within the paper [211]. For example, pharmaceutical companies have the money to put forward numerous studies for botulinum injections, so there is an inherent bias toward the use of that particular intervention, and numerous other biases were noted that were not mentioned in the review. Additionally, the authors on the systematic review were not experts on all of the topics within every paper that was reviewed, so it is difficult and potentially unreliable for them to make appropriate recommendations for such a broad range of interventions. However, at the very least, their systematic review shed light on the fact that successful participation and environment based interventions are extremely lacking and, as these are critical domains to the overall health of an individual with CP, they need to be integrated into therapeutic interventions.

Conclusions

Cerebral Palsy is a complex, multifaceted disorder, and thus a multimodal approach to the study of the disorder is necessary. The current review has covered a wide range of the various neurophysiological and musculoskeletal impairments that exist across the population, measured using a variety of methodologies at various levels of the nervous and musculoskeletal system. Additionally, a review of MEG and TMS was provided to bring further understanding to how these methods can be employed in the study of CP. Numerous areas for future research were highlighted in order to continue to gain a comprehensive understanding of CP.

The relationship between the functional and structural abnormalities in CP remains elusive. Structural abnormalities that are seen within the nervous system of individuals with CP are not always consistent with functional deficits. On a gross level, cortical and subcortical lesions, white matter damage, malformations, infarcts, and increased ventricle size are among the most common abnormal findings on conventional MRI, although a significant percentage of individuals, across various levels of functional severity, have completely normal MRI findings [159,156,157]. A few studies have utilized DTI to provide evidence that abnormalities in both ascending and descending tracts are detectable in individuals with conventional MRIs [168,212,166], but the relationship between structure and function in CP requires further investigation.

In addition to structural abnormalities, functional imaging modalities have revealed aberrant sensorimotor oscillatory surrounding motor planning and execution as well as processing of afferent somatosensory information, and this altered activity is related to the numerous clinical sensorimotor deficits that exist within the population [44,41,48,40]. Furthermore, TMS has revealed that GABAergic mechanisms are hindered within the motor cortex, which leads to decreased inhibition along the CST and subsequently increased hyper excitability of the spinal cord [182,116]. Hyper excitability successively contributes to heightened reflexes, abnormal contractions of muscles, and gait aberrancies [192,138].

Thus, anomalous oscillatory activity and GABAergic mechanisms have downstream effects on the functional deficits seen in CP. However, it is unknown whether oscillatory activity and the altered excitatory/inhibitory balance are related to one another. Potentially, the altered excitatory and inhibitory mechanisms drive the altered oscillatory activity, or vice versa. For example, is the weaker beta ERD that is present in individuals with CP related to more hindered inhibitory mechanisms? Furthermore, there has not been a comprehensive assessment of how inhibitory/excitatory balance of the cortex and the spinal cord and the neural oscillatory activity interact to contribute to the sensorimotor clinical deficits in CP.

Finally, there is a paucity of studies investigating the neurological correlates of sensorimotor deficits in adults with CP. This is a likely contributor to the scarcity of specialized treatment strategies for this subpopulation [213]. In order to develop more effective treatment strategies aimed at targeting the neurological impairments in adults with CP, a more thorough understanding of the way in which neurological impairments may contribute to clinical presentation needs to be discovered. Resolving these knowledge gaps will help to delineate specific levels of the nervous system that comprise the bases for the clinical sensorimotor deficits seen within adults with CP. This is critical baseline knowledge for the development of effective therapeutic intervention that, ideally, not only will contribute to beneficial outcomes relating to body structure and function but also those that enable the individual to participate more in activities and reach personal goals.

CHAPTER 2: THE SOMATOSENSORY CORTICAL ACTIVITY IN INDIVIDUALS WITH CEREBRAL PALSY DISPLAYS AN ABERRANT DEVELOPMENTAL TRAJECTORY

Introduction

Cerebral palsy (CP) refers to a general class of movement disorders resulting from an early insult to the developing brain [125]. Approximately 3 out of every 1,000 children have CP, making it one of the most prevalent and costly pediatric neurological disorders diagnosed in the United States [126,127]. In addition to the motor deficits, impairments in proprioception, stereognosis, and tactile discrimination have been noted in the clinic [1-4,6-8]. Therefore, the classification of CP has expanded to not only include motor deficits but also sensory and perceptual deficits. Although CP is a non-progressive neurological disorder, the musculoskeletal system appears to show aberrant developmental effects that lead to increased mobility impairments across the lifespan [10]. In particular, the transition from adolescence to adulthood appears to be a critical window where there is often a marked decline in gross motor function and mobility [11]. It is possible that somatosensory processing also declines during this critical window since many adults with CP report sedentary lifestyles, fatigue, and balance problems [10,14,13,214]. Such lifestyle and physiological changes may limit the richness of the daily sensory experiences. Despite this conjecture, we still have a substantial knowledge gap in our understanding of the cortical somatosensory processing of adults with CP, let alone what happens during this critical transition period.

Numerous magnetoencephalographic (MEG) and electroencephalographic (EEG) studies have shown that somatosensory cortical activity is diminished in youth with CP relative to their typically developing peers. These studies have illustrated that somatosensory cortical oscillations are weaker in the theta-alpha (4–14 Hz) and beta (18–34 Hz) frequency bands following both tactile and electrical stimulation of the feet and hands [44,46,47,43,45]. These attenuated frequency-specific neuronal oscillations appear to be related to deficits in the ankle plantarflexor strength and mobility

of youth with CP [47,44]. This observation implies that individuals with higher Gross Motor Function Classification System (GMFCS) levels (i.e., greater mobility impairments) would likely have weaker somatosensory cortical oscillations. In addition to measuring oscillatory activity, several studies have also evaluated the phase-locked somatosensory-evoked cortical responses in individuals with CP. These investigations have consistently found similar outcomes for youth with CP, in that the somatosensory-evoked cortical activity for both upper and lower extremities are attenuated and, in some cases, have longer response latencies [49,50,7,51,43,52]. However, these studies have broadly focused on children and adolescent populations, which has significantly limited the field's understanding of how the transition to adulthood affects the strength of such somatosensory cortical responses in individuals with CP.

Previous studies by Riquelme and colleagues aimed to address this knowledge gap by assessing whether the somatosensory processing of tactile sensations applied to the hand differed between youth (5-14 years) and adults (22-55 years) with CP [215,151]. Their clinical assessments suggested that upper extremity proprioception and finger tactile sensitivity deficiencies were not appreciably different between youth and adults with CP. Their EEG results corroborated this notion by showing that the amplitude of the P50 and P100 somatosensory-evoked cortical responses following stimulation of the finger were similar between the two groups [215]. This implies that the somatosensory processing of the afferent feedback from the hands may not further decline as individuals with CP maturate into adults. However, of note, the progressive motor declines reported in the clinical literature are predominantly centered on mobility and not hand function [11,10,14,13,12]. Thus, there may be a stronger connection between somatosensory processing declines and age for lower extremity areas such as the feet in individuals with CP.

In the current study, we used MEG to image and quantify the primary somatosensory response following electrical stimulation of the tibial nerve in a cohort of individuals with CP and healthy controls. Based on the prior MEG literature, we hypothesized that these somatosensory responses would be weaker in those with CP compared to the healthy controls. Additionally, we

postulated that there would be a link between the magnitude of the somatosensory response and age, and that older participants with CP would tend to have weaker cortical responses. Lastly, we hypothesized that the magnitude of the somatosensory response would be tightly coupled with the GMFCS levels, such that individuals with greater mobility impairments would have more diminished somatosensory cortical activity.

Methods

Ethical Approval

The study protocol conformed with the standards set by the Declaration of Helsinki, except the study was not registered in a database. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this investigation. Informed consent was acquired from the adult participants and parents of the youth participants, and the youth assented to participate in the experiment. This study was not registered in a database.

Participants

Forty-two individuals with a diagnosis of spastic diplegic CP and GMFCS levels between I-IV completed this study (Age = 9 – 28 years, mean = 15.23 ± 4.55 yrs.). Individuals with GMFCS levels of I and II typically ambulate independently, although with slowed gait speed and abnormal gait patterns. Individuals with GMFCS level of III often require assistive devices to ambulate, such as crutches, ankle-foot orthoses, or wheelchairs. Individuals with GMFCS levels IV and V often require powered mobility devices. An additional twenty-three healthy youth and young adults (Age range = 11 – 23 years, mean = 15.03 ± 3.10 years) served as a control group (HC). The two groups did not significantly differ by age (P = 0.4313). Exclusionary criteria included any medical illness affecting CNS function, any neurological disorder, history of head trauma, any non-removable metal implant that would adversely affect data acquisition, and current substance abuse.

Furthermore, the included participants with CP did not have noticeable volume loss on the MRI that would have impacted the integrity of the cortices.

MEG Acquisition and Experimental Paradigm

Throughout the somatosensory experiment, the participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array while focusing on a fixation cross. A single pulse, unilateral electrical stimulation was applied using electrodes that were affixed to the skin overlying the right tibial nerve. The intensity of stimulation was set to the individual's motor threshold to control for impedance differences among participants. To find the motor threshold, the intensity of stimulation was gradually increased until an overt muscle twitch from the toes was elicited. During the experiment, a single-pulse of stimulation was applied every two seconds for four minutes, yielding a total of 120 trials.

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. With an acquisition bandwidth of 0.1 – 330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta MEG system (Helsinki, Finland) with 306 sensors, including 204 planar gradiometers and 102 magnetometers. Each MEG data set was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension [216].

MEG Coregistration and Structural MRI Processing

Four coils were affixed to the head of the participant and were used for continuous head localization during the experiment. Prior to the experiment, the location of these coils, three fiducial points and the scalp surface were digitized to determine their three-dimensional position (Fastrak

3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data was coregistered with structural T1-weighted MRI data prior to source reconstruction. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into a standardized space. Structural MRI data were acquired using a Siemens Skyra 3T scanner. High-resolution T1-weighted sagittal images were obtained with a 32-channel head coil using a 3D fast field echo sequence with the following parameters: TR: 2400 ms; TE: 1.94 ms; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm^3.

MEG Preprocessing

The raw MEG recordings were initially filtered with a 200 Hz zero order low pass digital filter, and a 0.5 zero order high pass digital filter. Additionally, a notch filter was applied to remove the 60 Hz line noise. Cardiac artifacts were subsequently removed from the data using signal-space projection, which was accounted for during source reconstruction [64]. The continuous magnetic time series was divided into epochs of 1100 ms duration, from -500 to 600 ms with the baseline being defined as -400 to -100 ms and 0.0 ms being stimulation onset. Epochs containing artifacts (e.g., eye blinks, muscle artifacts, etc.) were rejected based on a fixed-threshold method using individual amplitude and gradient thresholds, supplemented with visual inspection. An independent samples t-test revealed that the number of trials accepted between groups was not significantly different (CP = 102.31 ± 2.60, HC = 104.68 ± 2.65, P = 0.6374).

Sensor-level Analysis

The artifact-free epochs were next averaged across trials to generate a mean time series per sensor and participant, and the specific time windows used for subsequent source imaging were determined by statistical analysis of the sensor-level time series across all participants using the entire array of gradiometers. Each data point in the time series was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired-sample t-tests were conducted to test for differences from baseline at each data point and the output time series of t-values was threshold at $P < 0.05$ to define time bins containing potentially significant phase-locked activity across all participants. In stage two, the time points that survived the threshold were clustered with temporally and/or spatially neighboring time points that were also above the threshold ($P < 0.05$), and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution [217]. For each comparison 1,000 permutations were computed to build a distribution of cluster values. Based on these analyses, the time windows that contained significant phase-locked events across all participants were used to guide subsequent time-domain source level analysis.

Source Imaging (sLORETA)

Time domain source images were computed using standardized low resolution brain electromagnetic tomography (sLORETA). [218] The resulting whole-brain maps were 4-dimensional estimates of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the

units are arbitrary. These maps were then averaged temporally over the time windows identified in the sensor-level analysis. The resulting maps were then grand-averaged across all participants to determine the location of the peak voxel. From this peak voxel, the sLORETA units were extracted to derive estimates of the time-domain response amplitude for each participant. All imaging procedures were done with the Brain Electrical Source Analysis (BESA) software (BESA v7.0; Grafelfing, Germany). For additional methodological detail, please see our recent paper [219].

Statistical Analysis

The Shapiro-Wilk test of normality was used to determine whether the data were normally distributed. The data that failed the test were subsequently logarithmically transformed for statistical testing. An ANCOVA model with group as the independent variable, age as a covariate, and the extracted peaks from the sLORETA analysis as the dependent variable was calculated. Spearman correlation coefficients were also calculated between the overall severity of gross motor function (i.e., GMFCS) and the magnitude of the somatosensory cortical response, as well as GMFCS and age. The statistical analyses were conducted with SPSS (Version 22.0; IBM Corporation, Armonk, NY). Data within the text and the figures are presented as the mean plus/minus the standard error of the mean.

Results

MEG Findings

Robust somatosensory cortical responses appeared in a wide array of sensors within the frontal and parietal cortices, with the strongest activity present within the medial sensors near what was likely the leg region of the contralateral (left) somatosensory cortex. Permutation testing of the sensor-level data revealed that the somatosensory cortical response was significantly different from baseline during the 112 – 252 ms time window; thus, source activity estimates were averaged across

this window and then across all participants. Not surprisingly, the resulting grand-averaged sLORETA data revealed that the peak neural response emanated from the contralateral somatosensory cortices. To highlight the similarity, we show the images separately for each group in Figure 2. These images clearly show that the somatosensory cortical response was weaker in the individuals with CP, although the location of the peak response was similar. We subsequently extracted the peak voxel (Talairach coordinates: -6, -32, 49) from the grand-averaged image to confirm this observation. Our ANCOVA model confirmed that there was a significant main effect of group (HC = 286.53 ± 30.51, 95% CI [226.74, 346.32]; CP = 208.30 ± 19.66, CI [169.77, 246.83], P = 0.0126), indicating that somatosensory cortical activity was weaker in individuals with CP (Figure 3). To visualize the difference in the dynamics, we subsequently extracted the neural time course from the peak voxel; note that this time course was extracted per participant, once the coordinates of interest were known from the grand-averaged image, and subsequently averaged within group. As shown in Figure 3, these time courses indicate that the somatosensory cortical activity was clearly weaker in the individuals with CP.

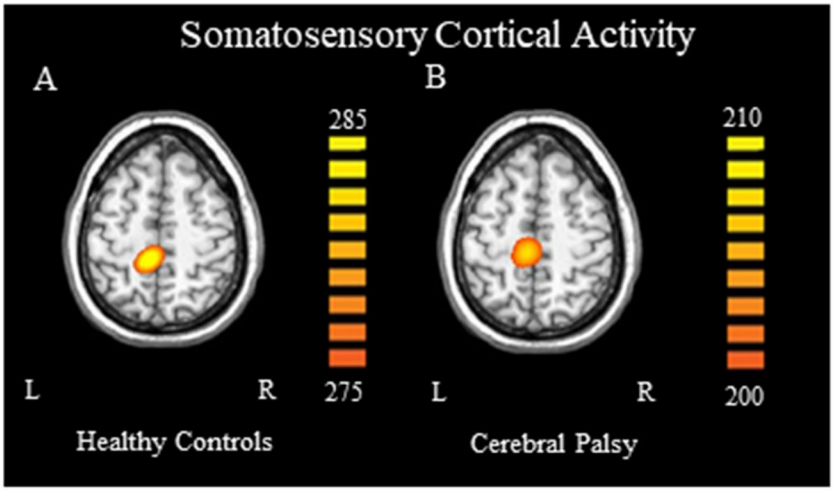

Figure 2: Source Level Somatosensory Cortical Activity Group averaged sLORETA images across the time window identified through cluster-based permutation testing of the sensor level results (112–252 ms) for the healthy controls (A) and individuals with CP (B). All responses were located in the leg region of the somatosensory cortex contralateral (left) to stimulation. Note that the units are arbitrary, and the threshold is lower for the group with CP in order to visualize the response.

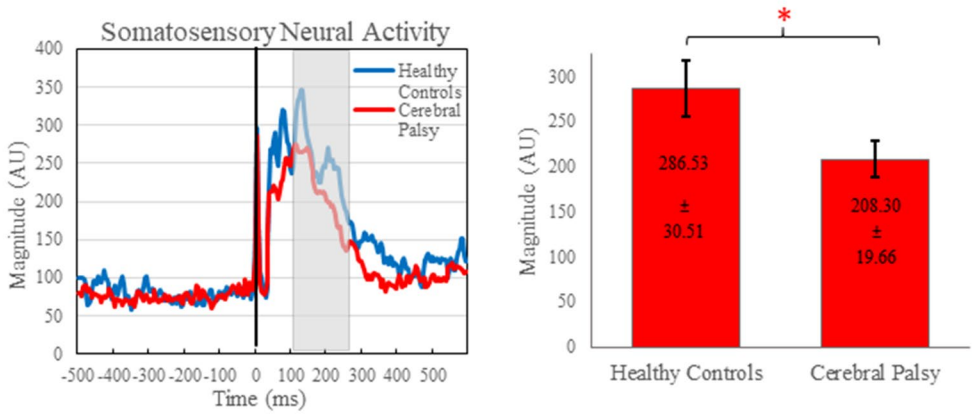

Figure 3: Somatosensory cortical activity was stronger in healthy controls Left, peak voxel time series. The stimulus was administered at time 0.0 ms (black line). The main somatosensory response, depicted in arbitrary units (AU), begins around 40 ms and diverges group-wise shortly thereafter. The time bin containing significantly different activity relative to baseline, which was subsequently used for further imaging analysis, is demarcated by the grey box (11viii2–252 ms). Blue depicts the healthy controls and red depicts the individuals with cerebral palsy. The somatosensory response was notably weaker in the individuals with cerebral palsy. Right, bar graph representing the difference in magnitude of the response between the healthy controls and the individuals with CP. The healthy controls had a significantly stronger response than the individuals with CP (P = 0.0126).

The ANCOVA model additionally confirmed that the somatosensory cortical activity covaried with age (P = 0.0168). Our post-hoc Pearson correlation indicated that the somatosensory cortical activity tended to decrease with age in all participants (r = -0.30, P = 0.0164). The interaction effect between group and age was not significant (P = 0.8790), indicating that the change in somatosensory cortical activity with age displayed parallel changes in the respective groups. To further conceptualize these results, we fit linear regression models to the data from the respective groups (Figure 4). Inspection of these models conveyed that the slopes were relatively similar between groups, but the intercept was notably shifted downward for the individuals with CP. This indicates that the individuals with CP had weaker somatosensory cortical activity overall, and it implies that youth with CP may have somatosensory cortical activity that is similar to an older adult controls. For example, the regression lines depict that an individual with cerebral palsy 9.8 years old has predicted somatosensory cortical activity similar to that of a neurotypical individual that is

16.8 years old. This suggests that at least some individuals with CP exhibit aberrant maturation of their somatosensory system.

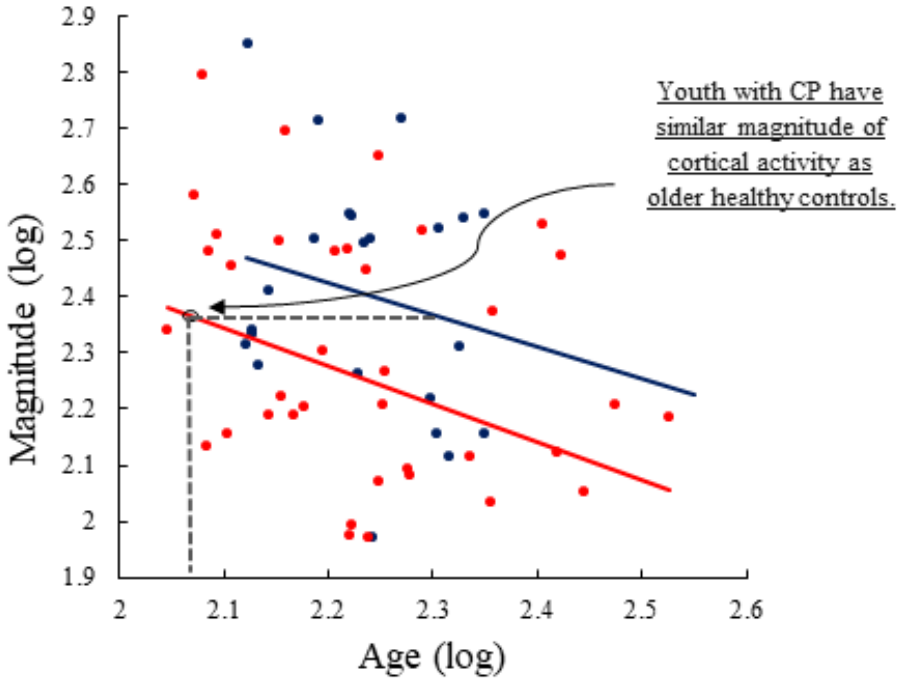

Figure 4: Parallel age-related declines in somatosensory cortical activity between controls (blue) and individuals with CP (red)

Inspection of linear regression models fitted to the log transformed data of the respective groups conveyed that the slopes were relatively similar between the respective groups, but the intercept was shifted downward for the individuals with CP. The shifted intercept reflects the weaker somatosensory cortical activity seen in the individuals with CP across the examined age range. Inspection of the respective models indicates that the youth with CP exhibited somatosensory cortical activity that was similar to much older controls. This suggests that some of those with CP exhibit accelerated ageing in the somatosensory system.

Correlation Analysis

GMFCS levels and the magnitude of the somatosensory cortical responses were not significantly associated with each other ($r = -0.18$, $P = 0.2603$), suggesting that the strength of the somatosensory response was likely not connected with the degree of the participant's mobility impairment. Age was also not significantly associated with GMFCS level ($r = 0.16$, $P = 0.3087$), suggesting that GMFCS level did not change as a function of age.

Discussion

We used MEG brain imaging to evaluate the magnitude of the somatosensory response that was evoked after a peripheral stimulation was applied to the tibial nerve in a cohort of individuals with CP and healthy controls. Overall, our results align with prior research that has shown that somatosensory cortical activity is diminished in individuals with CP [49,50,7,51,43]. Our results also suggest that somatosensory cortical activity tends to become weaker with age; yet, the rate of this neurophysiological change in individuals with CP appears to parallel that seen in healthy controls, at least within the age range that we examined. Nonetheless, the overall age-related trajectories suggest that youth with CP have an altered maturation trajectory within the somatosensory system that emerges during youth and is maintained into early adulthood. Further discussion of this premise and the implications of these experimental findings appear in the following sections.

Compared with healthy controls, our results show that the somatosensory cortical responses seen in the leg region of the somatosensory cortices are reduced in amplitude in individuals with CP. This is in line with several neuroimaging studies that have previously identified alterations in somatosensory processing in individuals with CP, in response to both tactile and electrical stimulation paradigms [49,50,7,51,1,220,221,6,43,46,44,48,52]. Thus, it is likely that this altered activity contributes to the somatosensory deficits that are reported clinically for this patient population. The previous MEG studies that have evaluated the somatosensory cortical responses have primarily utilized sensor space or dipole analyses, or have focused only on youth with CP. While these prior experimental outcomes have provided valuable insights on the differences in amplitude and latency of somatosensory processing in youth, the sample demographics and imaging methods used in the current investigation significantly enhance these prior outcomes by verifying the precise neural tissue underlying the response across youth and early adulthood.

Overall, our results identified that the somatosensory cortical activity tended to become weaker as adolescents transitioned into adulthood. These results align with a prior study that

reported the strength of the somatosensory cortical responses are reduced in healthy adults compared with newborns [222]. Hence, corroborating the notion that the cortical activity decreases as the somatosensory system matures. There are several anatomical changes that occur within the brain throughout development which may contribute to this maturation-related reduction. Cortical gray matter thickness tends to increase during the pre-adolescent period but then decreases in frontal and parietal lobes around 12 years of age [223-227]. Furthermore, synaptic density within gray matter tends to peak between four and eight years of age and then declines into adulthood [228-230,227]. Altogether these structural changes might partially account for the reduction in somatosensory activity across development.

Our results illustrated that individuals with CP also display a reduction in the somatosensory cortical activity with age. Despite having a parallel trajectories with the healthy controls, the younger individuals with CP tended to have somatosensory cortical activity that was more aligned with what was seen in the older healthy controls. For example, our results showed that an individual with CP that is 9.8 years old has predicted somatosensory cortical activity similar to that of a healthy control that is 16.8 years old. This implies that at least some youth with CP have an aberrant developmental trajectory in regard to somatosensory processing that might set them up for having an aberrant profile later in life. That being said, a diffusion weighted imaging (DWI) and transcranial magnetic stimulation (TMS) study showed the corticospinal tracts in both hemispheres appeared to arrest in maturation in children with hemiplegic CP when compared with typically developing children [231]. This would imply that there would be a point in development where there would not be further changes in the cortical activity with age. Potentially, this discrepancy might be due to the different time windows for the maturation of the sensory and motor fibers.

We suggest that the aberrant maturation of the somatosensory cortices may partially be a contributing factor to the degraded motor actions often reported as youth with CP transition into young adulthood [11]. Furthermore, we imply that the aberrant trajectory of the somatosensory

cortical activity could be partially attributable to the more sedentary lifestyles seen in individuals with CP, which would make the system prematurely degenerate [10,14,13,214]. However, this inference is at odds with previous studies reporting that somatosensory tactile sensitivity and evoked potentials do not significantly differ between children and adults with CP [151,215]. Of note, these prior outcomes were based on studies that focused on somatosensory processing of the hand and not the foot, and it is well recognized that individuals with CP are more likely to have lower extremity versus upper extremity impairments [232]. Hence, the connection between the reduced somatosensory cortical activity and age found in this investigation may be more representative of the average case with CP.

Previous studies utilizing MEG brain imaging have reported that the strength of somatosensory cortical oscillations in the theta-alpha range are related to diminished ankle strength and mobility [47,44]. Based on these previous outcomes, we presumed that the magnitude of the somatosensory responses would be related to the GMFCS levels that were used to clinically classify the degree of mobility impairments seen in individuals with CP (e.g., weaker responses for higher GMFCS levels). However, surprisingly, our results suggested that GMFCS levels were not directly related to the magnitude of somatosensory cortical responses following tibial nerve stimulation. It is plausible that the GMFCS levels provide a clinical gestalt on the overall presentation, but may lack the specificity for separating the patient's presentation on a continuum. In other words, although two patients may have similar GMFCS levels, their individualized sensorimotor presentations can be quite different.

Despite our novel findings, several limitations should be kept in mind. First, the heterogeneity seen in CP inherently leads to variability in the cortical function within this population, which may then affect the somatosensory responses examined in this study. Nevertheless, as previous studies have consistently confirmed, somatosensory cortical activity is reduced in those with CP across a range of presentations, substantiating the robustness of this finding. Additionally, the participants included in this investigation were between 9-28 years of

age. It is possible that assessing a larger cohort of individuals across a broader age range would allow for stronger conclusions to be made regarding somatosensory cortical activity, its trajectory of change, and the notion of accelerated development across the lifespan. That said, this is one of the few studies to date that has evaluated cortical activity in adults with CP, or considered the dimension of age as an important neurophysiological variable.

Conclusions

Our experimental results illustrate that the magnitude of somatosensory cortical responses in the feet are reduced in individuals with CP and tend to become weaker with maturation. We suggest that the weaker somatosensory cortical activity seen in youth with CP may reflect an altered developmental course than typically seen within the somatosensory system. Currently, specialized treatments for adults with CP are extremely limited and have gathered less attention compared with the pediatric population with CP [213]. The results of this investigation imply that attention to the aberrant somatosensory processing seen in youth as they transition toward adulthood is of critical importance. Potentially, somatosensory training (i.e., limb awareness, heightened tactile sensations during gait) might be a key ingredient that could alter the trajectory of the aberrant maturation of the somatosensory system noted in this investigation.

CHAPTER 3: ALTERED SOMATOSENSORY CORTICAL ACTIVITY IS ASSOCIATED WITH CORTICAL THICKNESS IN ADULTS WITH CEREBRAL PALSY

Introduction

Cerebral palsy (CP) is the most prevalent and costly pediatric movement disorder in the United States, and is often accompanied by disturbances in the hand motor actions [126,127,233]. These disturbances impact the ability of individuals with CP to perform a wide range of activities of daily living (i.e., buttoning shirt, grasping objects, writing, using utensils, etc.) [234]. Although these motor disturbances have traditionally been characterized as a deficiency in the musculoskeletal machinery, numerous clinical studies have illustrated that individuals with CP have notable deficits in tactile registration/discrimination, proprioception and stereognosis [6,2,4,152,153]. Furthermore, the severity of such sensory deficits appear to be tightly related with the altered hand motor performance reported in the clinical literature [6]. These clinical observations have sparked a series of studies that have been directed at uncovering the neurophysiological mechanisms that play a role in the altered hand motor actions and uncharacteristic somatosensory processing.

Numerous magnetoencephalography (MEG) and electroencephalography (EEG) neuroimaging studies have identified that the somatosensory cortical activity is reduced in magnitude and latent in individuals with CP in comparison to their age-matched peers [7,49-51,44,47,46]. Additionally, our recent experimental results have shown that the uncharacteristic somatosensory-evoked cortical activity seen in youth with CP becomes even more aberrant when they transition into adulthood [235]. There are several anatomical changes that occur within the brain throughout neurotypical development that may contribute to this reduced somatosensory cortical activity during adulthood. For one, the cortical gray matter thickness tends to increase during the pre-adolescent period but then decreases in frontal and parietal lobes in adulthood [223-227]. Furthermore, synaptic density within gray matter tends to peak between four and eight years of age and then

declines into adulthood [228-230,227]. Presumably the brain injuries incurred by children with CP might interrupt or accelerate the course of the regional changes in the cortical grey matter density, which in turn might influence the strength of the somatosensory cortical activity seen adults with CP. This premise is partly supported by several MRI structural imaging studies that have shown that early on youth with CP may have altered grey matter thickness across a number of cortical regions that include the sensory, motor, occipital, temporal, parietal and insula areas (Schech et al., 2014; Liu et al., 2019; Pagnozzi et al., 2016). Furthermore, it has been demonstrated that a reduction in the cortical volume of the primary somatosensory cortices is strongly associated with more impaired hand motor function (Pagnozzi et al., 2016). However, the potential connection between the reduced somatosensory cortical thickness and the weaker neuronal activity seen in individuals with CP has yet to be fully established.

Sensory gating is a phenomenon that occurs when two identical stimuli are presented in short succession (i.e., a paired pulse), and the cortical response to the second stimulus is reduced in comparison to the first. Gating has been extensively studied within the somatosensory cortex of healthy individuals [236-238], and it is thought that the attenuation of the response to the second stimulus represents the filtering of redundant and/or irrelevant information to allow for adequate resources for more task-relevant information [91,239]. GABAergic inhibitory interneurons regulate this process of pre-attentive inhibitory control of redundant information to prevent sensory and perceptual overload [240], and these inhibitory interneurons are likely aberrant in youth with CP [241,242,91,243]. Our prior research is aligned with this premise since it has identified that children with CP hyper-gate redundant somatosensory information in response to paired pulse electrical stimulations applied to the foot [48]. Whether similar hyper-gating is seen when paired stimulations are applied to the hand is unknown. Furthermore, it is unknown if the altered somatosensory gating is also connected with the altered grey matter thickness seen in the somatosensory cortices of

individuals with CP. Such information would provide new insights on the neurophysiological mechanisms responsible for the altered sensory processing reported for individuals with CP.

This multimodal neuroimaging study aimed to address if the somatosensory gating is altered when somato-senations are applied to the hands of adults with CP, and if the strength of the somatosensory cortical activity is linked with the cortical structure. To this end, we used MEG brain imaging to quantify the evoked somatosensory cortical activity and amount of gating that occurred when two identical electrical stimulations were applied to the median nerve. Secondarily, we used an MRI surface-based morphometry protocol to quantify the potential differences in the somatosensory cortical thickness in the region generating the activity. Overall, the results of this experimental work show that the somatosensory-evoked cortical activity is directly associated with the somatosensory cortical thickness. Hence, this illustrates that the functional alterations in the somatosensory activity seen adults with CP throughout the literature may be attributed to structural changes in the cortex that are a sequelae of the early brain insult.

Methods

Participants

Seventeen adults with a diagnosis of spastic CP and GMFCS levels between I-IV completed this study (Age Range = 20.7 – 48.8 years, mean =32.8 ± 9.3 years) and MACS levels between I and III. An additional cohort of eighteen healthy adults (Age range = 19.3 – 49.4 years, mean = 30.7 ± 9.9 years) served as a control group (HC). The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this investigation. Informed consent was acquired from all participants.

MEG Acquisition and Experimental Paradigm

Throughout the somatosensory experiment, the participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array with their eyes closed. Electrical stimulation was applied to the right median nerve using external cutaneous stimulators connected to a constant-current stimulator system (Digitimer Limited, Letchworth Garden City, UK). For each participant, we collected at least 80 paired-pulse trials with an inter-stimulation interval of 500 ms and an inter-pair interval that randomly varied between 4500 and 4800 ms. Each pulse generated a 0.2 ms constant-current square wave that was set to the motor threshold required to elicit a subtle twitch of the thumb.

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. With an acquisition bandwidth of 0.1 – 330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta MEG system (Helsinki, Finland) with 306 sensors, including 204 planar gradiometers and 102 magnetometers. Each MEG data set was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension [216].

MEG Coregistration and Structural MRI Processing

Four coils were affixed to the head of the participant for continuous head localization during the experiment. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in

reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data were coregistered with structural T1-weighted MRI data prior to source reconstruction. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into a standardized space. Structural MRI data were acquired using a Siemens Skyra 3T scanner. High-resolution T1-weighted sagittal images were obtained with a 32-channel head coil using a 3D fast field echo sequence with the following parameters: TR: 2400 ms; TE: 1.94 ms; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm^3.

MEG Preprocessing

Cardiac artifacts were removed from the data using signal-space projection, which was accounted for during source reconstruction [64]. The continuous magnetic time series was divided into epochs of 3700 ms duration, from -800 to 2900 ms with the baseline being defined as -700 to -300 ms and 0.0 ms being the first stimulation onset. Epochs containing artifacts (e.g., eye blinks, muscle artifacts, etc.) were rejected based on a fixed-threshold method using individual amplitude and gradient thresholds, supplemented with visual inspection. An independent samples t-test revealed that the number of trials accepted between groups was not significantly different (CP = 74.65 ± 2.32, HC = 75.78 ± 4.92, P = 0.375).

Sensor-level Analysis

The artifact-free epochs were next averaged across trials to generate a mean time series per sensor, and the specific time windows used for subsequent source analysis were determined by statistical analysis of the sensor-level time series across all conditions. Each data point in the time

series was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired-sample t-tests were conducted to test for differences from baseline at each data point and the output time series of t-values was threshold at $P < 0.05$ to define time bins containing potentially significant phase-locked deviations across all participants. In stage two, the time points that survived the threshold were clustered with temporally and/or spatially neighboring bins that were also above the threshold ($P < 0.05$), and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution [217]. For each comparison 1,000 permutations were computed to build a distribution of cluster values. Based on these analyses, the time windows that contained significant phase-locked events across all participants were used to guide subsequent time-domain source level analysis.

Source Imaging (sLORETA)

Time domain source images were computed using standardized low resolution brain electromagnetic tomography (sLORETA) [218]. The resulting whole-brain maps were 4-dimensional estimates of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the units are arbitrary. These maps were then averaged temporally over the time windows identified in the sensor-level analysis. The resulting maps were then grand-averaged across the participants to determine the location of the peak voxel of the time-domain neural response to the stimuli across participants. The neural time course was then extracted from this peak voxel; note that this time course was extracted per participant, once the coordinates of interest were known from the grand-averaged image, and the maximum peak within the defined time windows were used to derive

estimates of the time-domain response amplitude for each participant. The gating ratio was subsequently calculated as the maximum peak from the second pulse divided by the maximum peak from the first pulse. All imaging procedures were done with the Brain Electrical Source Analysis (BESA) software (BESA v7.0; Grafelfing, Germany).

Structural MRI acquisition and processing

The structural MRI data were processed using the standard pipeline in the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/, version 12.6) at a resolution of 1 mm^3 within SPM12 (Wellcome Trust Center for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) using MATLAB (2017b) software (MathWorks, Natick, Massachusetts, USA). The surface-based morphometry pipeline in CAT12 is fully automated and utilizes a projection-based thickness (PBT) approach to estimate cortical thickness and reconstruct the central surface in one step [244]. Essentially, following tissue segmentation [245] the white matter (WM) distance is estimated, and the local maxima (which is equal to the cortical thickness) are projected onto other gray matter voxels using a neighboring relationship described by the WM distance. PBT accounts for partial volume correction, sulcal blurring, and sulcal asymmetries without sulcus reconstruction. To rectify topological defects, a correction based on spherical harmonics was employed [246], and the cortical surface mesh was re-parameterized into a common coordinate system via an algorithm that reduces area distortion. Finally, the resulting maps were resampled and smoothed using a 15 mm FWHM Gaussian kernel.

For quality assurance, a two-step process was adopted. First, prior to segmentation, data were visually inspected for artifacts. Second, the quality control measures incorporated in the CAT12 processing pipeline were utilized to identify the most deviant data following segmentation. These data were inspected further for the presence of newly introduced artifacts.

Region of Interest Analysis

Utilizing the peak voxel coordinates identified in the grand-averaged sLORETA images, a mask was constructed for the cortical surface mesh. Specifically, a 4 mm cortically-constrained sphere centered on the peak voxel coordinates was generated using the WFU Pickatlas (version 3.0) [247,248]. A 4 mm sphere was selected since it aligned with the 4 mm native resolution of the sLORETA source images. This mask was spatially resampled to 1 mm isotropic voxels to align with the processed structural MRI and MEG data.

Finally, the normalized volume mask was transformed into the surface template space using the transform provided in CAT12. Cortical thickness values were then extracted per participant utilizing this ROI mask. Thus, the attained values reflect the average cortical thickness within the estimated group-wise peak voxel of the somatosensory-evoked cortical activity. Of note, the same procedure was applied to derive the average cortical thickness across spheres of varying sizes (4 mm, 8 mm, and 12 mm) to ensure the robustness of any statistically significant findings seen at the 4 mm ROI.

Statistical Analysis

The data were tested for normality using the Shapiro Wilke test, and any data that failed the test were log transformed for statistical analysis. A repeated measures ANOVA (group X stimulation) was used to test if there were differences in the somatosensory evoked somatosensory cortical responses. The gating ratios and cortical thickness at the extracted ROI for the respective groups were also compared using separate independent samples t-tests. Lastly, Pearson correlation coefficients were calculated between the extracted cortical thickness values and the magnitude of the somatosensory cortical activity and gating ratios to identify any potential relationship between the functional brain activity and structure. The statistical analyses were conducted with JASP (Version 12.2.0) using a 0.05 alpha level.

Results

MEG Imaging

Permutation testing of the sensor-level data revealed that the somatosensory cortical response was significantly different from baseline during the 32 – 136 ms time window for the first stimulus, and 532 – 636ms for the second stimulus (P's < 0.001, Figure 5A); thus, source activity estimates were averaged across these time windows and then across all participants. Not surprisingly, the resulting grand-averaged sLORETA data revealed that the peak neural response emanated from the hand region of the contralateral (left) somatosensory cortices (Figure 5B).

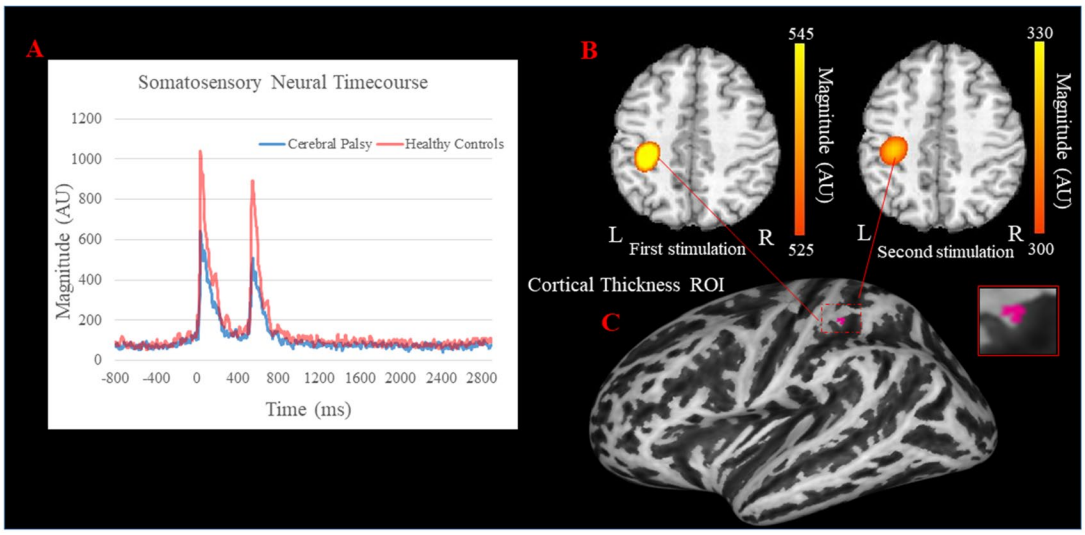

Figure 5: Somatosensory Gating and Cortical Thickness ROI A). Individuals with CP hyper-gated the response to the second stimulus in comparison to the healthy adult controls. B.) Group averaged sLORETA image of the somatosensory-evoked cortical activity emanating from the contralateral (left) somatosensory cortex for the first peak (32 – 136ms, left) and the second peak (532 – 636ms, right). The magnitude of the response is significantly decreased in the second stimulation, indicating a gating effect (P = 0.001). C.) The coordinates of the peak voxel from the grand averaged sLORETA image were used to generate a mask around the area from which the somatosensory cortical activity was generated.

Our statistical analysis revealed that there were main effects for stimulation (P=0.001) and group (P=0.004). Hence, indicating that the second stimulation was reduced for both groups (Stim 1 = 1100.85 ± 91.68 AU; Stim 2 = 886.62 ± 71.23 AU; P = 0.001), and that the evoked

somatosensory cortical activity was weaker for the adults with CP (CP= 796.73 ± 92.01 AU; AC= 1206.979 ± 121.43 AU; Figure 6A). These effects are clearly depicted within the neural time course shown in Figure 5A. Furthermore, the gating ratio was significantly lower in the adults with CP in comparison to the controls (CP = 0.79 ± 0.04 AU; AC = 0.91 ± 0.04 AU; P = 0.030; Figure 6B), indicating that the adults with CP hyper-gated the second stimulation.

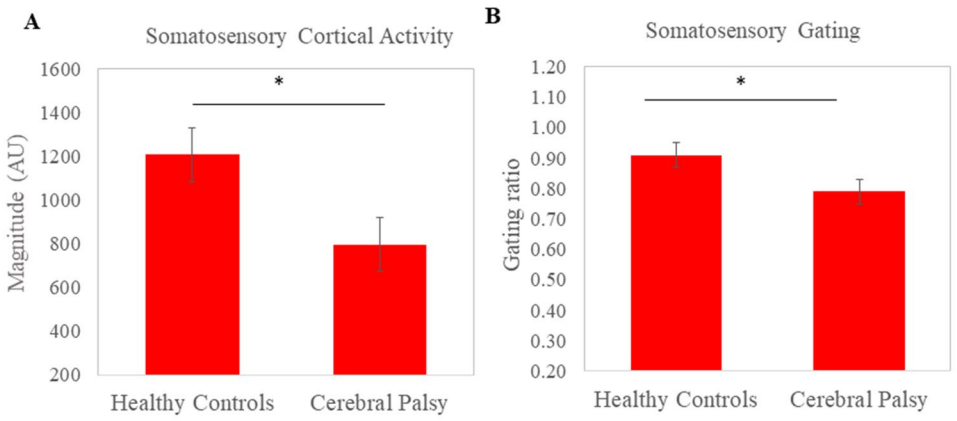

Figure 6: Altered Somatosensory Activity in Adults with CP A.) Somatosensory cortical activity across both peaks was decreased in magnitude in the adults with CP in comparison to the healthy adult controls (P = 0.004). B.) The gating ratio was significantly lower in the adults with CP, indicative of hypergating and abnormal inhibition within the somatosensory cortices (P = 0.03).

Cortical Thickness is Associated with Somatosensory-Evoked Cortical Activity

The coordinates from the peak voxel of the evoked somatosensory activity were subsequently used to generate a cortically constrained sphere (Figure 5C). The cortical thickness within the ROI was reduced in the adults with CP in comparison to the controls within the 4mm ROI (CP = 2.471 ± 0.023 mm, NT = 2.554 ± 0.22 mm, P = 0.015, Figure 7A), the 8mm ROI (CP = 2.217 ± 0.031 mm, NT = 2.419 ± 0.040 mm, $P < 0.001$), and the 12mm ROI (CP = 2.206 ± 0.030 mm, NT = 2.389 ± 0.035 mm, $P < 0.001$). The magnitude of the somatosensory-evoked cortical activity for the first stimulation was positively correlated with the cortical thickness seen in the 4mm ROI (r = 0.41, P = 0.023, Figure 7B), the 8mm ROI (r = 0.46, P = 0.013), and 12mm ROI (r= 0.49, P = 0.006). Similarly, the magnitude of the somatosensory-evoked cortical activity for the

second stimulation was positively correlated with the cortical thickness seen in the 4mm ROI (r = 0.36, P = 0.04), the 8mm ROI (r = 0.44, P = 0.014), and 12mm ROI (r= 0.47, P = 0.008). Overall, these correlations indicate that stronger somatosensory cortical activity was linked with greater cortical thickness. However, the cortical thickness was not associated with the gating ratio for any of the ROI sizes (Ps < 0.05).

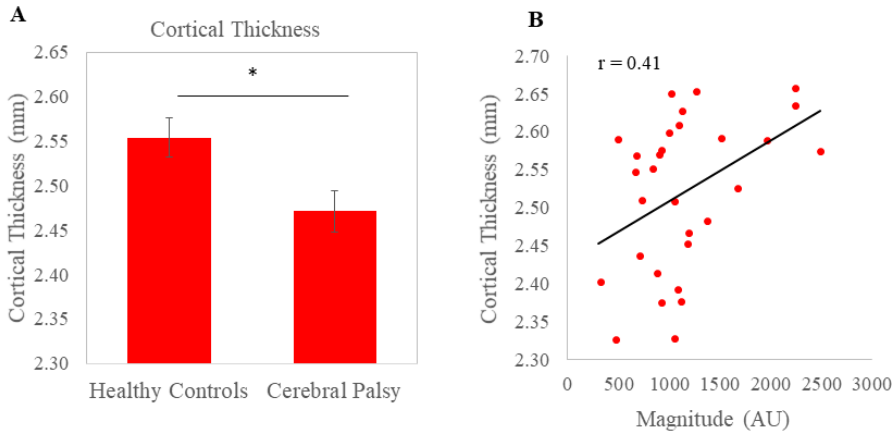

Figure 7: Cortical thickness is associated with Somatosensory Cortical Activity A.) Cortical thickness in the region of the cortex generating the somatosensory response. The cortical thickness was significantly decreased in the adults with CP in comparison to the healthy adult controls (P = 0.015). B.) Scatterplot depicting the relationship between the cortical thickness and somatosensory cortical activity evoked by the first stimulus. Individuals with increased cortical thickness also tended to have greater somatosensory-evoked cortical activity (P = 0.023).

We performed a follow-up analysis on the significant relationships found between cortical thickness and somatosensory-evoked cortical activity to ensure that this relationship was not a result of differences in the respective variables for the groups. This follow-up consisted of performing Fisher's Z transformations to determine whether this relationship differed when calculated separately for the adults with CP and the controls. We found that the relationship between the somatosensory-evoked cortical activity and cortical thickness for the 4mm (Z = 0.08, P = 0.936), 8mm (Z = -0.15, P = 0.881), and 12mm (Z = -0.18, P = 0.857) regions of interest were each similar between the groups. Thus, this follow-up analysis confirmed that the group differences in cortical thickness and somatosensory-evoked cortical activity cannot solely explain the association between these variables.

Discussion

Our results build upon the scientific premise that adults with CP have decreased somatosensory-evoked cortical activity by showing that they tend to hyper-gate hand somato-sensations. We also determined that the cortical region from which the somatosensory cortical activity was generated is thinner in the adults with CP. Finally, we have identified that the strength of the somatosensory-evoked cortical activity is linked with the cortical thickness. This connection implies that the functional alterations in the somatosensory cortical activity of adults with CP is partially attributed to structural changes in the cortex that are likely a downstream effect of the early brain insult. Further implications of these novel experimental results are presented below.

Our results corroborate the numerous studies that have identified that the somatosensory-evoked cortical activity is reduced in amplitude in individuals with CP compared with neurotypical controls [49,50,7,51,1,220,221,6,43,46,44,48,52,235]. However, the prior literature on the somatosensory processing deficits has predominately been focused on youth with CP. Our results have added new insights to this literature by showing that the somatosensory cortical activation for the hand continues to be weaker well into adulthood. This notion is aligned with our recent outcomes that have also shown the somatosensory cortical activity is aberrant when a stimulation is applied to the tibial nerve of adults with CP [235]. Our prior results have also identified that compared with youth with CP the somatosensory processing deficits are more pronounced in adults with CP. We suggest that the greater alterations seen in the somatosensory cortical activity of adults with CP may partially be a contributing factor to the further degraded motor actions reported as youth with CP transition into adulthood [11].

Our results also showed that adults with CP hyper-gate repeated somato-sensations applied to the hand, which is remarkable because they also had weaker somatosensory cortical responses to the first stimulation. It is likely that the hyper-gating of subsequent somato-sensations may even

further diminish the processing of important peripheral information. These results are also aligned with our prior study that has shown youth with CP hyper-gate repeated and similar somato-sensations that are applied to the feet [48]. Sensory gating is reflective of pre-attentive inhibition and has been used as a marker to assess the inhibitory functioning within the somatosensory cortices [236-238,249]. The hyper-gating effect seen in the respective studies is likely indicative of heightened activity within cortical GABAergic inhibitory interneurons. Previous Hoffmann reflex studies have demonstrated hyperexcitability in the spinal cord of individuals with CP [189,192]. This hyperexcitability may result in an overall increase in afferent information, albeit noise, that ascends from the spinal cord through the thalamocortical tracts, heightening the activity of GABAergic interneurons in the cortex meant to filter the incoming information [212,169,168]. Damage to the structural integrity of the thalamocortical tracts seen in CP [167-169,212] may result in an even further increase in noise within the pathways transmitting somatosensory information to the cortex, resulting in added increases in GABAergic inhibitory activity. Altogether, this increase in information ascending from the spinal cord and thalamocortical tracts may create difficulty for adults with CP in deciphering the salience of incoming information, resulting in the second stimulus being interpreted as noise and thus being hyper-gated.

Our structural imaging also illustrated that the somatosensory cortical thickness was significantly decreased in the adults with CP. These results are aligned with several studies that have shown youth with CP may have altered grey matter thickness in the somatosensory cortical area [250-252]. Research on the healthy aging population has identified that there is age-dependent cortical thinning in this region [253]. These changes have been largely attributed to both neuronal cell death and a reduction in synaptic density, dendritic arborization, and an overall decrease in neural cell size. Thus, there are likely fewer neuronal cell bodies and synapses within the somatosensory cortex of the adults with CP, and this could directly contribute to the potentially aberrant processing of the incoming sensory information. That being said, it still remains unknown if the cortical

thinning seen in the older population with CP reflects what is seen in the typical healthy aging population or if it represents an accelerated/altered trajectory.

Our results are the first to show that the strength of the somatosensory-evoked cortical activity is associated with the thickness of the somatosensory cortices. This relationship suggests that the individuals with more gray matter tend to have greater somatosensory cortical activity. MEG primarily detects cortical oscillatory activity generated by the underlying postsynaptic potentials of pyramidal neuronal populations. Thus, if there are fewer cell bodies and there is a reduction in dendritic arborization within a given neuronal population, then there will be fewer synapses contributing to the underlying electrical activity generating the neural response. This would in turn be reflected by a reduction in magnitude of neural activity in response to a given stimulus, which aligns with the relationship between structure and function that we have identified in the somatosensory cortex. Contrary to our expectation, the somatosensory gating was not related to the cortical thickness. This implies that the gating ratio may provide a normalized metric that more accurately quantifies the extent of the cortical activation because it is not dependent on the number of neurons that are activated in the cortical region of interest.

The source of this reduction in the somatosensory cortical gray matter and altered somatosensory activity seen in adults with CP could be a result of a lack of enriched somatosensory experiences. We suspect that the greater sedentary behavior and reduced social/environmental experiences often reported for individuals with CP would inherently lead to fewer somatosensory experiences [254] With a lack of input to the somatosensory system, there is less capacity for neuroplastic change within the somatosensory cortices, which would result in alterations in the synaptic connections that are involved in processing incoming information. The emerging clinical question is how the somatosensory cortical processing deficits reported here and across several other studies can be overcome and if a lack of enriched experiences play a central role in the altered somatosensory processing we have seen for adults with CP. A few studies that have shown that

clinical assessments of proprioception and tactile acuity can improve after undergoing a sensory-based training protocol or hand-arm bimanual intensive therapy [152,255,256]. Albeit for the lower extremity, a preliminary study we conducted also suggested that the somatosensory cortical activity might be enhanced after youth with CP undergo an intensive gait training protocol [257]. Further testing of these therapeutic concepts would be laudable, and may have the potential to alter the treatment strategies currently being used to improve the motor actions of individuals with CP.

In conclusion, we have demonstrated that the altered somatosensory cortical activity and gating that has been shown in children with CP persists into adulthood. Potentially, increased noise from a hyperexcitable spinal cord and damaged thalamocortical tracts results in overactivity of GABAergic inhibitory interneurons that are meant to suppress incoming redundant information. We have expanded on these findings by showing that the cortical thickness within the area of the cortex generating this response is reduced in adults with CP and is directly associated with the strength of the somatosensory cortical activity. This indicates that adults with CP likely have decreased cell number and synaptic density within their somatosensory cortices, likely stemming from abnormal development of the somatosensory system or perhaps an accelerated aging effect, which ultimately contributes to their clinical sensorimotor impairments of the upper extremities.

CHAPTER 4: MICROSTRUCTURAL CHANGES WITHIN THE SPINAL CORD OF ADULTS WITH CEREBRAL PALSY

Introduction

Cerebral palsy (CP) consists of a general class of movement disorders that result from an insult to the developing brain [125]. A substantial portion of these individuals have a life expectancy of at least 58 years [258], indicating that many individuals in this population survive well into late adulthood. Lack of participation in activities, weight gain, fatigue, and accelerated sarcopenia each contribute to progressive deterioration of the musculoskeletal system that occurs throughout the lifespan in CP [14,13]. Such deterioration is presumed to impact the ability to perform upper extremity tasks of daily living (i.e., buttoning shirt, brushing teeth), as completing such tasks often becomes progressively more difficult with age [9]. Despite these recognized functional declines, there is an incredible lack of specialized treatments for adults with CP [213]. This lack of treatments at least partially exists because we have limited insight on the neuronal changes seen in the aging CP population.

Previous transcranial magnetic stimulation (TMS) studies have established that the perinatal brain insults that occur in persons with CP can induce activity-dependent neuroplastic changes. When a unilateral brain insult occurs, the ipsilateral hemisphere may assume control of the affected side of the body [53]. Essentially, the paretic hand may become either partially, or fully, controlled by corticospinal tract projections from the ipsilateral motor cortex. The likelihood of this occurring is often dependent on the timing of the insult and size of the lesion in the developing brain. Smaller lesions are less likely to result in corticospinal tract reorganization, and intermediate lesions result in partial reorganization where the paretic limb is controlled by both the contralateral and ipsilateral hemisphere. Alternatively, large lesions are the most likely to lead to complete reorganization, where the paretic limb is completely controlled by ipsilateral connections. While the motor cortex is susceptible to reorganization, the ascending somatosensory tracts do not appear

to reorganize [259,207]. This creates a dissociation between the motor and somatosensory cortices, such that the somatosensory information is being processed in a different hemisphere than the hemisphere controlling movement for the paretic limb. This dissociation likely helps to explain why the amount of reorganization present within the motor cortex has consistently been associated with increased sensorimotor impairments [53].

Numerous animal studies have expanded on these findings by demonstrating that changes in brain activity can also result in alterations within the structure of the spinal cord. For example, the outcomes from several animal models have shown that inactivation of one hemisphere can result in the corticospinal neurons terminating more dorsally in the spinal cord gray matter, potentially leading to competition for the dorsal horn real-estate where the sensory neurons typically reside [55,56]. Thus, the structural integrity of the spinal interneuronal pool is partly dependent upon cortical activity and the integrity of the corticospinal tracts. Despite these novel insights, the translation of the outcomes from these animal models to what is seen in humans with CP is largely lacking.

No studies to date have examined the microstructural changes within the spinal cord of individuals with CP. The lack of this information also creates difficulties in interpreting functional brain imaging results, as little is known about the integrity of the fibers connecting the brain to the body in this population. The objective of the current investigation was to begin to address this knowledge gap by using high-resolution MRI to quantify the potential spinal cord microstructural differences between adults with CP and a cohort of healthy controls Specifically, we aimed to assess the gray and white matter cross sectional area (CSA), the fractional anisotropy (FA), and the magnetization transfer ratio (MTR) within the upper spinal cord. Analysis of the white and gray matter CSA can provide information regarding the total number of cell bodies and myelination within the spinal cord. FA describes the movement of water molecules, in which a value of zero represents isotropic diffusion and a value of one indicates complete anisotropic movement. FA tends to be higher in regions of greater uniformity (i.e., fiber bundles) and lower in regions in which

there is no specific orientation of cell shape or diffusion.[260] Therefore, it is a viable outcome measure that can be used to assess the integrity and overall uniformity of the descending and ascending sensorimotor tracts[163].

MTR is a measurement that can be used as an accessory to MR angiography or to improve gadolinium enhancement from T1-weighted scans, and it can also be used in conjunction with T2-weighted images in order to assess the potential gray matter damage and loss of myelination persistent in the spinal cord. Briefly, there is a bound pool and a free pool of hydrogen nuclei that are involved in the generation of MR signal. The bound pool has extremely short relaxation times that are not normally detectable by standard MRI. However, applying a magnetization transfer pulse that selectively saturates protons in the bound pool results in energy transfer and saturation of the free pool. Subsequently, when a radiofrequency pulse is applied, the measured signal from the free pool will be lower due to the partial saturation[261]. Thus, depending on the macromolecular composition of the tissue, the signal will be more or less affected by a magnetization transfer pulse, allowing for inferences to be made regarding the underlying microstructure. For example, extensive gray matter damage and significant demyelination has been associated with a lower MTR[262,263]. Previously, MTR in the spinal cord has also been associated with the degree of sensorimotor impairments in patients with spinal cord injury [264] and clinical outcomes after surgical interventions in patients with degenerative cervical myelopathy.[265] Assessing how these various microstructural outcome measures may be altered in adults with CP can provide insight into the neurophysiological origins of the upper extremity impairments seen in this population.

Methods

A cohort of adults with CP that had a spastic diplegic or quadriplegic presentation (N = 13; Age = 31.93 ± 8.61 yrs; Females = 8, Manual Ability Classification System levels I - III) and healthy adult controls (N = 16; Age = 31.32 ± 9.79 yrs, Females = 7) completed this study. Further

details on the individuals with CP are presented in Table 1. The participants with CP had not undergone upper extremity surgeries, had not had botulinum toxin injections in the past year, and were not on anti-spastic medications. The Institutional Review Board, a research ethical review committee, at the University of Nebraska Medical Center reviewed and approved this investigation. Informed consent was acquired from all of the adult participants.

MRI Acquisition & Data Processing

Cervical-thoracic spinal cord MRI scans were acquired with a Siemens Prisma 3T scanner. High-resolution T1-weighted axial MPRAGE images were obtained with a 64-channel head/neck coil (voxel size = 1.0 mm x 1.0 mm x 1.0 mm; TR/TE 2000/ 3.72 ms; flip angle = 9 deg; FOV: 320 mm X 320 mm; slice thickness: 1 mm slice; slices = 192, scan time = 56 s).T2 weighted images were collected across C1-T6 (voxel size = 0.8 mm x 0.8 mm x 0.8 mm, slices= 64, TR/TE= 1500/120 ms, flip angle= 120 degrees, and FOV= 256 mm x 256 mm, scan time = 240 s). Gradient recalled echo (GRE) T2* images were collected across C6 – T3 (voxel size = 0.5 mm x 0.5 mm x 5.0 mm, slices = 15, TR/TE = 600/14 ms, flip angle = 30 deg, and FOV = 224 mm x 224 mm, scan time = 283 s). Diffusion weighted images (DWI) were collected across C6-T3 (voxel size = 0.4 mm x 0.4 mm x 5.0 mm; slices = 15, TR/TE = 610/60 ms, b-values = 0 s/mm^2, 100 s/mm^2, 30 non-collinear gradient directions, scan time = 122 s). Magnetization transfer (MT) scans were also collected across C6-T3 (voxel size = 0.9 mm x 0.9 mm x 5.0 mm; slices = 22, TR/TE = 35/3.13 ms, flip angle = 9 deg, and FOV = 230 mm x 230 mm, scan time = 130 s) using a vendor-equipped saturation pulse.

The partially automated Spinal Cord Toolbox (version 3.2.2) was subsequently used for spinal cord and gray and white matter segmentation, vertebral labeling, cross-sectional measurement, and template registration of the spinal tracts [266]. After vertebral labeling, the spinal cord was initially straightened, as described in De Leener, 2017[267] , which was then followed by

inferior-superior affine alignment which was based on vertebral levels. The spinal cord centerline was then aligned between the template and the subject using the center of mass of the spinal cord segmentation, which was then followed by a non-linear within-plane BSplineSyN registration[268]. The spinal cord internal structure was accounted for by assuming a linear deformation based on the outer shape of the spinal cord.

The total CSA across C6 – T3 was extracted from the T2 images and the T2* was used for gray and white matter extraction. In order to determine the relative proportion of gray and white matter, these values were normalized to the total spinal cord CSA. The PAM50 template was registered to the diffusion-weighted images and MT images after motion correction, and the diffusion tensors for the respective spinal cord tracts were calculated. The FA values from the left and right corticospinal and cuneatus tracts were subsequently calculated from the DWI. The MTR of the corticospinal tract and cuneatus tracts were additionally calculated from the MT scans.

Lastly, each participant completed the box and block clinical test of hand dexterity[269]. For this test, the participant was instructed to move as many blocks as possible from one compartment to another in a 60 second time period. We assessed whether the number of blocks moved was correlated with the respective spinal cord outcome measures.

Statistical Methods

The respective outcome measures were tested for normality using the Shapiro-Wilkes test, and the data that were not normally distributed were log transformed before further analysis. In order to test for equality of variance between samples, the Levene's test was used. When the samples did not have equal variances, the Welch's t-test was used to compare outcome measures between groups. When the samples did have equal variances, the Student's t-test was used to compare outcome measures between groups. We also ran Pearson Product-Moment Correlation analyses to assess whether the amount of gray matter, white matter, FA, or MTR measures were associated with each other. All results are presented as mean plus/minus the standard deviation.

JASP was used for statistical analysis (JASP Team (2020). JASP (Version 0.12.2.0)[Computer software]).

Results

An independent samples t-test revealed that the adults with CP and healthy controls did not differ by age ($p = 0.860$). Outcome measures were successfully extracted for all 13 adults with CP and 16 healthy adult control participants that completed the study. Figure 8 shows exemplary images from the processing pipeline where the spinal cord was segmented (Figure 8A) and the grey and white matter in the respective segments was parcellated (Figure 8B). The results indicated that the total CSA of the C6-T3 portion of the spinal cord was smaller in the adults with CP compared with the controls (CP = 66.22 ± 8.60 mm^2, 95% CI [61.55, 70.89]; Controls = 76.75 ± 8.77 mm^2, 95% CI [72.45, 81.05], $p = 0.002$, Figure 8C). In addition, the gray matter CSA (CP = 9.42 ± 1.41 mm^2, 95% CI [8.62, 10.22]; Controls = 12.22 ± 1.29 mm^2, 95% CI [11.59, 12.85], $p < 0.001$, Figure 1D) and white matter CSA (CP = 61.93 ± 8.81 mm^2; 95% CI [57.14, 66.72]; Controls = 69.27 ± 8.59 mm^2, 95% CI [65.06, 73.48], $p = 0.032$, Figure 8E) were also significantly lower in individuals with CP. When normalized to the total spinal cord CSA, the gray matter remained smaller in the adults with CP relative to the controls (CP = 14.2 ± 1.9%, 95% CI [13.13, 15.28]; TD = 16.2 ± 2.7%, 95% CI [14.88, 17.52], $p = 0.041$), but the white matter no longer differed between the respective groups (CP = 93.7 ± 8.4%, 95% CI [89.13, 98.27]; TD = 90.2 ± 4.6%, 95% CI [87.95, 92.45], $p = 0.208$).

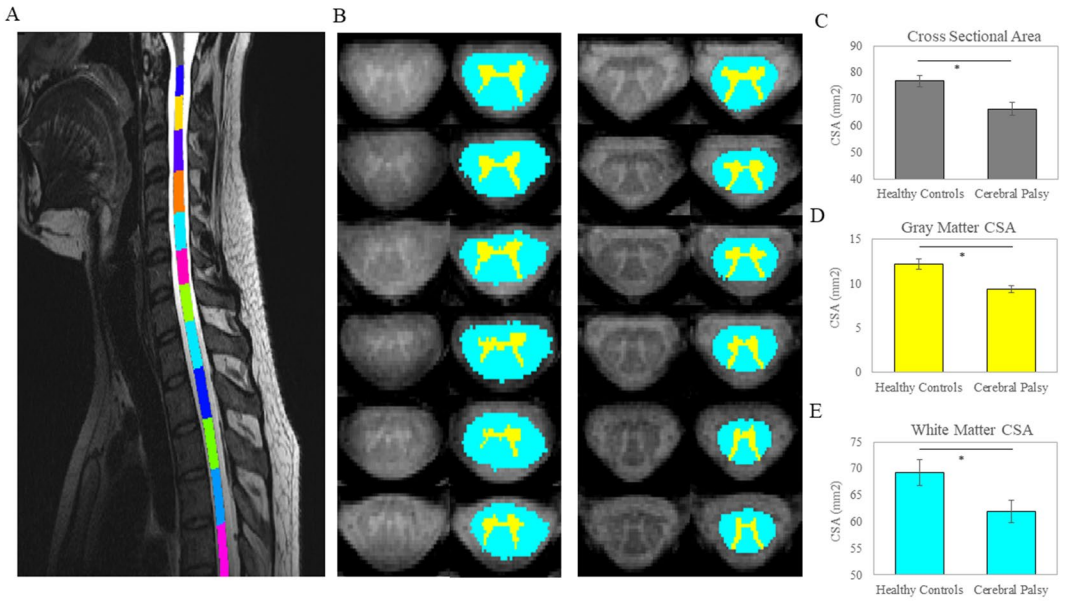

Figure 8: Microstructural Changes within the Spinal Cord of Adults with Cerebral Palsy A) The sagittal view of the cervical-thoracic spinal cord segmentation for a single representative adult with cerebral palsy, B.) Parcellations of the cross sectional area (CSA) from C6 to T3 for a representative adult participant with cerebral palsy (left) and healthy adult control (right). The aqua represents white matter while the yellow represents gray matter. C) Average spinal cord CSA for the adults with cerebral palsy and healthy adult controls. The CSA was significantly less for the adults with cerebral palsy. D) Average gray matter CSA for the adults with cerebral palsy and healthy adult controls. As shown, the CSA was significantly less for the adults with cerebral palsy. E) Average white matter CSA for the adults with cerebral palsy and controls. The white matter CSA was also significantly less for the adults with cerebral palsy. Bar graphs represent the mean $\pm$ the standard error of the mean. *$P \leq 0.05$.

Figure 9A and 9B display an FA map and MTR scan, respectively, from representative subjects. The MTR was significantly lower in the corticospinal tracts in the adults with CP (CP = 42.61 ± 5.69%, 95% CI [39.52, 45.70]; Controls = 46.64 ± 3.18%, 95% CI [45.082, 48.20], p = 0.023; Figure 10A), but not in the cuneatus tracts (CP = 46.71 ± 6.73%, 95% CI [43.05, 50.37]; Controls = 47.09 ± 3.34%, 95% CI [45.45, 48.73], p = 0.712). The FA values were not significantly different between groups in either the corticospinal (CP = 0.63 ± 0.09, 95% CI [0.58, 0.68]; TD = 0.66 ± 0.06, 95% CI [0.63, 0.69], p = 0.207) or cuneatus tracts (CP = 0.65 ± 0.07, 95% CI [0.61, 0.69]; TD = 0.66 ± 0.08, 95% CI [0.62, 0.70], p = 0.800). We found a moderate positive correlation between the MTR in the corticospinal tracts and gray matter CSA across all participants (r = 0.42, p = 0.027, Figure 10B). This correlation implies that participants who had less gray matter also tended to have lower MTR values. We also found a positive correlation between the box and block

clinical test and the gray matter CSA ($r = 0.53$, $p = 0.004$; Figure 10C), as well as the total CSA ($r = 0.40$, $p = 0.031$), indicating that the individuals that moved more blocks tended to have more gray matter and total CSA within their upper spinal cord. No other correlations between outcome measures were significant (p's > 0.05).

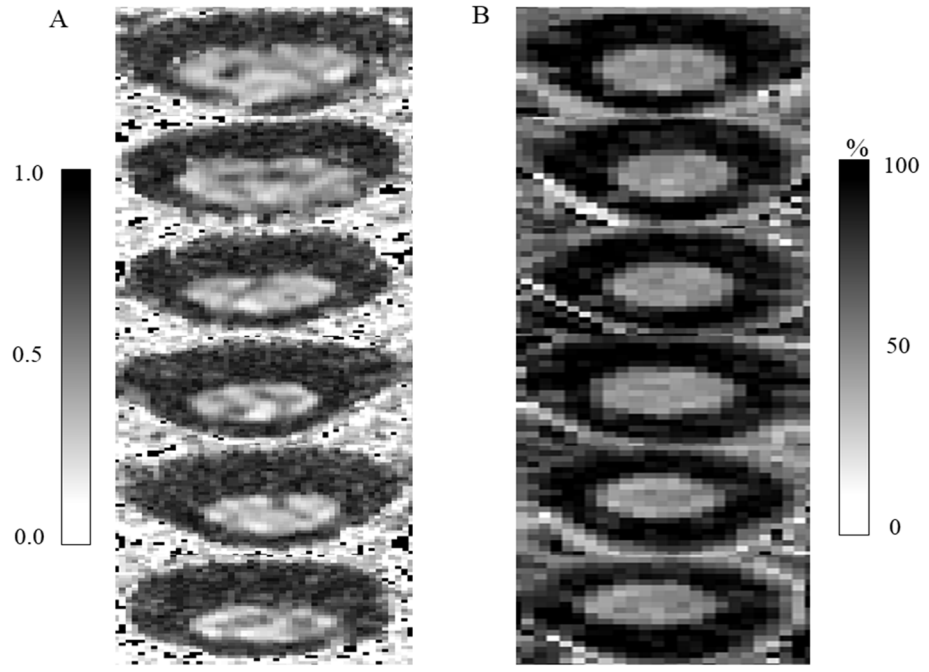

Figure 9: Fractional Anisotropy and Magnetization Transfer Images Ratio A.) Example fractional anisotropy (FA) map from a representative subject. B) Example magnetic transfer ratio (MTR) images from a representative subject. The two images are from unique subjects.

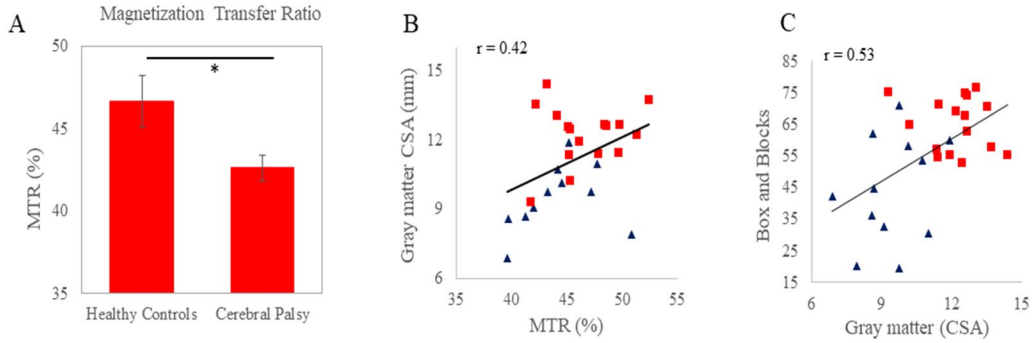

Figure 10: Spinal Cord Microstructure Correlates with Motor Functioning A) The magnetic transfer ratio (MTR) in the corticospinal tracts for the adults with cerebral palsy and healthy adult controls. The adults with cerebral palsy had significantly lower MTR in the corticospinal tracts, suggesting greater microstructural disruptions. B) Scatter plot depicting the positive relationship between the corticospinal tract MTR and gray matter cross sectional area (CSA). Adults with CP are depicted with blue triangles, and the healthy adult controls are depicted with red squares. Less gray matter was associated with a reduction in the corticospinal tract MTR, suggesting that participants with less grey matter CSA tended to have greater damage to the corticospinal tract microstructure. $*P \leq 0.05$. C) Scatter plot depicting the relationship between the gray matter CSA and box and block test scores. More gray matter was associated with improved hand dexterity.

Discussion

We used high-resolution MRI to image the cervical-thoracic spinal cord (C6-T3) in order to quantify the microstructural differences between adults with CP and a cohort of controls. Our results revealed that the spinal cord CSA was smaller in those with CP, including specific CSA reductions in both white and gray matter. The spinal cord CSA and gray matter CSA were each associated with improved clinical scores of hand dexterity. Furthermore, the relative proportion of gray matter within the spinal cord was also notably less in the adults with CP. Our imaging approach also indicated that the MTR of the corticospinal tracts was lower in adults with CP, which suggests that there were greater microstructural disruptions. Further discussion of the implications of these results are detailed in the following sections.

The spinal cord CSA was notably smaller in the adults with CP, and our normalization analysis suggested that this reduction was primarily due to a reduction in the gray matter, which indicates that those with CP likely have fewer neural cell bodies within the spinal cord. This gray

matter reduction likely reflects a reduction in GABAergic interneuronal network activity within the spinal cord. As GABAergic interneuronal cells are reciprocally connected with glutamatergic cells[76,270], this would lead to heightened glutamatergic activity and ultimately increased spinal cord excitability, which has often been reported in individuals with CP based on assessments of the Hoffmann reflex [192].

Alternatively, the decrease in gray matter may partially be a result of activity-dependent competition and reorganization within the spinal cord. Using an animal model, Friel et al. (2007) demonstrated that inactivation of one hemisphere of the brain early in development can result in structural changes within the spinal cord. Specifically, the non-affected hemisphere may assume control over the paretic limb, and the descending motor tract terminations shift towards occupying the real-estate of the dorsal horn of the spinal cord [55,56]. Thus, an insult to the developing brain can result in the motor tracts terminating in areas that are normally occupied by the sensory neurons. In turn, this may result in activity-dependent competition for space in the dorsal horn of the spinal cord that leads to an overall pruning of corticospinal and sensory neurons. In either case, we suggest that the reduction in gray matter may also be a result of the activity-dependent plastic changes that occur as a downstream effect from the insult to the developing brain. This may ultimately contribute to sensorimotor impairments, which is supported by the observation that the individuals that had lower box and block test scores tended to have decreased gray matter.

Although the total white matter CSA differed between groups, the proportion of the white matter that comprised the spinal cord CSA was not different. However, the MTR of the corticospinal tracts was notably less in the adults with CP. This implies that there are likely microstructural disruptions that could affect the transmission of the descending motor signals between the brain and the spinal cord interneurons. In addition, participants that had a reduction in the spinal cord gray matter also tended to have diminished MTR values for the corticospinal tracts. These results further support the notion that disruptions in the fidelity of the corticospinal tract signals may influence their spinal cord terminations and ultimately the organization of the spinal

cord interneurons [55]. In other patient populations, a decreased MTR has been associated with inflammation and the extent of gray matter lesions [271]. Hence, it is alternatively plausible that the lower MTR values seen in our adults with CP might reflect similar underlying pathophysiology, as it is well recognized that CP can be associated with chronic inflammatory responses in the CNS, which are associated with neural cell apoptosis [272].

Despite our novel findings, this study had several limitations. Our cohort consisted only of adults with spastic diplegic or quadriplegic CP, making it difficult to draw conclusions about how these findings may extend to children or other types of CP. Even with the novel information DTI can provide regarding the integrity and organization of the spinal cord, several limitations on its use within the spinal cord exist. Firstly, the signal to noise ratio (SNR) decreases when imaging further down the cord, likely due to the morphology of the body and geometry of the surface coil[273]. This may lead to an overestimation of the FA values in areas in which the SNR is lower, resulting in lower FA values further down the spine. Additionally, FA values differ greatly between gray and white matter, indicating that populations with reduced gray matter may have altered FA values as a result of volume differences. In our study, there were differences in gray and white matter distribution within the upper spinal cord, which could potentially alter the FA values. MTR comes with several limitations as well. MTR scans are generally susceptible to motion error, and they can have high variability depending on the properties of the MT pulse (*i.e.*, the shape, bandwidth, frequency offset).

In conclusion, our results are the first to identify microstructural changes in the spinal cord of adults with CP. The CSA of the spinal cord and proportion of the gray matter were markedly reduced, and this was related to reduced hand dexterity. Additionally, the MTR implied that there were notable disruptions in the fidelity of the corticospinal tracts, and these were directly linked to the gray matter structural changes. Based on previous animal literature and H-reflex/TMS studies in humans [55,56,192], we suspect that the initial insult to the developing brain induces long-lasting

downstream effects in the spinal cord microstructure. Ultimately, the disrupted spinal cord microstructure likely plays a prominent role in the sensorimotor deficits and spasticity seen in adults with CP.

Table 1: Demographics of adults with cerebral palsy

Subject age (years)	Sex	MACS	Type	Assistive mobility
47.5	F	1	Spastic Diplegic	None
37.5	F	1	Spastic Diplegic	None
20.7	F	2	Spastic Diplegic	Forearm crutches
35.9	F	2	Spastic Diplegic	Forearm crutches
35.4	M	3	Spastic Quadriplegic	Powered chair
27.8	F	2	Spastic Quadriplegic	Walker
20.9	M	1	Spastic Diplegic	None
31.8	M	1	Spastic Diplegic	None
35.8	M	1	Spastic Quadriplegic	Wheelchair
21.2	M	1	Spastic Diplegic	None
43.3	F	2	Spastic Diplegic	None
33.2	F	1	Spastic Diplegic	None
24.2	F	2	Spastic Diplegic	Wheelchair

CHAPTER 5: SPINAL CORD MICROSTRUCTURAL CHANGES ARE CONNECTED WITH THE ABERRANT SENSORIMOTOR CORTICAL OSCILLATORY ACTIVITY IN ADULTS WITH CEREBRAL PALSY

Introduction

Cerebral Palsy (CP) refers to a group of movement disorders that are a result of an insult to the developing brain[125]. The disorder is primarily characterized by musculoskeletal impairments, although recent literature has identified that deficits of sensation and perception are an integral component to the disorder [6,2,4,152,153]. While CP is not considered a neurologically progressive disorder, accelerated sarcopenia, weight gain, sedentary lifestyles, and balance deficits result in a progressive deterioration of the musculoskeletal system[274,9,10,213,275,12,14,13]. This progressive decline may result in increased difficulty in performing upper extremity tasks of daily living (brushing teeth, buttoning shirt)[9]. Although a wide breadth of occupational therapeutic approaches have been employed to improve the hand motor actions of individuals with CP, there are very few approaches that are considered to be "green light" therapies [210]. Potentially, the underlying issue stems from a lack of understanding of the neurophysiological components that contribute to the altered upper extremity motor actions of individuals with CP.

Previous neuroimaging studies have well established that there are stage-dependent changes in the strength of the sensorimotor cortical oscillatory activity within the beta (15-30 Hz) and gamma bands (>30 Hz) when planning and executing a hand motor action. Prior to movement onset, there is a decrease in power in the beta band which is sustained throughout the movement duration[15-19]. The beta event-related desynchronization (ERD) that occurs prior to movement onset is linked with movement planning, begins earlier for easier movements, and its strength is related to the certainty of the motor action to be completed [19-29]. After movement completion, there is an increase in the beta power, termed the post movement beta rebound (PMBR)[15,17,21-24,18,19], which is

thought to reflect either afferent feedback to the motor cortices [30,31], active inhibition of cortical networks after movement termination [32-34], or confidence in the motor actions executed based on the internal model[35,36]. The gamma event-related synchronization (ERS) is closely yoked with movement onset and is transiently sustained for less than 200 ms[37-39,19]. Historically, the gamma ERS has been perceived to be involved with the initialization and execution of a motor command[37,78,17,67,79]. However, more recent studies have also linked changes in the strength of the gamma ERS with the motor response certainty and cognitive response selection interference [20,276-278]Altogether these seminal neurophysiological studies have highlighted that the changes seen in the strength of the beta and gamma cortical oscillations are well connected with the cognitive-motor decisions.

Prior investigation have shown that the strength of the beta and gamma sensorimotor cortical oscillations are altered in in youth with CP. Specifically, several investigations have reported that the beta ERD within the primary motor cortex, the premotor cortex, and the supplementary motor area is stronger in youth with CP in comparison to age-matched controls while performing a leg motor action[41,40,279]. Furthermore, the gamma ERS has been reported to be weaker in youth with CP during a lower extremity task. Fewer studies have evaluated if these altered cortical oscillations are also seen in the hand motor actions performed by youth with CP. The only study to date has identified that the strength of the PMBR and gamma ERS in the motor hand knob region of the sensorimotor cortices were weaker when youth with CP performed an arrow-based version of the Eriksen flanker task[42]. Although these investigations have advanced our understanding of the impact that the early brain insult has on the sensorimotor cortical oscillations, we still have a substantial knowledge gap in our understanding of these cortical oscillations in adults with CP despite the overwhelming clinical impression that there can be a decline in the hand motor function throughout adulthood.

While an understanding of the underlying cortical activity that contributes to the altered hand motor actions is imperative, recent fMRI results have demonstrated that the fidelity of the

hand motor actions are dependent upon the coherence activity between the cortex and the spinal cord [280]. Thus, the spinal cord also likely plays a prominent role in the uncharacteristic hand motor actions seen in individuals with CP. Using an animal model, Friel and colleagues (2007) demonstrated that inactivation of one hemisphere of the brain early in development can result in structural changes within the spinal cord. Specifically, the non-affected hemisphere may assume control over the paretic limb, and the descending motor tract terminations shift towards occupying the real-estate of the dorsal horn of the spinal cord[55,56]. Thus, an insult to the developing brain can result in the motor tracts terminating in areas that are normally occupied by the sensory neurons. In turn, this may result in activity-dependent competition for space in the dorsal horn of the spinal cord that leads to an overall pruning of corticospinal and sensory neurons. Our recent structural imaging results have follow-up on this premise by showing that the cross-sectional area (CSA) of the spinal cord and proportion of the gray matter are markedly reduced in adults with CP, and that these structural changes are connected with the reduced hand dexterity[281]. Based on the prior work of Friel et al. (2007), we suspect that these microstructural changes are partially linked with the altered cortical activity seen in individuals with CP. However, this conjecture has yet to be tested.

We sought to address these knowledge gaps by using a multimodal neuroimaging approach. We utilized the high temporal and spatial resolution of MEG to investigate the motor-related oscillations associated with the arrow-based version of the Eriksen Flanker task. This cognitive-motor task was chosen as prior studies have demonstrated that it's associated with robust beta and gamma oscillatory activity[42,276]. Secondarily, we utilized MRI to investigate how the spinal cord microstructure may be connected with the extent of the sensorimotor cortical activity. Based on the prior literature, we hypothesized that the beta ERD, PMBR, and gamma ERS would each be altered in the adults with CP in comparison to their adult peers. Secondarily, we hypothesized that the fidelity of the spinal cord microstructure would be connected with the altered sensorimotor cortical oscillatory activity.

Methods

Participants

Fourteen adults with CP (Age = 33.1 ± 8.6 years, Range = 20 – 47 yrs, MACS = I – III, Females = 8) and sixteen healthy controls (Age = 33.3 ± 9.8 yrs, Range = 19 – 49 yrs, Females = 9) participated in the experimental investigation. The participants with CP had Manual Ability Classification System (MACS) levels between I-III. MACS level of I indicates that the participant can easily handle objects, while a MACS level of III indicates that has difficulty handling object and requires some assistance. None of the participants had a prior history of epilepsy or seizure activity. Participants were excluded according to MEG/MRI exclusionary criteria such as metal implants, dental braces or permanent retainers, or other metallic or otherwise magnetic non-removable devices. Each participant provided written consent to participate in the investigation. The protocol for this investigation was approved by the Institutional Review Board and in compliance with the Code of Ethics of the World Medical Association.

Experimental Paradigm

During MEG recording, participants were seated in a nonmagnetic chair within the magnetically-shielded room with their right hand positioned on a custom-made five-finger button pad. Each button press sent a unique signal (i.e., TTL pulse/trigger code) to the MEG acquisition computer, and thus behavioral responses were temporally synced with the MEG data. The participants completed an arrow-based version of the Eriksen flanker task[282]. Each trial began with a fixation cross that was presented for an interval of 1500 ± 50 ms. A row of five arrows was then presented for 2500 ms and the participants were instructed to respond about the direction of the middle target arrow with their second (left arrow) or third (right arrow) digit of the right hand using a custom 5-button pad (Figure 11). Visual presentation consisted of either a series of flanking arrows that had directions that were congruent (*i.e.,* same direction) or incongruent (*i.e.,* opposite

direction) of the middle target arrow. The task stimuli were visually projected onto a screen that was approximately one meter from the participant. A total of 200 trials were presented, making the overall MEG recording time about 14 minutes. Trials were equally split and pseudo-randomized between congruent and incongruent conditions, with left and right pointing arrows being equally represented in each condition. Only correct responses were included for further analysis.

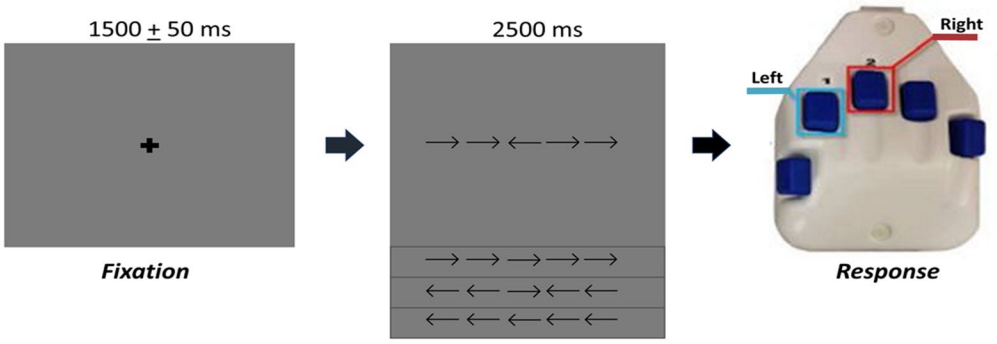

Figure 11: Flanker Task Design For each trial, the adults fixated on a crosshair for 1500 ± 50 ms, then a display with a series of five arrows appeared for 2500 ms. Upon arrows appearing, the children responded with their right hand regarding the center arrow pointing to the left (2nd digit) or right (3rd digit). In the congruent condition, the flanking arrows pointed in the same direction as the middle arrow. In the incongruent condition, the flanking arrows pointed in the opposite direction than the middle arrow.

MEG Acquisition Parameters and Coregistration with MRI

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1–330 Hz using an Elekta MEG system with 306 magnetic sensors (Elekta, Helsinki, Finland). Using MaxFilter (v2.2; Elekta), MEG data from each subject were individually corrected for head motion and subjected to noise reduction using the signal space separation method with a temporal extension [283,216].

Prior to starting the MEG experiment, four coils were attached to the subject's head and localized, together with the three fiducial points and scalp surface, with a 3-D digitizer (Fastrak

3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the subject was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the coils. This induced a measurable magnetic field and allowed for each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system, each participant's MEG data were coregistered with structural T1-weighted MRI data prior to source space analyses using BESA MRI (Version 2.0). Structural T1-weighted MRI images were acquired using a Siemens Prisma 3-Tesla MRI scanner with a 64-channel head/neck coil and a sequence with the following parameters: TR = 2400 ms; TE = 1.96 ms; flip angle = 8°; FOV = 256 mm; slice thickness = 1 mm (no gap); voxel size = 1 x 1 x 1 mm. These data were aligned in parallel to the anterior and posterior commissures and transformed into standardized space. Each participant's 4.0 x 4.0 x 4.0 mm MEG functional images were transformed into standardized space using the transform that was previously applied to the structural MRI volume and spatially resampled.

MEG Time-Frequency Transformation and Statistics

Cardiac artifacts were removed from the data using signal-space projection (SSP), which was accounted for during source reconstruction [64]. The continuous magnetic time series was divided into epochs of 4000 ms duration from -2000ms to 2000ms, with the baseline being defined as -1600 to -800 ms and 0.0 ms being movement onset (i.e., button press). Epochs containing artifacts (e.g., eye blinks, muscle artifacts, etc.) were rejected based on a fixed-threshold method using individual amplitude and gradient thresholds, supplemented with visual inspection. The number of trials used were neither significantly different between group nor condition (Ps > 0.05).

Artifact-free epochs were transformed into the time-frequency domain using complex demodulation, and the resulting spectral power estimations per sensor were averaged over trials to

generate time-frequency plots of mean spectral density. These sensor-level data were normalized using the respective bin's baseline power, which was calculated as the mean power during the –1600 to -800 ms time period. The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point and the output spectrogram of t-values was thresholded at $P < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations relative to baseline across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the ($P < 0.05$) threshold, and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values, and the significance level of the observed clusters (from stage one) were tested directly using this distribution [217,284]. For each comparison, at least 1,000 permutations were computed to build a distribution of cluster values. Based on these analyses, the time-frequency windows that corresponded to events of a priori interest (i.e., the beta ERD and PMBR) and contained significant oscillatory events across all participants were subjected to the beamforming analysis.

MEG Imaging & Statistics

Cortical networks were imaged using an extension of the dynamical imaging of coherent sources (DICS) beamformer [285,286], which employs spatial filters in the frequency domain to calculate source power for the entire brain volume. The single images were derived from the cross-spectral densities of all combinations of MEG gradiometers averaged over the time-frequency range of interest, and the solution of the forward problem for each location on a grid specified by

input voxel space. Following convention, we computed noise-normalized, source power per voxel in each participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth [285,287]. Such images are typically referred to as pseudo-*t* maps, with units (pseudo-*t*) that reflect noise-normalized power differences (i.e., active vs. passive) per voxel. MEG pre-processing and imaging used the Brain Electrical Source Analysis (BESA version 6.1) software.

Normalized differential source power was computed for the statistically-selected time-frequency bands (see below) over the entire brain volume per participant at 4.0 x 4.0 x 4.0 mm resolution. The resulting 3D maps of brain activity were averaged across participants to assess the neuroanatomical basis of significant oscillatory responses identified through the sensor-level analysis. We then extracted virtual sensors (i.e., voxel time series) for the peak voxel of each oscillatory response. To compute the virtual sensors, we applied the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series corresponding to the location of interest. Note that this virtual sensor extraction was done per participant, once the coordinates of interest (i.e., one per cluster) were known. Once these virtual sensors were extracted, the magnitude of the beta ERD, PMBR, and gamma ERS were calculated as the minimum (for the beta ERD) and maximum (for the PMBR and gamma ERS) amplitude within the target period of interest.

Motor Behavioral Data

The output of the button pad was simultaneously collected at 1 kHz along with the MEG data. Accuracy was defined as the number of correct responses divided by the total number of trials. The time the participant took to decide the direction of the target arrow (*i.e.*, reaction time) was calculated based on the time from when the arrow array was presented to when the button was pressed.

Spinal Cord MRI Processing

A portion of this investigation follows up on the original MRI spinal cord project that was published previously [281]. In brevity, cervical-thoracic spinal cord MRI scans were acquired with a Siemens Prisma 3T scanner equipped with a 64-channel head/neck coil. The calculated total CSA across C6 – T3 was extracted from the T2 images and the T2* was used for gray and white matter extraction. Furthermore, the PAM50 template was registered to the diffusion-weighted images and MT images after motion correction, and the diffusion tensors for the respective spinal cord tracts were calculated. As the task was performed with the right hand, the fractional anisotropy (FA) and magnetization transfer ratio (MTR) values from the right CST and cuneatus tracts were subsequently calculated from the DWI. These respective values were used to evaluate the relationship between the strength of the cortical oscillations and the integrity of the spinal cord structure. Complete details of the spinal cord imaging acquisition parameters and processing pipelines detailed in Trevarrow et al. (2021).

Statistical Analysis

We performed 2 x 2 x 2 mixed model ANOVAs with condition (congruent and incongruent) as a within subjects factor, group (CP and HC) as a between subjects factor, and sex (male and female) as a between subjects factor in order to determine group, condition, and sex differences and interactions with respect to the reaction times and accuracy within the task. Sex was included as an exploratory variable in the model since CP has been reported to be more common in males than females[288]. For the motor related-oscillatory activity, we utilized 2 x 2 x 2 ANOVAs with condition (congruent and incongruent) as a within subjects factor, group (CP and HC) as a between subjects factor, and sex (male and female) as a between subjects factor in order to determine any group, condition, or sex effects and interactions with respect to the motor-related oscillatory activity. Lastly, Pearson correlations were used to determine the relationship between

the behavioral data and strength of the beta responses, as well as the spinal cord structural MRI measures and the MEG/behavioral measures. All statistical analyses were conducted at a 0.05 alpha level.

Results

Behavioral Results

There was a main effect of condition, consistent with the well-established "flanker effect" which indicated that the accuracy was higher in the congruent condition in comparison to the incongruent condition (congruent = 97.2 ± 1.1%, incongruent = 96.2 ± 1.3%, P = 0.009). There was also a main effect of group indicating that the controls were more accurate than the adults with CP (CP = 93.5 ± 2.2%, NC = 99.4 ± 0.2%, P = 0.002). There was also a main effect of sex (Males = 94.27 ± 2.47%, Females = 98.53 ± 0.50%, P = 0.019), indicating that females were more accurate than males. There was an interaction between group and condition (P = 0.010). Post hoc analysis revealed that the individuals with CP had reduced accuracy for the incongruent condition compared with the congruent condition (Congruent = 94.64 ± 2.12%, Incongruent = 92.43 ± 2.33%, P = 0.004). This was not the case for the controls (Congruent = 99.44 ± 0.32%, Incongruent = 99.44 ± 0.18%, P = 1.00). Finally, there was a significant interaction between sex and group, in which the males with CP had decreased accuracy in comparison to the females with CP (Males with CP= 88.67 ± 4.44%, Females with CP = 97.19 ± 0.85, P = 0.019), but control males did not have different accuracy than control females (NC Males = 99.07 ± 0.44%, NC Females = 99.72 ± 0.12%,P = 0.994).

For the reaction time data, there was a main effect of condition, again indicative of a flanker effect in which the reaction time was faster in the congruent condition in comparison to the incongruent condition (congruent = 597.4 ± 38.8 ms, incongruent = 653.0 ± 38.4 ms, P < 0.001). There was also a main effect of group indicating that the controls had faster reaction times than the

adults with CP (CP = 754.4 ± 64.1 ms, NC = 512.2 ± 21.5 ms, P < 0.001). However, there was no significant main effect of sex, and there were no interactions between the variables (P's > 0.05).

Sensor-level and Beamforming Analyses

Since only correct trials were used in the analysis, and the adults with CP had significantly fewer correct responses, trials were randomly removed from the controls to achieve similar signal-to-noise ratios between the groups. This was accomplished by randomly rejecting trials (i.e., sections of the raw data) in the control group to ensure that the total number of trials included in the final MEG analysis did not statistically differ between groups. The resulting number of trials per participant did not significantly differ between groups (CP = 172.43 ± 4.70, TD = 175.94 ± 1.65; $P = 0.478$).

Analysis of the sensor spectrograms collapsed across all participants and conditions for the correct response revealed that there was a significant beta (18 – 26Hz) ERD (i.e., power decrease) across a range of sensors that covered the sensorimotor cortices, and that this response lasted from about -300 to 300 ms (p < 0.0001, corrected). There also was a significant PMBR (16-22Hz; i.e., power increase) that occurred from 500 to 800 ms (P < 0.0001, corrected). Finally, there was a significant gamma ERS (68 – 82Hz) that occurred from -100 to 100 ms (P < 0.0001; Figure 12A and 12B). To identify the brain regions generating the responses noted in the sensor analysis, a beamformer was applied to each participant's responses using the time-frequency windows identified in the sensor-level analyses and an equal time-frequency window from the pre-stimulus baseline period.

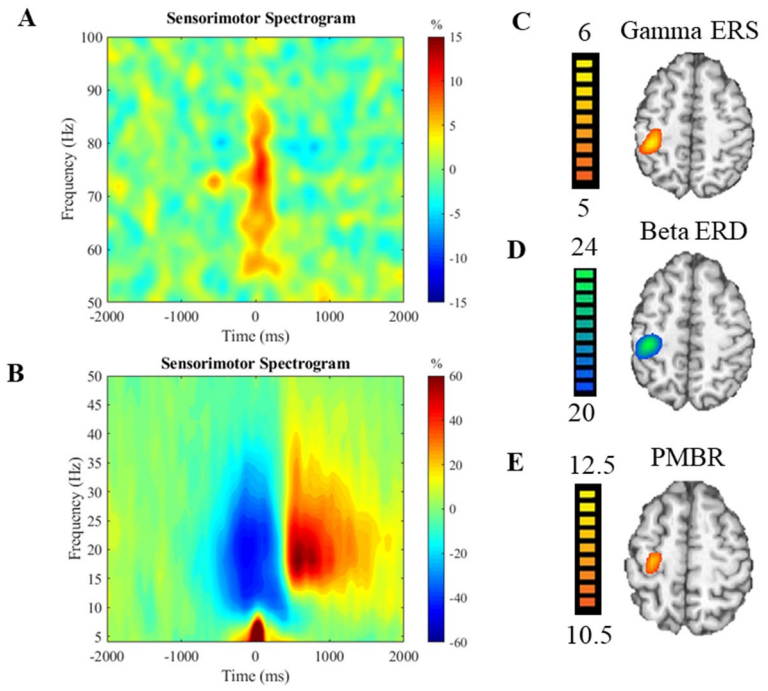

Figure 12: Motor-related oscillations A). Averaged time-frequency spectrogram from a sensor located near the hand region of the contralateral (left) motor cortex averaged across all subjects. Time is denoted on the x-axis in milliseconds with 0.0 ms being movement onset, and frequency (Hz) is denoted on the y-axis. Beginning before movement onset around -100 ms and lasting until about 100 ms after movement was a gamma ERS. B.) Averaged time-frequency spectrogram from a sensor located near the hand region of the contralateral (left) motor cortex averaged across all subjects depicting the motor-related beta responses. There was a beta ERD (18 – 26Hz) that began about -300 ms prior to movement onset and lasted until about 300 ms until the movement finished. After movement termination, there was a post-movement beta rebound (16 - 22Hz) that lasted from about 500 to 800 ms before beginning to dissipate. C.) Group averaged beamformed response of the gamma ERS located in the contralateral (left) motor cortices. Averaged beamform images of the beta ERD (D) and the PMBR (E) depict that these responses were both located within the left sensorimotor cortices, with the beta ERD slightly more posterior.

Gamma ERS

The gamma ERS (68 – 82Hz) was imaged from -100 to 100 ms with a baseline of -1600 to -1400 ms. The grand averaged images showed that the gamma ERS was localized to the motor hand knob area of the contralateral (left) motor cortex (Figure 12C). Next, we extracted the individual relative timeseries from the peak voxel of this image and computed the magnitude of the response in the -100 to 100 ms time window. Our statistical analyses revealed that there were no main effects of condition, sex, or group, and there were no significant interactions (P's > 0.05).

Beta ERD

The beta ERD (18 – 26Hz) was imaged from -300 to 300 ms with a baseline period of -1600 to -1000 ms. The grand averaged images showed that the beta ERD (Figure 12D) was localized to the contralateral (left) sensorimotor cortices' hand knob region. We subsequently extracted the individual relative timeseries from the peak voxel and computed the magnitude of the response in the -300 to 300 ms time window (Figure 13A). Our statistical analysis revealed that there was a main effect of group, in which the adults with CP had a significantly weaker (i.e., less power) beta ERD than the HC (CP = -42.0 ± 4.3%, HC = -54.1 ± 2.9%, P = 0.026) (Figure 13B). However, there were no significant main effects of condition nor sex, and there were no significant interactions (Ps > 0.05).

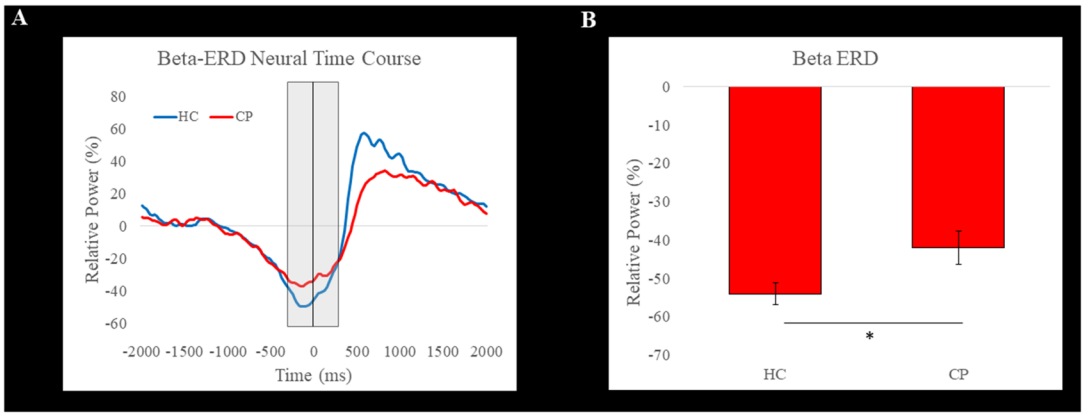

Figure 13: Beta ERD neural time course A.) Neural time courses of the beta ERD activity in individuals with CP (red) and the HC (blue) extracted from the peak voxel of the beamformed beta ERD response. The black line at 0.0 ms denotes movement onset, and the gray box is the window of interest (-300 to 300 ms). B.) Bar graph depicting the difference in beta ERD strength between the healthy controls and adults with CP. As depicted, the beta ERD was stronger in the healthy adults in comparison to the adults with CP (P = 0.026).

PMBR

The PMBR (16 – 22Hz) was imaged from 500 to 800 ms with a baseline of -1600 to -1300 ms. The grand averaged images showed that the PMBR was also localized to the contralateral (left) sensorimotor cortices' hand knob region (Figure 12E). Next, we extracted the individual relative timeseries from the peak voxel of this image and computed the magnitude of the response in the

500 to 800 ms time window (Figure 14A). There was a significant main effect of group which revealed that the adults with CP had significantly weaker (i.e., less power) PMBR in comparison to the healthy controls (CP = 39.6 ± 12.8%, HC =79.6 ± 16.3% P = 0.043) (Figure 14B). There was also a significant main effect of sex, in which males had a significantly stronger PMBR than females (Males = 92.9 ± 16.7%, Females = 34.7 ± 11.1%, P = 0.004). However, there were no significant main effects of condition, and there were no significant interactions (Ps > 0.05).

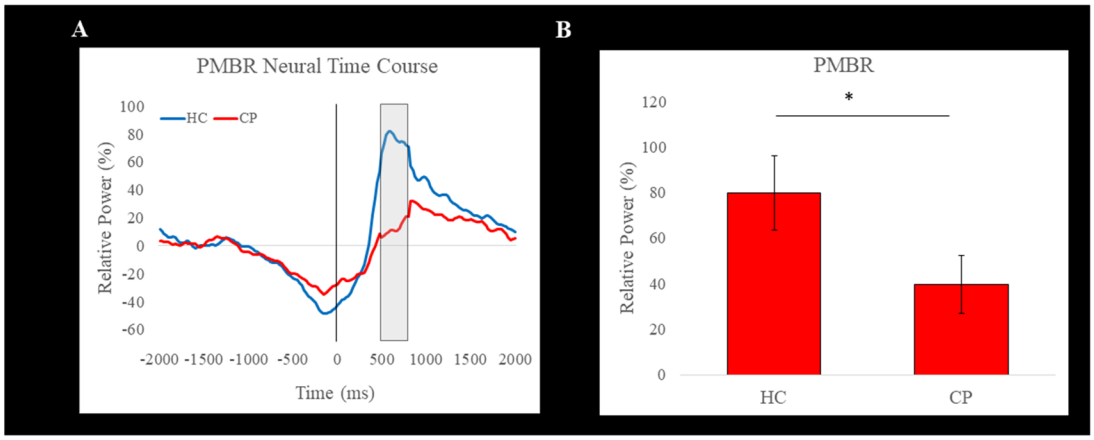

Figure 14: PMBR neural time courses A.) Neural time courses of the PMBR activity in individuals with CP (red) and the HC (blue) extracted from the peak voxel of the beamformed PMBR response. The black line at 0.0 ms denotes movement onset, and the gray box is the window of interest (500 to 800 ms). B.) Bar graph depicting the difference in PMBR strength between the healthy controls and adults with CP. Overall, individuals with CP had a weaker PMBR than the healthy controls (P = 0.043).

Spinal Cord Structure

As previously reported in Trevarrow et al. (2021), the total CSA of the spinal cord was smaller in the adults with CP compared with the controls (CP = 66.22 ± 8.60 mm^2, HC = 76.75 ± 8.77 mm^2, P = 0.002). In addition, the gray matter CSA (CP = 9.42 ± 1.41 mm^2, HC = 12.22 ± 1.29 mm^2, P < 0.001) and white matter CSA (CP = 61.93 ± 8.81 mm^2; Controls = 69.27 ± 8.59 mm^2, P = 0.032) were also significantly lower in individuals with CP. When normalized to the total spinal cord CSA, the gray matter remained smaller in the adults with CP relative to the controls (CP =

14.2 ± 1.9%, HC = 16.2 ± 2.7%, P = 0.041), but the white matter no longer differed between the respective groups (CP = 93.7 ± 8.4%, HC = 90.2 ± 4.6%, P = 0.178).

Correlation Analysis

Reaction time was associated with the strength of the beta ERD (R = 0.40, P = 0.032) and the PMBR (R = -0.39, P = 0.041), indicating that participants who had stronger beta responses also had quicker reaction times. The strength of the beta ERD was also associated with total cross-sectional area (CSA) of the spinal cord (R = -0.43, P = 0.031) and white matter CSA (R = -0.40, P = 0.048) (Figure 15), indicating that individuals who had greater myelination also tended to have a stronger beta ERD. No other correlations were significant (Ps > 0.05).

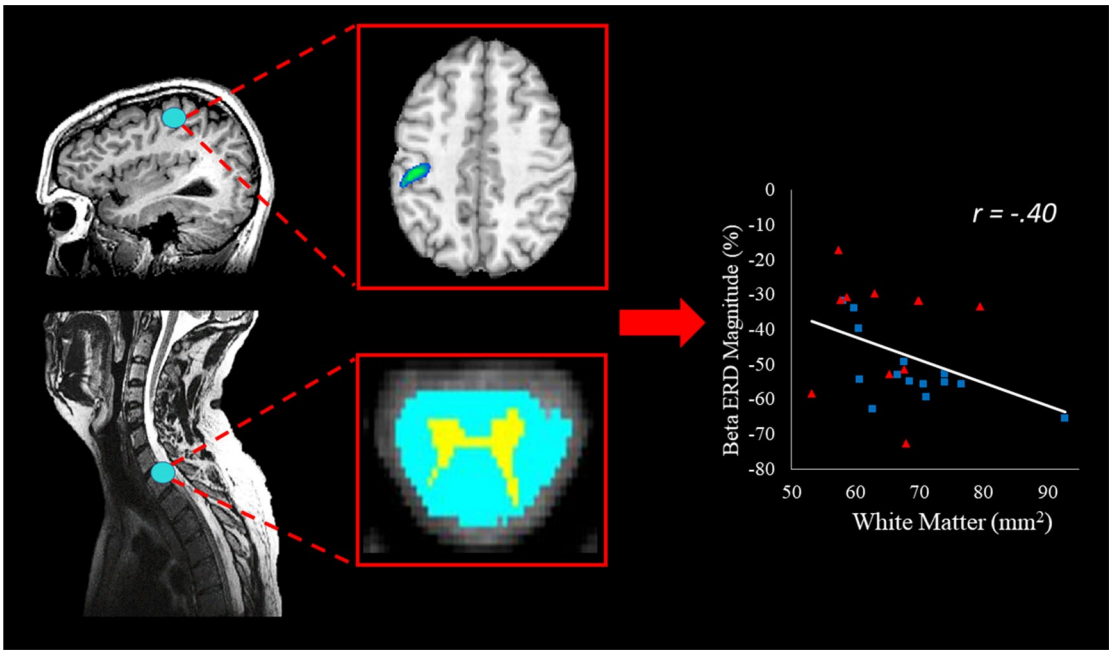

Figure 15: Cortical oscillations drive changes in spinal cord microstructure *Left*: Representative T1 weighted images of the brain and spinal cord from an adult with CP. The light blue circles denote the area of the brain and spinal cord that the strength of the beta ERD and white matter CSA were taken, respectively. *Middle*: Representative beta ERD response (top) and CSA of the spinal cord (white matter depicted in light blue and gray matter depicted in yellow). Right: Scatterplot depicting the relationship between the strength of the beta ERD and the white matter CSA. As depicted, individuals with a stronger beta ERD tended to have more white matter within their upper spinal cord.

We performed a follow-up analysis to ensure that these relationships were not a result of group differences. This follow-up consisted of performing Fisher's Z transformations to determine whether these relationships differed when calculated separately for the adults with CP and the controls. We found that the relationship between the beta ERD and the total CSA ($Z = 1.52$, $P = 0.129$) and the beta ERD and the white matter CSA ($Z = 1.65$, $P = 0.100$) were not significantly different between the respective groups. Hence, this indicates that the respective correlations were not driven by the group differences.

Discussion

In the current investigation, we utilized a multimodal neuroimaging approach to evaluate the potential neurophysiological underpinnings of the uncharacteristic cognitive-motor decisions of adults with CP. Our results show that the strength of both the beta ERD and the PMBR in the sensorimotor cortices were reduced in the adults with CP in comparison to the controls. We also identified that the total CSA and white matter CSA of the spinal cord was partially linked with the strength of the beta ERD. Hence, aligning with the premise that the spinal cord microstructure is likely influenced by the strength of the sensorimotor cortical activation. Further discussion of these novel findings is presented in the following sections.

One of our key findings was that the strength of the sensorimotor beta cortical oscillations were reduced in amplitude in the adults with CP in comparison to the controls. Furthermore, our results also showed that a weaker beta ERD was linked with a slower reaction time. These combined results indicate that the uncharacteristic cognitive-motor decisions seen in adults with CP might be partially dependent on the weaker sensorimotor beta oscillations. However, this finding differs from our prior studies that have shown the beta ERD is stronger in youth with CP when compared with controls for a lower-extremity task[41,40,42]. This discrepancy might be due to the neurophysiological mechanisms that govern the relative amplitude change of the the cortical

oscillations during the respective motor tasks. For one, the strength of the power change at the beta frequency is influenced by the number of interconnected glutamatergic pyramidal neurons that are collectively active. In this case, the stronger power reduction seen for the leg motor task might be related to fewer neurons oscillating at the beta frequency relative to the baseline. In other words, more neurons in the sensorimotor cortices switched to oscillating at a different frequency when execution of the leg motor action ensues. Given that the nature of the insults seen in individuals with CP tends to cause greater disruptions in the leg region, the stronger beta ERD might represent the necessity for a greater number of neurons to switch to the gamma frequency to execute the motor command. This premise seems to align with the TMS literature that has suggested youth with CP must generate a stronger cortical response to adequately excite the spinal motor neuron pools involved in the generation of a leg muscular contraction[183]. Alternatively, we speculate that the weaker beta oscillation seen in this investigation for a hand motor action might be related to alterations in the γ-Aminobutyric acid (GABA) interneurons. Pharmaco-MEG studies with healthy controls have provided supporting evidence that an increased concentration of the inhibitory GABA neurotransmitter within the sensorimotor cortices results in a stronger motor related beta ERD[76,77]. Based on this scenario, the weaker beta ERD seen for the hand motor action of the adults with CP could also be related to a reduced effect of the inhibitory interneurons. While both of these alternative conjectures seem plausible, they need to be thoroughly tested to better understand the neurophysiological mechanisms governing the different changes seen in the relative amplitude of the beta oscillations during leg and hand motor actions. We propose that these potential alternative explanations could be tested through multimodal neuroimaging approaches that combine TMS, GABA spectroscopy, and the MEG methods employed in this investigation.

We further speculate that the differences in the strength of the beta ERD seen for the leg and hand motor actions could also be a result of the cognitive load for the respective tasks. Prior research has identified that the beta ERD is stronger for movements with greater certainty[27,28 276].

In the prior lower extremity task mentioned, the goal is to generate an isometric muscular contraction that matches a target force that is shown on the screen. While movement planning is still inherent, the fact that the movement is the same for each trial may create less of a cognitive challenge compared with the motor decisions that must be made for the Eriksen flanker task. In other words, the weaker beta ERD seen for the hand task might signify that the adults with CP had less certainty on the selected motor actions to be performed by the respective digits, while they have greater certainty in generating a simple leg motor action. Alternatively, prior research has also shown that the strength of the beta ERD increases linearly with age in healthy controls[289]. Currently, the trajectory of the changes in the strength of the sensorimotor oscillatory activity throughout the lifespan has not been established in individuals with CP. Potentially, the differences seen across the respective studies on youth and adults with CP might represent uncharacteristic age dependent changes in the sensorimotor cortical oscillations and not the task *per se*.

Our results also revealed that the PMBR was weaker for the adults with CP. This result is well aligned with our prior study that has identified that the PMBR is weaker in youth with CP compared with controls when performing the same Eriksen flanker task[42]. The PMBR is assumed to reflect the afferent sensory feedback upon completion of the motor action[30,31]. Thus, the adults with CP may have reduced feedback about the final success of their motor actions. This reasoning seems to align with the numerous investigations that have shown the somatosensory cortical activity is weaker in individuals with CP and connected with their tactile acuity[43,44,290,47,46,49,50,7,51,52]. If sensory feedback is uncharacteristic, then this may create serious difficulties in sensorimotor integration and a decreased certainty of the feedforward predictions that are based on the internal model. Essentially, this concept may partially explain the association between a weaker PMBR and slower reaction times seen in this investigation. It has alternatively been suggested that a weaker PMBR may reflect inadequate inhibition of cortical networks once the motor action is terminated[32-34]. Conceptually, this could also affect the fidelity of the motor actions seen in this patient population.

Our multimodal imaging illustrated that participants with a stronger beta ERD also tended to have more white matter CSA and total spinal cord CSA. Previous animal models illustrated that an insult to the developing brain leads to activity-dependent plastic changes within the spinal cord [55,53,54]. Potentially, the weaker oscillatory activity seen in the sensorimotor cortices of the adults with CP noted in this study might contribute to maladaptive neuroplastic changes within the spinal cord that affect the myelination of the fiber tracts and synaptic connections. In other words, the nature of the cortical oscillations has a downstream effect on the spinal cord microstructure. Ultimately, the fidelity of the hand motor actions in adults with CP might be dependent upon the coherent activity between the sensorimotor cortex and the spinal cord.

Somewhat surprisingly, we did not find any differences in the strength of the gamma ERS between the adults with CP and the controls. This went against our initial hypothesis, as our previous studies have demonstrated that the gamma ERS was reduced in strength in youth with CP during both a lower extremity target matching task[41] as well as the same Eriksen Flanker task.[42] Prior pharmaco-MEG studies have shown that N-methyl-D-aspartate (NMDA) receptor antagonist can result in an increased strength of the sensorimotor gamma oscillations, while GABA agonists do not have an effect [76,77,291]. Potentially, the amplitude differences seen across the respective studies for the youth and adults with CP might be NMDA receptor dependent. This would imply that the weaker gamma amplitude seen in the prior studies might be related to greater inhibition of the pyramidal cell population that play a role in the motor actions of youth with CP. Potentially, the perceived NMDA receptor dysfunction may normalize with experience and age. Lastly, it is alternatively possible that the lack of group differences in this investigation might relate to the greater between-subject variations reported for the gamma oscillations[67]. As such, a lack of sufficient power may have played a role in our null effects.

In conclusion, we have expanded on previous literature by demonstrating that the beta cortical oscillations are weaker in adults with CP for tasks that involve cognitive-motor decisions. More importantly, we have revealed that the microstructural changes within the spinal cord of

adults with CP appear to be connected with the strength of the sensorimotor cortical oscillations. These results further fuel the impression that the altered sensorimotor cortical activity instigates activity-dependent plastic changes within the spinal cord. Ultimately, the alterations seen both within the cortex and the spinal cord likely interact to contribute to the upper extremities deficits seen in individuals with CP.

CHAPTER 6: A VAL^{66}MET POLYMORPHISM IS ASSOCIATED WITH WEAKER SOMATOSENSORY CORTICAL ACTIVITY IN INDIVIDUALS WITH CEREBRAL PALSY

Introduction

Cerebral palsy (CP) consists of a general class of movement disorders that are a result of an insult to the developing brain [125], and it is one of the most costly neurological disorders in the United States, with a prevalence of approximately 3 out of every 1,000 children receiving a diagnosis [126,127]. The disorder is marked with mobility issues stemming from increased muscle tone, hyperexcitable reflexes, spasticity, hypertonia and joint contractures [134]. Sensorimotor clinical deficits in motor planning and execution [6,139,141-145], as well as deficits in proprioception, stereognosis and tactile discrimination [1-4,7,6,8], have been consistently documented in this patient population. Currently, the results of treatment paradigms for individuals with CP are highly variable, with some individuals exhibiting extensive sensorimotor improvements following therapy, while others are clear non-responders [210]. Yet, the physiological factors responsible for this response variability remains unknown.

Part of this problem with advancing our understanding of the variable treatment outcomes is the ideology that the response variability primarily resides in the musculoskeletal system, with less attention paid to the neurological factors that influence the potential for neuroplastic change [292]. Several studies have examined whether this response variability may be attributed to factors such as the corticospinal projection pattern, but the outcomes from these studies have been inconclusive [175-178]. Recently, there has been a growing interest in identifying whether there are genetic factors that regulate the extent of the therapeutically driven neuroplasticity [293]. In particular, brain derived neurotropic factor (BDNF) and genetic variations at the *BDNF* gene have been suggested to play a vital role in the neuroplasticity and motor performance. For example, studies utilizing animal models have shown that an up-regulation of BDNF occurs within the sensorimotor

cortices while a new motor skill is being learned, and this leads to reorganization of the cortical areas that represent the motor action [57,58]. Similarly, an inhibition of BDNF in the motor cortex hinders motor performance and results in decreased cortical reorganization in an animal model [59]. These results emphasize the critical role that BDNF plays in the neuroplastic reorganization within the sensorimotor cortices that occurs while an individual is learning a new motor skill.

A single nucleotide polymorphism that produces a valine-to-methionine amino acid substitution at codon 66 at either one or both alleles in the human *BDNF* gene (Val66Met or Met66Met) has been shown to disrupt the protein's activity-dependent release, which in turn adversely impacts the capacity for neuroplastic change [60]. Approximately 30% of the general population has the Val66Met or Met66Met genetic polymorphism [294]. Prior fMRI studies have identified that individuals with the polymorphism tend to have a smaller volume of sensorimotor cortical activation [60]. The reduction is presumed to have been instigated by the polymorphism's influence on the prevalence of BDNF. Prior transcranial magnetic stimulation (TMS) studies have also shown that healthy adults with the *BDNF* polymorphism exhibit less change in their motor-evoked potentials and cortical reorganization after practicing a motor skill [61,60], as well as decreased ability to undergo motor improvements behaviorally after practicing a motor task [295]. Altogether these results clearly point to the notion that the polymorphism is a marker for a reduced potential for neuroplasticity.

While these findings clearly exemplify the adverse impacts on neuroplasticity that can occur for individuals with the *BDNF* polymorphism, there is a paucity of studies investigating how the *BDNF* genotype may influence the sensorimotor cortical activity in individuals with CP. Our laboratory and others have demonstrated that youth with CP have reduced somatosensory cortical activity in response to both electrical and tactile stimulation of the hand and foot mechanoreceptors [46,44,47,43,51,52]. We posit that the weaker somatosensory cortical activity seen across these investigations may be partly driven by an individual's *BDNF* genotype. In other words, we hypothesize that those with the *BDNF* Val66Met or Met66Met genotype would have weaker

somatosensory-evoked potentials compared with those that have the Val66Val genotype. To address this hypothesis, we used magnetoencephalographic (MEG) brain imaging to determine if the somatosensory-evoked cortical activity is different in individuals with CP that have the *BDNF* Val66Val genotype in comparison with the individuals that have the Val66Met or Met66Met genotypes.

Methods

Participants

The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this investigation. Informed consent was acquired from the adult participants and parents of the children participants, and the children assented to participate in the experiment. Thirty-eight individuals participated in this neurogenetics investigation. Twenty of the participants had a diagnosis of spastic CP and eighteen were neurotypical (NT) controls (CP = 15.37 ± 5.52 years, Females = 10, GMFCS = I - IV; Healthy controls = 14.21 ± 2.51 years, Females = 5). The two groups did not significantly differ by age ($P = 0.290$). Participants were excluded according to MEG/MRI exclusionary criteria such metal implants, dental braces or permanent retainers, or other metallic or otherwise magnetic non-removable devices. The participants with CP also did not have orthopedic surgery or undergo Botulinum toxin injections within the last 6 months. Furthermore, none of the participants with CP had a dorsal rhizotomy. The participants with GMFCS levels of I and II typically ambulate independently, although with slowed gait speed and abnormal gait patterns [296]. Individuals with GMFCS level of III often require assistive devices to ambulate, such as crutches, ankle-foot orthoses, or wheelchairs. Individuals with GMFCS levels IV and V often require powered mobility devices.

BDNF Genotyping

Saliva samples were collected from the participants with CP using the Oragene kit (DNA Genotek, Ottawa, Ontario, Canada). Genomic DNA was isolated according to standard laboratory procedures using a manual DNA extraction protocol and was quantified using the NanoDrop ND-1000® spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). Polymerase chain reaction (PCR) amplification of the 274-bp fragment containing codon 66 of the *BDNF* gene (RefSeq NM_170735.5) was performed according to standard procedures (Sen et al., 2003). The PCR products were analyzed by direct sequence analysis in both the forward and reverse directions utilizing automated fluorescence dideoxy sequencing methods to determine the amino acid status at codon 66. Participants with the *BDNF* polymorphism included those with either the Val66Met or Met66Met genotype, while participants without the polymorphism had the Val66Val genotype.

MEG Acquisition and Experimental Paradigm

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. During data acquisition, participants were monitored via real-time audio-video feeds from inside the shielded room. With an acquisition bandwidth of 0.1 – 330 Hz, neuromagnetic responses were sampled continuously at 1 kHz using an Elekta MEG system (Helsinki, Finland) with 306 sensors, including 204 planar gradiometers and 102 magnetometers. Each MEG data set was individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension [216].

Throughout the somatosensory experiment, the participants were seated in a custom-made nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array and with their eyes closed. A single pulse, unilateral electrical stimulation was applied using electrodes that were affixed to the skin overlying the right tibial nerve. The intensity of stimulation was set to the

individual's motor threshold to control for impedance differences among participants. To find the motor threshold, the intensity of stimulation was gradually increased until an overt muscle twitch from the toes was elicited. The stimulation was sent once every two seconds for four minutes, eliciting a total of 120 somatosensory-evoked cortical responses.

MEG Coregistration and Structural MRI Processing

Four coils were affixed to the head of the participant and were used for continuous head localization during the experiment. Prior to the experiment, the location of these coils, three fiducial points and the scalp surface were digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for the MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the four coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each participant's MEG data was coregistered with structural T1-weighted MRI data prior to source reconstruction. Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into a standardized space. Structural MRI data were acquired using a Siemens Skyra 3T scanner. High-resolution T1-weighted sagittal images were obtained with a 32-channel head coil using a 3D fast field echo sequence with the following parameters: TR: 2400 ms; TE: 1.94 ms; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm^3.

MEG Preprocessing

Cardiac artifacts were removed from the data using signal-space projection, which was accounted for during source reconstruction [64]. The continuous magnetic time series was divided into epochs of 1100 ms duration, from -500 to 600 ms with the baseline being defined as -400 to -100 ms and 0.0 ms being stimulation onset. Epochs containing artifacts (e.g., eye blinks, muscle artifacts, etc.) were rejected based on a fixed-threshold method using individual amplitude and gradient thresholds, supplemented with visual inspection. An independent samples t-test revealed that the number of trials accepted between groups was not significantly different (NT = 102.5 ± 2.92, CP = 106.4 ± 2.16, P = 0.28).

Sensor-level Analysis

The artifact-free epochs were averaged across trials to generate a mean time series per sensor, and the specific time windows used for subsequent source analysis were determined by statistical analysis of the sensor-level time series across all conditions and the entire array of gradiometers. Each data point in the time series was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired-sample t-tests were conducted to test for differences from baseline at each data point and the output time series of t-values was threshold at $P < 0.05$ to define time bins containing potentially significant phase-locked deviations across all participants. In stage two, the time points that survived the threshold were clustered with temporally and/or spatially neighboring bins that were also above the threshold ($P < 0.05$), and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution [217]. For each comparison 1,000 permutations were

computed to build a distribution of cluster values. Based on these analyses, the time windows that contained significant phase-locked events across all participants were used to guide subsequent time-domain source level analysis.

Source Imaging (sLORETA)

Time domain source images were computed using standardized low resolution brain electromagnetic tomography (sLORETA). [218] The resulting whole-brain maps were 4-dimensional estimates of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the units are arbitrary. Using the time windows identified in the sensor-level analysis, these maps were averaged over time following the somatosensory stimulation. The resulting maps were then grand-averaged across the participants to determine the location of the peak voxel of the time-domain neural response to the stimuli across participants. From this peak voxel, a virtual sensor was created, and a neural time course was extracted for each individual. To compute the virtual sensor, we applied the sensor weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series corresponding to the location of interest [286]. Note that this virtual sensor extraction was done per participant, once the coordinates of interest (i.e., one per cluster) were known. We then averaged the neural time course across the time window derived from the cluster based permutation testing to use for group level comparison of the magnitude of the somatosensory-evoked cortical response. All imaging procedures were done with the Brain Electrical Source Analysis (BESA) software (BESA v7.0; Grafelfing, Germany).

Mobility analysis

All participants were instructed to walk across a 5.75-m digital mat (GAITRite, Sparta, NJ) at their fast-as-possible walking speeds. The fast-as-possible walking speed was used since it

provides a metric of the gait adaptability and provides a greater challenge to the participant's mobility. Each participant performed two trials and the fastest walking speed was used as the primary outcome measure. The mat digitized the locations of the feet, which were used to quantify the participant's spatiotemporal kinematics (velocity, step length, cadence).

Statistical Analysis

Independent samples t-tests was used to discern if the strength of the somatosensory-evoked activity and gait variables were different between the controls and participants with CP. Secondarily, one-way ANOVAs were used to determine whether there were significant differences in strength of the somatosensory-evoked cortical activity and gait variables between the individuals with CP that had a polymorphism at the *BDNF* gene, individuals with CP that did not have the polymorphism at the *BDNF* gene, and the control group. Independent samples t-tests were used post hoc to determine group differences. All statistical tests were performed at the 0.05 alpha level.

Results

Genotyping Outcomes

Of the individuals with CP, 70% were Val66Val genotype (N=14; Age = 14.30 ± 4.90 years, Females = 6, GMFCS = I - IV), while 30% of the individuals with CP had at least one Met allele at codon 66 of *BDNF* (N = 6; Age = 17.86 ± 6.54 years, Females = 4, GMFCS = I - IV). These two groups did not significantly differ by age (P = 0.19).

MEG Source Imaging Results

The permutation testing at the sensor level revealed two peaks of evoked activity that were significantly different from the baseline. The first peak began around 36ms post stimulation and

lasted until about 100ms, and the second peak began around 164ms and lasted until 252 ms. These time windows were then used for the subsequent source imaging. The sLORETA images generated from the combined data from both groups revealed that the evoked-activity emanated from the leg region of the somatosensory cortices (Figure 16A). We subsequently determined the peak voxel of activity from the average image across all participants and extracted the neural time course for each individual. From the neural time course we determined the magnitude of the response by averaging across the windows of interest (36 – 100ms and 164 – 252ms). Consistent with the current literature, the qualitative inspection of the extracted somatosensory neural time courses appeared to be weaker for the individuals with CP compared with the controls (Figure 16B). Our statistical analysis revealed that there was not a difference in strength of somatosensory cortical activity between the control group and all individuals with CP (Controls = 272.42 ± 31.21, CP = 216.27 ± 28.88, P = 0.19) during the first time window (36 – 100 ms). However, during the second time window (164 – 252ms), the somatosensory-evoked cortical activity for the entire group of participants with CP was weaker than the controls (Controls = 273.73 ± 21.80, CP = 202.98 ± 24.23, P = 0.04).

Next, we wanted to further examine whether the somatosensory-evoked cortical activity during the second time window (164 – 252 ms)was weaker for the individuals with CP who had the BDNF polymorphism compared with those that had the Val66Val genotype (Figure 16B). Our statistical analysis confirmed that there was a significant group main effect for the magnitude of the somatosensory cortical response (P = 0.03). The post-hoc analyses revealed that the somatosensory-evoked cortical activity in the individuals with CP who had the BDNF polymorphism was significantly weaker than the activity in those who did not have the polymorphism (Val66Val = 227.05 ± 32.53, Val66Met and Met66Met = 146.83 ± 10.76, P = 0.03), and the controls (Controls = 273.73 ± 21.80, Val66Met and Met66Met = 146.83 ± 10.76, P < 0.01). Interestingly, the individuals with CP who did not have the polymorphism exhibited somatosensory

cortical activity that did not statistically differ from the controls (Controls = 273.73 ± 21.80, Val66Val =227.05 ± 32.53, P = 0.23; Figure 16C).

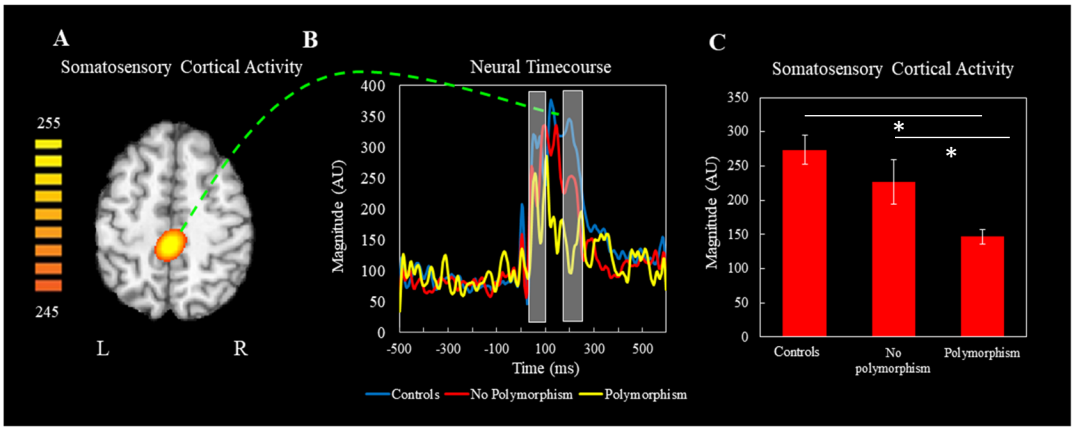

Figure 16: A BDNF polymorphism is associated with weaker somatosensory cortical activity A.) The somatosensory-evoked cortical activity emanated from the leg region of the contralateral (left) postcentral gyrus across all individuals. B.) Source level neural time course depicting somatosensory-evoked cortical activity across the epoch. The tibial nerve stimulation occurred at time zero, and the gray boxes indicate the time windows used for analysis (36 – 100ms and 164 – 252 ms), which were derived from the sensor level cluster-based permutation testing . The blue line represents the healthy controls, the red line represents the individuals with CP without a polymorphism at the BDNF gene, and the yellow line represents the individuals with CP who had a polymorphism at the BDNF gene. C.) Bar graphs depicting the difference in magnitude of somatosensory-evoked cortical activity between the healthy controls, individuals with CP who had a polymorphism at the BDNF gene, and individuals with CP without a polymorphism at the BDNF gene during the second time window (164 – 252 ms). The individuals with CP who had a polymorphism at the BDNF gene had a significantly reduced somatosensory cortical response to tibial nerve stimulation in comparison to the individuals with CP without a polymorphism (P = 0.03) and the healthy controls (P < 0.01). Additionally, the healthy controls had a significantly greater cortical response than the individuals with CP altogether (P = 0.04).

Clinical Outcomes

The individuals that had the BDNF polymorphism tended to have higher GMFCS level scores (GMFCS = 2.83+ 0.40) compared to those without the polymorphism (GMFCS= 1.79 + 0.26; P= 0.04; Figure 17A). This implies that those with more severe classifications of CP tended to have the BDNF polymorphism.

Our biomechanical analysis of the spatiotemporal gait kinematics revealed that the individuals with CP overall had slower walking velocity in comparison to the controls (CP = 1.39 ± 0.11 m/s; controls = 1.91 ± 0.05 m/s; P < 0.01). Furthermore, our ANOVA revealed that there was a main effect of group for walking velocity (P < 0.01). Post hoc analysis revealed that the

individuals with the BDNF polymorphism tended to have slower maximum walking velocity in comparison to the individuals without the polymorphism (Val66Val = 1.54 ± 0.10 m/s; Val66Met and Met66Met = 1.07 ± 0.24 m/s; P = 0.05), as well as the controls (controls = 1.91 ± 0.05 m/s; P = 0.02; Figure 17B). Additionally, the controls had faster walking velocity in comparison to the group without the polymorphism (Val66Val = 1.54 ± 0.10 m/s; P < 0.01).

The step length was also longer for the controls in comparison to the individuals with CP

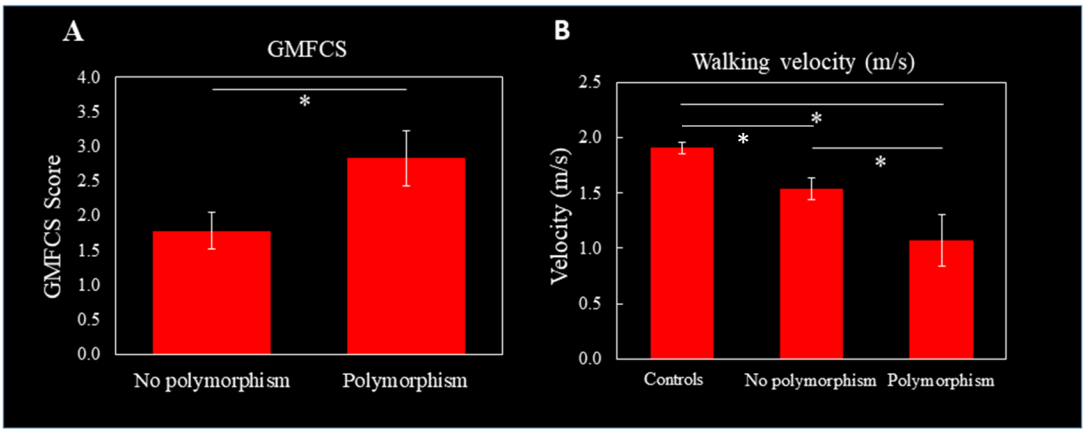

Figure 17: A BDNF polymorphism is related to altered mobility Bar graphs representing the difference in GMFCS score (A) and walking velocity (B) between the individuals with CP who had the polymorphism at the *BDNF* gene, those who did not have the polymorphism, and the controls. Walking velocity was slower in those with the polymorphism (P = 0.05) and GMFCS scores were higher (P = 0.04) depicting decreased gross mobility in individuals with CP who have a polymorphism at the *BDNF* gene. The walking velocity was also higher in controls than both groups with CP (Ps < 0.05).

(CP = 0.62 ± 0.04 m; controls = 0.83 ± 0.03 m; P < 0.01). Our ANOVA revealed a significant main effect of group for step length (P < 0.01). The post hoc analysis showed that the controls (controls = 0.83 ± 0.03 m) had longer step lengths than the group with the polymorphism (Val66Met and Met66Met = 0.54 ± 0.10 m; P = 0.04) and without the polymorphism (Val/Val = 0.66 ± 0.04 m; P < 0.01), but the group of individuals with CP that had the polymorphism were not different from the group without the polymorphism (P = 0.16). Finally, cadence was not different between the controls compared with the individuals with CP (CP = 134.09 ± 7.64 steps/min, controls = 137.18 ± 3.91 steps/min, P = 0.71). There was also no significant main effect of group within the ANOVA for cadence (P = 0.128). Hence, the cadence was similar across the respective groups.

Discussion

Overall our experimental results are aligned with the numerous studies that have identified individuals with CP have decreased somatosensory-evoked cortical activity in comparison to neurotypical controls [1,6,7,43,49-51,220,221], and the numerous studies that have shown shown reduced oscillatory activity following somatosensory stimulation in those with CP[46,48,44]. Hence, there is mounting evidence that the altered somatosensory cortical activity likely contributes to the sensory deficits that are largely reported in the clinical literature for this patient population [2-4,6,7]. Prior DTI studies have suggested that damage to the thalamocortical tracts is related to the somatosensory impairments seen in children with CP [169,168,52]. These results suggest that the abnormal activity within somatosensory cortices reported here may have been instigated by perinatal damage to the thalamocortical tracts. Potentially, this damage may alter the signal-to-noise ratio in such a way that the threshold for activation of the somatosensory cortices becomes uncharacteristic and perhaps unresponsive to important peripheral feedback. It is also conceivable that the decreased mobility in individuals with CP restricts interaction with the environment throughout development, which may result in altered development of the somatosensory system and, ultimately, the aberrant processing seen within the sensorimotor cortices. In support of this notion, prior studies have noted that the clinical motor and mobility deficits are highly related to the extent of the somatosensory deficits [6,44,47].

Our results show that approximately 30% of our sample had the *BDNF* Val66Met or Met66Met polymorphism, which is representative of what is seen in the general population [294]. Remarkably, the participants with the polymorphism had a more attenuated somatosensory-evoked cortical activity in comparison with their peers with CP that do not have the *BDNF* polymorphism. BDNF is a neurotrophic factor that provides support with a number of cellular functions, including neuronal resilience and survival. BDNF is transported to synapses, where it can modify neurotransmitter release, receptor sensitivity, and synaptic morphology [297,298]. BDNF also improves

neuroplasticity by stimulating synaptophysin and synaptobrevin synthesis to enhance synaptic transmission [299,297] and plays a critical role in motor learning [57,58]. The Val66Met and Met66Met nucleotide polymorphisms result in reduced activity-dependent release of the BDNF protein and consequently reduced capacity for these neuroplastic changes [60,61]. Thus, we suspect that the individuals that had the *BDNF* polymorphism likely have a decreased capacity for neuroplastic change, resulting in further detriment to the development of the somatosensory system and ultimately weaker somatosensory cortical activity.

Individuals who had the *BDNF* polymorphism also tended to have higher GMFCS level scores and slower walking velocities than those without the polymorphism. This suggests that individuals with CP who have a more severe classification may be more likely to have the *BDNF* polymorphism. Based on the concepts outlaid in the previous paragraph, it is possible that the reduced BDNF released in patients with the polymorphism may impact the ability to develop beneficial compensatory neural pathways after the initial perinatal neurological insult. As such, these individuals might be more likely to have more severe presentations and might be less responsive to the current physical therapy treatment protocols. An alternative perspective is the *BDNF* polymorphism may have some neuroprotective effects in patients with higher GMFCS since there is a lack of BDNF released. Hence, there might be greater stability of the current brain networks and less susceptibility for further maladaptive plastic changes across the lifespan.

The ability of the brain to undergo neuroplastic change is essential to acquiring and refining new sensorimotor skills. Currently, there is a substantial portion of individuals with CP that do not respond well to therapeutic interventions, creating an urgency for steering treatment toward a more individualized approach. Potentially, this subpopulation of non-responders is made up of individuals that have the *BDNF* polymorphism. A reduction in capacity for neuroplastic change implies that these individuals may need increased therapy intensity or longer therapy sessions in order to stimulate the same neuroplastic change seen in those that do respond well to therapy. Alternatively, there has been recent interest in utilizing non-invasive brain stimulation to alter the

resting state excitability of the neuronal populations within the sensorimotor cortices. This effectively primes the system and increases the capacity for neuroplastic change, which has been shown to be an effective strategy during neurorehabilitation [300]. Potentially, motor priming could be a means for increasing the beneficial therapeutic outcomes for the individuals with the polymorphism at the *BDNF* gene.

In conclusion, the somatosensory-evoked cortical activity demonstrated a stepwise pattern of aberrant activity, in which the individuals with CP showed weaker activity than the controls, but this aberrant activity was more pronounced in those with the *BDNF* polymorphism. The *BDNF* polymorphism decreases the capacity for neuroplastic change, which likely has downstream effects on the organization and development of the somatosensory cortices. Ultimately, these findings point toward a new understanding of the potential neuronal barriers that limit the ability of some individuals with CP to demonstrate clinically relevant improvements in their motor actions and somatosensory perception.

DISCUSSION

Main Outcomes

The first main objective of this dissertation was to investigate the sensorimotor cortical activity throughout the transition from adolescence to adulthood in individuals with CP and healthy controls, as well as uncover how this activity may be related to structural changes within the cortex. As individuals with CP transition from adolescence to adulthood, mobility declines and daily tasks become increasingly difficult to complete[274,9,10,213,301,275,12,13]. Thus, assessing the neurophysiological changes that are occurring throughout this transition period is critical for the development of effective strategies aimed at improving therapy for this cohort of the population. In chapter two, we utilized MEG in order to quantify the strength of the somatosensory-evoked cortical activity in children, adolescents, and adults with CP during a single pulse, unilateral tibial stimulation paradigm. We uncovered that the somatosensory-evoked cortical activity was reduced in strength in the individuals with CP, and this activity decreased at a similar rate throughout the transition from adolescence to adulthood in the individuals with CP and healthy controls. However, the individuals with CP had a reduction in the somatosensory activity at a much younger age, pointing to an accelerated developmental effect.

Essentially, a younger individual with CP displays somatosensory cortical activity similar to that of an individual several years older at a different developmental stage. Previous literature has put forth the concept of accelerated development and aging by illustrating that the musculoskeletal system deteriorates at a much more rapid rate in individuals with CP[13,12,10]. Sarcopenia is a term that refers to muscle atrophy and weakness, which can result from normal aging, chronic inflammation, nutritional deficits, and disuse[302,303]. Overall, these factors all contribute to an imbalance in the muscle protein synthesis versus the muscle protein breakdown, resulting in a net loss of muscle. In individuals with CP, sedentary lifestyles, weight gain, balance deficits, and nutritional deficiencies are each factors that may contribute to sarcopenia at a much

younger age than what is seen in the healthy population. Similar to what we found in the somatosensory cortices, a younger individual with CP may show signs of sarcopenia similar to that seen in older adults[214].

In addition, this accelerated aging effect has been noted in other systems, such as the cardiovascular system. Certain risk factors for cardiovascular disease, such as flow-mediated dilation and carotid artery thickness, change at an accelerated rate in individuals with CP, increasing their likelihood of cardiovascular disease[304]. Thus, accelerated aging may be a process existent throughout numerous systems in individuals with CP. In the nervous system, in particular, accelerated aging may be a direct result of neuroplastic changes (or lack thereof) that occur as downstream effects after an insult to the developing brain. For example, the mobility difficulties that are inherent to CP lead to a lack of sensory experiences throughout development. Ultimately, a lack of adequate interaction with the environment may lead to inadequate synaptic connections to be formed in the somatosensory cortices for processing incoming information. This, in turn, may affect the strength of this activity and ultimately contribute to the altered somatosensory cortical activity at a younger age. Ultimately, these accelerated aging effects may contribute to declines in mobility and other functional measures that are commonly seen throughout the transition from childhood to adolescence in individuals with CP.

In chapter three, we utilized MEG in order to quantify the gating of somatosensory-evoked cortical activity using a paired pulse stimulation paradigm to the median nerve in a group of adults with CP and healthy adult controls. This provided a direct assessment of in what way the somatosensory cortical processing of upper extremities may be impacted in adults with CP, as well as the functioning of the underlying GABAergic inhibitory circuits. We identified that the somatosensory-evoked cortical activity was reduced in magnitude across both stimulations in the adults with CP. Furthermore, we confirmed our hypothesis that the gating ratio was significantly lower in the adults with CP, indicating that the second stimulus was gated (ie inhibited) more in the adults with CP in comparison to the healthy adult controls. Finally, we confirmed our hypothesis

that the cortical thickness in the region generating the somatosensory cortical response was reduced in the adults with CP and was also directly connected to the strength of the somatosensory-evoked cortical activity.

As mentioned before, tasks of daily living (buttoning shirt, brushing teeth) become increasingly difficult to perform for adults with CP, and the altered activity within the somatosensory cortices may introduce difficulties in sensorimotor integration that contribute to this phenomenon. Furthermore, the altered gating ratio demonstrates that the cortical inhibitory processing is aberrant within this population. Sensory gating is a necessary mechanism that is typically thought to serve as a filtering process, such that an organism is not overwhelmed with the extensive amount of external stimuli it is constantly receiving[91,239]. However, the excessive filtering that is seen in the adults with CP may create difficulties in distinguishing salient information. Potentially, this stems from the excessive noise ascending from both the spinal cord and thalamocortical tracts. Studies investigating the H-reflex and other spinal pathways have illustrated hyperexcitability in the spinal cord of individuals with CP [192,193], and DTI studies have demonstrated that the thalamocortical tracts that transmit information to the somatosensory cortices exhibit structural changes that impact the integrity of this information [168,169,212]. These alterations in the spinal cord and thalamocortical tracts likely result in an overall increase in noise ascending to the somatosensory cortex, which could result in heightened activity of the GABAergic inhibitory interneurons that filter this information.

The reduction in cortical thickness in the adults with CP may demonstrate that there are underlying structural changes within the brain that are connected with the functional alterations. As mentioned above, reduced mobility and sensory experiences throughout development may lead to blunted synaptogenesis in individuals with CP, which could be a significant contributing factor to the reduction in cortical thickness and diminished cortical activity. Here, we also demonstrate that the somatosensory cortical activity was directly related to the cortical thickness in the region generating the response, which supports this idea. Reduced synaptic connections, dendritic

arborization, and overall cell size would lead to a reduction in the electrical current flowing through those neuronal populations, creating a dulled response to stimuli. Then again, cortical thinning is a natural phenomenon throughout aging, and so another possibility is that the reduction in gray matter seen in the adults with CP is not solely reflective of aberrant development of the somatosensory system, but simply that the process of cortical thinning begins much earlier within this population. In either case, underlying structural changes within the cortex may be at the forefront of the aberrant activity seen within the somatosensory cortices in individuals with CP.

The second primary objective within this dissertation was to assess the underlying microstructural changes within the upper (cervical-thoracic) spinal cord of adults with CP. Subsequently, we sought to determine how these structural changes may be related to alterations in motor-related oscillatory activity during an upper extremity motor task. Our MRI findings from chapter four were the first to show that the CSA of the spinal cord, gray matter, and white matter, as well as the MTR of the corticospinal tracts, were each reduced in the adults with CP, but the FA was not. Importantly, we found that the total CSA and the white matter were each related to motor hand dexterity as measured by the clinical box and blocks test.

Understanding the neurological impairments in individuals with CP that exist outside of the brain is critical for comprehension of the disorder from a broader perspective. Previous studies have identified that there are structural changes that occur in the spinal cord as a direct result of an insult to the developing brain. The corticospinal tracts may reorganize after a unilateral insult such that the contralesional hemisphere takes over partial or full control of the affected limb[54,53]. Most likely, the axons that cross the pyramidal decussation recross at the spinal cord to terminate ipsilaterally. This may either be a result of denervation factors that are released to the paretic side of the spinal cord, signaling the sprouting of axon collaterals that then branch out and recross the spinal cord, or ipsilateral connections that are normally pruned throughout development remain intact[54]. In either case, the ipsilateral projections still decussate, with an abnormal recrossing at the level of the spinal cord, and individuals with greater ipsilateral reorganization within their

corticospinal tracts also tend to have greater sensorimotor impairments[53,204,205]. Furthermore, the corticospinal tracts may terminate more dorsally[55]. Thus, insults incurred to the developing brain may result in long-lasting activity-dependent plastic changes within the spinal cord, of which the more neuroplastic change that occurs (eg reorganization) the more adverse the results of this impact may be. Yet, the specific neuroplastic changes that might occur to the microstructure of the spinal cord have not been studied prior to this investigation.

Overall, the total CSA of the spinal cord was smaller in the adults with CP. When normalized to the total CSA, gray matter was significantly reduced in adults with CP but the white matter was not, indicating that the reduction in gray matter was the most prominent contributor to the smaller spinal cord. The reduction in the gray matter in the spinal cord likely reflects an overall decrease in the number of cell bodies. This perhaps signifies a decrease in the number of GABAergic inhibitory interneurons, which could play a direct role in the increased excitability exhibited in the spinal cord in individuals with CP[192,193]. Alternatively, numerous studies utilizing animal models have demonstrated that there is significant synaptic competition between the somatosensory and motor system[305-307]. As the corticospinal tracts may terminate more dorsally within the spinal cord after a brain insult, this may ultimately result in competition for real estate between the motor and sensory neurons, leading to an overall pruning of cells. We also found that individuals with more total CSA and gray matter CSA tended to perform better on the box and blocks test of hand dexterity. These results provide direct evidence that activity-dependent microstructural changes seen within the spinal cord play a direct role in the upper extremity functioning of adults with CP, and the individuals that have more significant alterations also tend to have more significant sensorimotor impairments.

Our hypothesis that the FA would be reduced in both the corticospinal tracts and the cuneatus tracts was not confirmed. Previous literature has illustrated that the FA in stroke survivors within the corticospinal tracts is lowered, which initially prompted our hypothesis. However, the nature of the insult between populations is vastly different. Insults incurred in individuals with CP

happen during the pre, peri, or postnatal periods, a timeframe of development when the brain is highly plastic. The insult to the adult brain in stroke survivors occurs when the brain plasticity is much more limited. This is also likely the reason behind the vastly different presentations in the two populations (e.g. spasticity). Despite the lack of change in FA, we did uncover that the MTR was significantly lower in the corticospinal tracts in the adults with CP, and this was directly correlated with the amount of gray matter. We conjecture that changes in brain activity adversely impact the fidelity of the information being sent down to the spinal cord, altering the termination of corticospinal tracts and inducing changes within its microstructural organization.

Furthermore, we sought to determine whether the motor-related oscillatory activity during an upper extremity task was altered in adults with CP and in what way this may be related to the microstructural changes within the spinal cord described above. In chapter five we utilized MEG and performed a study in which a cohort of adults with CP and a cohort of healthy adult controls each completed an arrow based version of the Eriksen flanker task. We identified deficits in reaction time and accuracy throughout the task in adults with CP, and this was the first study to reveal that adults with CP have reduced strength of both the beta ERD and the PMBR, but not the MRGS. Furthermore, we illustrated that the strength of the beta ERD was associated with total CSA and white matter CSA, supporting and further corroborating the notion that an insult to the developing brain induces downstream neuroplastic changes within the spinal cord.

Interestingly, children with CP have been shown to have a stronger beta ERD in comparison with healthy controls[41,40], while we found that adults with CP had a weaker beta ERD compared to healthy controls. Potentially, this is a result of task differences in cognitive demand. The studies demonstrating a stronger beta ERD in children with CP utilized a lower extremity target matching task, in which the cognitive demand is fairly low in comparison to the flanker task, in which movement with a different finger has to be performed based on different condition parameters. As the beta ERD is stronger with greater movement certainty, it is possible that the increased cognitive demand of the flanker task could better exploit the motor planning deficits in

individuals with CP. Alternatively, it is possible that this discrepancy is a result of an altered trajectory of the beta oscillatory activity with age. The beta ERD gets stronger with age in healthy controls[289], but this has not been investigated in individuals with CP, and a different developmental trajectory could result in a different relationship between the strength of the beta ERD in children and adults with CP compared to healthy controls.

A previous study demonstrated that the PMBR is reduced in strength in children with CP when performing the Eriksen Flanker task[42]. However, our study is the first to demonstrate that motor-related beta oscillatory activity is also aberrant within adults with CP while performing the same task. This decrease in strength of the PMBR may be a result of altered sensory feedback to the motor cortex following movement, decreased force output of the adults with CP during the task, or altered ability to properly terminate movement. Furthermore, we found that the individuals that had a weaker beta ERD and PMBR also tended to have slower reaction times. The altered strength of the beta ERD and PMBR may result in difficulty with motor planning and sensorimotor integration, ultimately resulting in slowed responses, which may be exacerbated when there are distracting stimuli such as the case in a task as the Eriksen Flanker. These results corroborate the notion that there is a direct connection between the motor-related oscillatory activity and upper extremity sensorimotor deficits that persist within adults with CP.

We expanded on these findings by demonstrating that the altered motor-related oscillatory activity was directly connected with several outcome measures from the spinal cord MRI. The strength of the beta ERD was significantly associated with the CSA and white matter. Previous studies have shown that a stronger beta ERD is associated with greater movement certainty[27,28,72,71]. In our study, this was reflected by the fact that a stronger beta ERD was associated with quicker reaction times. Thus, a weaker beta ERD and greater movement uncertainty seems to affect the fidelity of the information being transmitted to the spinal cord, resulting in neuroplastic changes to its organization. The activity within the motor cortices may contribute to the organization of the spinal cord interneurons, such that abnormal oscillatory activity that affects the planning and

execution of motor actions alters the integrity of information reaching the spinal cord and subsequently results in reduced cell bodies and/or myelination.

We have presented evidence that consistently supports the notion that alterations in cortical activity can induce activity-dependent plastic changes within the spinal cord. Thus, neuroplasticity plays a key role in the sequelae of sensorimotor deficits in individuals CP, and therefore it is critical to the understanding of the disorder as a whole. While many individuals with CP respond very well to therapy, gaining advancements in mobility, strength, and sensorimotor functioning, there is also a substantial portion of individuals with CP that do not respond to therapy in any way. Potentially, these individuals have a decreased capacity for neuroplastic change, creating difficulties with therapeutic improvements and resulting in the need for more specific or intense therapeutic intervention. Recently, BDNF has been considered a key protein within the central nervous system involved in regulating neuroplasticity, as it facilitates synaptic transmission by regulating proteins at the snare complex such as synaptobrevin and synaptophysin [297,299]. Healthy individuals that have a polymorphism at the *BDNF* gene experience decreased neuroplastic change and motor learning retention, suggesting that individuals with CP that do not respond well to therapy may reflect the sub portion of the population that has the polymorphism. Our last objective within this dissertation was to understand whether the mutations in the gene that codes for the protein BDNF significantly impacts the sensorimotor cortical activity in individuals with CP.

To address this objective, we utilized MEG to assess the somatosensory-evoked cortical activity in a group of individuals with CP that had the polymorphism at the *BDNF* gene, individuals with CP that did not have the polymorphism, and a group of healthy controls. We confirmed our hypothesis that the individuals with CP that had a polymorphism at the *BDNF* gene would have weaker somatosensory-evoked cortical activity in comparison with the individuals with CP that did not have a polymorphism at the *BDNF* gene. Interestingly, the group of individuals with CP that did not have the polymorphism did not have significantly different magnitude of the somatosensory cortical activity in comparison with the healthy controls, but the individuals with the polymorphism

had significantly weaker somatosensory cortical activity than the healthy controls. Furthermore, the individuals with a polymorphism also had significantly higher GMFCS levels and slower walking velocity than the group without the polymorphism, indicating greater deficits in mobility.

The individuals with CP that had the polymorphism at the BDNF gene likely have decreased capacity for neuroplastic changes within their brain due to an overall reduction in the BDNF protein available upon activity-dependent release. As mentioned previously, the accelerated aging effect within the somatosensory cortices that we uncovered could be attributed to mobility deficits that limit interaction with the environment and ultimately result in a lack of adequate stimulation of the somatosensory cortices and reduction in synapse formation. Following this conjecture, it is plausible that this effect is more pronounced in the individuals with the polymorphism, as they had more severe mobility deficits (ie higher GMFCS) which would limit environmental interaction further. Moreover, as BDNF interacts with proteins within the SNARE complex that are directly involved in synaptic transmission, restriction of adequate synapse formation is a likely contributor to the decreased magnitude of the somatosensory response found in these individuals. When considering how this may impact an individual's response to therapy, it is therefore valid to suggest that the *BDNF* polymorphism may have an adverse impact on the capability to gain beneficial outcomes, and the sub portion of the individuals with CP that do not respond well to therapy may reflect those that have the polymorphism at the *BDNF* gene.

Limitations

Despite the novel and compelling findings within this dissertation, there were several limitations that should be noted. Firstly, within chapter two, the accelerated developmental effect that we uncovered in individuals with CP included participants in the age range from 9 – 28 years, limiting the knowledge of how this altered somatosensory activity progresses into later adulthood. Furthermore, within chapter four, when investigating the microstructure of the spinal cord, we noted that the signal to noise ratio decreases when imaging further down the cord [273], which could

potentially bias the FA values. Additionally, the FA values show substantial differences between gray and white matter. As the adults with CP had significantly different distributions of gray and white matter than the healthy controls, this could help to explain why we did not find differences in the FA values between the two populations. The MTR also comes with limitations as an outcome measure, as it can have substantial variability depending on the properties of the pulse, and MT scans tend to be more susceptible to motion error.

In chapter five, the reaction time differences between the individuals with CP and healthy adult controls could partially be attributed to an inability to isolate finger movements as opposed to complications with motor planning. However, we found that slower reaction times were linked with a weaker beta ERD, suggesting that the slowed reaction times were at least partially a result of motor planning deficits.

In chapter six, the sample sizes for the group of individuals with CP with and without the polymorphism were rather small, albeit the percentage of individuals with CP that had the polymorphism was very similar to the percentage of healthy individuals that have the polymorphism in the general population (about 30%). Finally, the results from chapter seven could be enhanced if genetic data was available for the controls.

Conclusions and Future Directions

In conclusion, this dissertation provided evidence for the neurophysiological and structural alterations in both the brain and spinal cord that contribute to the sensorimotor impairments in individuals with CP. Importantly, we demonstrated that individuals with CP may exhibit an accelerated developmental trajectory of their somatosensory system. This complements the findings from previous literature that highlight an accelerated aging effect of the musculoskeletal system, yet further investigation using a wider age range is required in order to determine how this trajectory progresses into later adulthood. Ultimately, the altered trajectory of this activity may

contribute to the mobility declines and increased difficulties in performing tasks of daily living that individuals with CP experience with increasing age.

We also demonstrated altered structural organization within the sensorimotor cortex and the upper spinal cord in individuals with CP, and we uncovered that these alterations were directly related to aberrant sensorimotor cortical activity as well as behavioral measures of motor performance. Overall, these findings lend support to the notion that the insult to the developing brain in individuals with CP results in a plethora of activity-dependent neuroplastic changes within both the brain and the spinal cord, and many of these changes may result in adverse effects on the sensorimotor system. We also revealed that individuals with CP that have a polymorphism at the *BDNF* gene have more significant detriment to their somatosensory system than individuals with CP that do not have this polymorphism. Due to the critical role in neuroplasticity that BDNF plays, this specific genetic polymorphism may make these individuals more susceptible to being non-responders following therapy.

Overall, findings from these studies provide a knowledge base for the specific activity-dependent plastic changes that the brain and spinal cord each undergo in response to the atrophy caused by the insult to the developing brain in individuals with CP. While these changes may be necessary for compensating the loss of functioning after brain injury, they ultimately may reflect maladaptive plasticity connected with the sensorimotor impairments seen in this population that extend into adulthood. Therefore, knowledge of these plastic changes is critical for functional rehabilitation and specialized therapeutic strategies for both younger and older individuals with CP.

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APPENDIX A: CURRICULUM VITAE

Appendix A: Curriculum Vitae
Michael Trevarrow, BS
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Curriculum Vita

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EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Nebraska at Omaha, Omaha, Nebraska	BS	2017	Neuroscience
University of Nebraska Medical Center, Omaha, Nebraska	PhD	2021(expected)	Neuroscience

Academic Positions/Employment

2017 – present	Graduate Research Assistant, University of Nebraska Medical Center, Omaha, Nebraska
2015 – 2017	Research Assistant, Munroe Meyer Institute, University of Nebraska Medical Center, Omaha, Nebraska

Professional Memberships

2018 – present	American Academy for Cerebral Palsy and Developmental Medicine (AACPDM)

Honors/Awards/Fellowships

2013-2017: Regents Scholarship, University of Nebraska at Omaha (full tuition)

2015: Gillespie Scholarship in Philosophy ($600)

2016: Phi Kappa Phi Honor Society

2017: Outstanding neuroscience major award (UNO)

2017: Summa Cum Laude, University of Nebraska at Omaha

2018: AACPDM student travel scholarship

2019: NASA Nebraska FY19 Space Grant Fellowship

2019: AACPDM student travel scholarship

2019: UNMC Graduate Research Fellowship Award

2019: Hazel V. Emley Scholarship

2020: NASA Nebraska FY20 Space Grant Fellowship

2020: AACPDM student travel scholarship

Research Publications

1.) **Trevarrow, M.P**. , McDermott T.J., Wiesman, A.I., Wang Y., Calhoun V.D., Stephen J.M., Kurz M.J., & Wilson, T.W. *The developmental trajectory of sensorimotor cortical oscillations.* Neuroimage, 2019. **184**: p.455-461.

2.) Dukkipati, S.S. and **M.P. Trevarrow.** *Breaking down the human motor cortex: the layer-specific measurement of corticospinal neuronal activity*. J Physiol, 2019. *Both authors contributed equally to this work.

3.) Gehringer, JE, Arpin, DJ, Vermaas, JR, **Trevarrow MP**, Wilson TW, Kurz MJ. *The Strength of the Movement-related Somatosensory Cortical Oscillations Differ Between Adolescents and Adults.* Sci Rep, 2019.

4.) Vermaas JR, Embury CM, Hoffman RM, **Trevarrow MP**, Wilson TW, Kurz MJ. *Beyond the eye: Cortical differences in primary visual processing in children with cerebral palsy.* Neuroimage Clin, 2020.

5.) Baker SE, **Trevarrow MP**, Gehringer JE, Bergwell HR, Arpin D, Heinrichs-Graham E, Wilson TW, Kurz MJ. *Gamma Somatosensory Cortical Oscillations are attenuated during the Stance Phase of Human Walking*. Neuroscience Letters, 2020.

6.) **Trevarrow, MP**, Kleinsmith, J, Taylor, BK, Wilson, TW, Kurz, MJ. *The somatosensory cortical activity displays an aberrant developmental trajectory in individuals with cerebral palsy* . The Journal of Physiology, 2020. Online ahead of print.

7.) **Trevarrow, MP**, Baker, S, Wilson, TW, Kurz, MJ. *Microstructural changes within the Cervical Spinal Cord of Adults with Cerebral Palsy.* DMCN, 2020.

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Research Abstracts

1.) Trevarrow, M.P. , McDermott T.J., Weisman, A.I., Wang Y., Calhoun V.D., Stephen J.M., Kurz M.J., & Wilson, T.W. *The strength of gamma oscillations decreases in the motor cortices from late childhood to adolescence.* Abstract, 21st International Conference on Biomagnetism, Philadelphia, PA, USA, 2018.

2.) Trevarrow, M.P., Smith, S., Sanmann, J., Kurz, M.J. *Children with cerebral palsy that have a BDNF Val66Met polymorphism need a longer motor planning period to improve their motor actions*. Abstract, American Academy of Cerebral Palsy and Developmental Medicine, Cincinnati, OH, 2018.

3.) Trevarrow, MP, Gehringer, JE, Wilson, TW, Kurz, MJ. *Cortical Processing of Somatosensory Information is Reduced While Performing a Motor Task.* Abstract, Nebraska Academy of Sciences Annual Spring Conference, 2019.

4.) Trevarrow, MP, Gehringer, JE, Wilson, TW, Kurz, MJ. *Spontaneous Somatosensory Cortical Activity is Diminished in Adolescents with Cerebral Palsy.* Abstract, American Academy of Cerebral Palsy and Developmental Medicine Conference proceedings, 2019.

5.) **Trevarrow, MP**, Baker, S, Wilson, TW, Kurz, MJ. *Microstructural changes within the Cervical Spinal Cord of Adults with Cerebral Palsy.* Abstract, American Academy of Cerebral Palsy and Developmental Medicine Conference Proceedings, 2020.

Research Presentations

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2.) **Trevarrow, M.P.,** Smith, S., Sanmann, J., Kurz, M.J. *Children with cerebral palsy that have a BDNF Val66Met polymorphism need a longer motor planning period to improve their motor actions*. Oral presentation,American Academy of Cerebral Palsy and Developmental Medicine, Cincinnati, OH, 2018.

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