Hemiplegic Cerebral Palsy: Mapping Brain Plasticity using Multimodal Neuroimaging

Abstract

Research Question:

With the use of functional and structural neuroimaging, such as magnetoencephalography (MEG) combined with high-density electroencephalography (HD-EEG), and diffusor tensor imaging (DTI), can we map and better characterize brain plasticity changes in pediatric patients with hemiplegic cerebral palsy (HCP)? Are the delays in visuomotor tasks in children with HCP strictly due to musculoskeletal impairments or do cortical oscillations play a role? Additionally, this study aimed to assess possible alterations in the cortical oscillations of children with HCP during a visuomotor integration task using a unique experimental setup that integrates brain imaging with magnetoencephalography (MEG) and high-density electroencephalogram (HD-EEG).

Background, Significance, and Rationale for the Question:

Cerebral Palsy (CP) is the most prevalent physical disability in early childhood in the United States. CP is deteriorating disease that affects both a child and a parent's leading to functional and motor impairments, which begin in early childhood. One of the common forms of CP, HCP affects only one side of the body, usually both upper and lower extremities. HCP is often caused by a periventricular white matter injury (PV-WMI) of the developing brain. Here, we mapped functional changes that occur at the primary motor and somatosensory cortices, as well as the white matter fibers [corticospinal motor (CST) & thalamocortical sensory tracts (TST)]. A common deficit in children with hemiplegic cerebral palsy (HCP) is abnormal upper limb motor functioning. Although musculoskeletal impairments are seen in most of these children, musculoskeletal deformations may not be the sole reason for their motor aberrations. Alterations in brain activity likely contribute to motor deficits in children with HCP. A handful of previous studies have examined this altered brain activity but mostly focused on lower extremities.

Materials & Methods:

A retrospective database was collected focusing on all children treated at Cook Children's Health Care System satisfying the following inclusion criteria: (i) a diagnosis of HCP due to PV-WMI identified by a neurologist and confirmed through a brain MRI; (ii) capable of staying relatively still for several minutes in order to perform functional neuroimaging studies; and exclusion criteria: (i) no history of trauma or brain operations; (ii) absence of metal implants, braces, baclofen pumps, and seizure history; and (iii) receiving occupational upper extremity treatment We delineated the brain plasticity changes that occur in HCP with TD children. We assessed both functional and structural mapping of the primary motor (M1) and somatosensory (S1) cortices using MEG and HD-EEG. Additionally, DTI was used to detect the integrity of the descending CMT and the ascending TST.

Results:

Initial studies performed by Papadelis et al. illustrated the importance of both motor and sensory tracts in predicting the severity of deficits in children with CP. With the utilization of novel neuroimaging techniques, they were able to correlate the degree of sensory tract injury to eventual sensory deficits. Using MEG, HD-EEG and DTI our study was able to further define the pathophysiology of musculoskeletal impairments in patients with hemiplegic CP. Our results show that HCP had a weaker event-related desynchronization (ERD) and event-related synchronization (ERS) than typically developing children, with regards to visual stimulation.

Conclusions:

Our study was able to further map the brain plasticity changes seen in HCP. We found that there were differing changes in the white matter tracts that were dependent on the initial brain injury and correlated them to impairments in visuomotor tasks. Through HD-EEG, MEG and DTI, we were able to measure the ERD: a short-lasting attenuation signal in the cortices right before a visual stimulation, as well as the ERS: the power of the increase or decrease in the EEG waveform of a specific frequency during motor execution. Comparing six typically developing children and six children who suffered from HCP, we saw a significant difference, with those with HCP having a weaker response. Lastly, we were able to pinpoint specific cortices of the brain that were primarily affected.

Introduction

Cerebral Palsy (CP) is defined as a syndrome of motor impairment that results from a lesion occurring in the developing brain; the disorder varies in the timing of the lesion, the clinical presentation, and the site and severity of the impairment[1]. CP is a relatively common motor disease of childhood that has everlasting impacts. In developed countries it occurs in every 2-3.5 births per 1000[1]. It can be classified anatomically, by extremity involvement, or by muscle tone[1]. One of the more common forms is hemiplegic cerebral palsy (HCP) or hemiplegia. Hemiplegia refers to one side of the body, therefore, HCP is presents with unilateral defects. In HCP, there is impairment of hand usage & bimanual coordination on one side of the body[2]. It can present with both upper and lower extremity motor and sensory defects. Additionally, HCP can result in cognition deficits as well, which can often be debilitating and irreversible.

HCP is thought to be due to a lesion in the periventricular white matter that occurs during the development of the human brain.[3]. The cause of the lesion can be either congenital or acquired. The common acquired causes are due to fetal stroke, ischemia, birth trauma, and preeclampsia. Lesions in white matter early in development can result in impactful deficits. For instance, a lesion early in the development of the corticospinal tract can lead to severe motor impairment as the nerve tracts cannot fully recover. It is important to note that the corticospinal tract is one of the first to mature. The periventricular white injury (PV-WMI) is variable and can cause different outcomes for each patient, depending on the extent, location, and timing of the injury in the developing brain (**Figure 1**)[4]. For instance, if there is a white matter mass that alters the corticospinal tract development on one side of the brain, but it occurs prior to the sensory tract development, it can possibly spare sensory deficits[4].

Despite its severity and prevalence, little is still known about the brain reorganization and changes that occur in the developing brain with those with HCP. With advancing neuroimaging techniques, such as MEG, HD-EEG, and DTI, there is potential to further the understanding of the developing brain. By simultaneously using MEG with HD-EEG (**Figure 2**), we can assess functional changes in the primary motor and primary somatosensory cortexes due to brain plasticity. Additionally, DTI can provide insights into the microstructure of white matter tracts to assess structural changes (**Figure 3**)[5]. Existing literature suggests that functional and anatomical mapping of the brain can be crucial to future CP treatment[6]. Another longitudinal study followed 17 children diagnosed with CP and confirmed that clinical symptoms were related to changes in the white matter, but also those children who had healthier white matter, had more favorable outcomes for treatment[7].

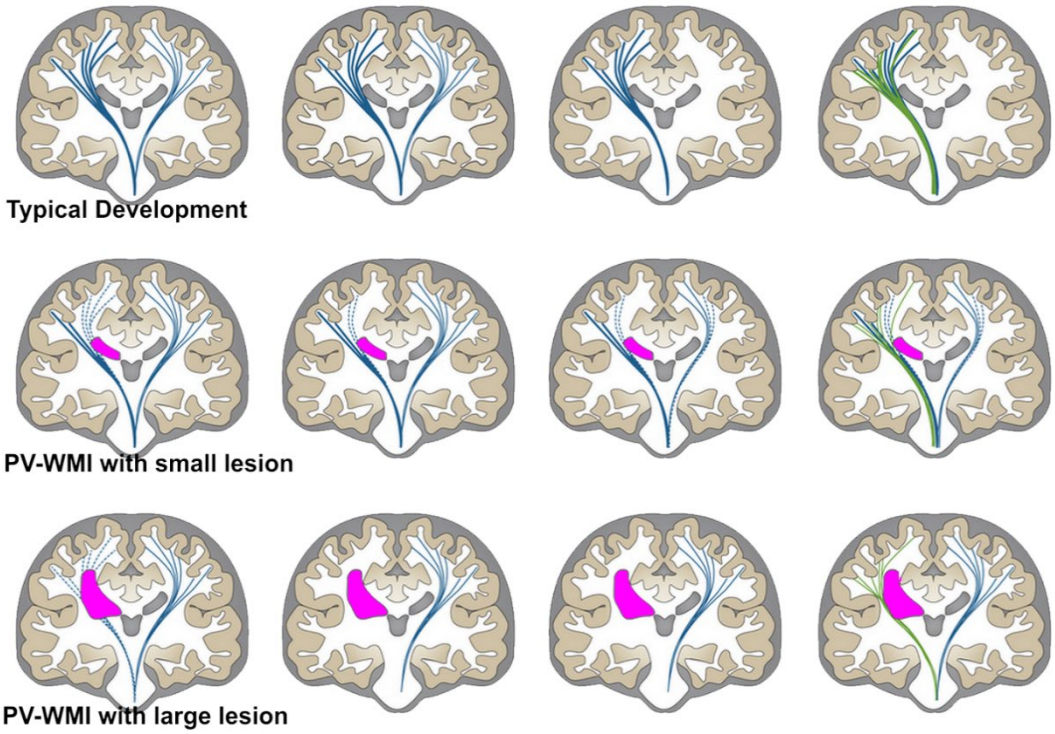

Figure 1. *Different periventricular white matter injuries (PV-WMI) and their concurrent effects on the developing brain corticospinal tract. In typical development, corticospinal motor tracts (blue) project bilaterally to the primary motor cortex. As the child grows, the ipsilateral tracts prune leading to an exclusive contralateral control of the hands. With a small lesion (pink) there is a disruption the corticospinal tract connection leading to bilateral motor cortex control of the affected side. With large lesions, there can be a total failure of one side of the tracts to form, causing a full motor control of the paretic hand from the ipsilateral hemisphere. Adapted from 'Rehabilitation and neuroplasticity in children with unilateral cerebral palsy' by Reid et al. 2015, Nature Reviews Neurology.*

The evidence to focus on functional mapping for the basis of therapy for CP is growing. Different therapy modalities may result in specific functional improvements. A cohort study compared constraint induced movement therapy (CIMT) and bimanual training (BIM) in patients

with congenital HCP, and found that CIMT significantly improved unimanual coordination, while BMI significantly improved bimanual coordination[8]. Each different type of training can have its own unique results. Combining the knowledge of neuroplastic changes with therapy can result in significant improvements in CP deficits. Novel therapeutic measures are continually developing. Still, more research is required to correlate brain reorganization in HCP children to clinical manifestations. It is imperative that we continue to build upon the foundational knowledge while applying it to new therapeutic avenues.

Figure 2*: MEG and HD-EEG set up. (a) The Philips EGI 400 (256 electrodes) is easy to put on kids because it does not require the use of a conductive gel. Instead of using gel, you soak the net with the attached sponges in water which allows the sponges to become conductive. This procedure is quick and easy, especially for children with motor and sensory deficits as children with hemiplegic CP. (b) Co-registration procedure in order to determine the relative localization of the HD-EEG sensors with respect to the child's head anatomy. (c) The child sits comfortably in the MEG with their head placed in the MEG helmet while they sit upright.*

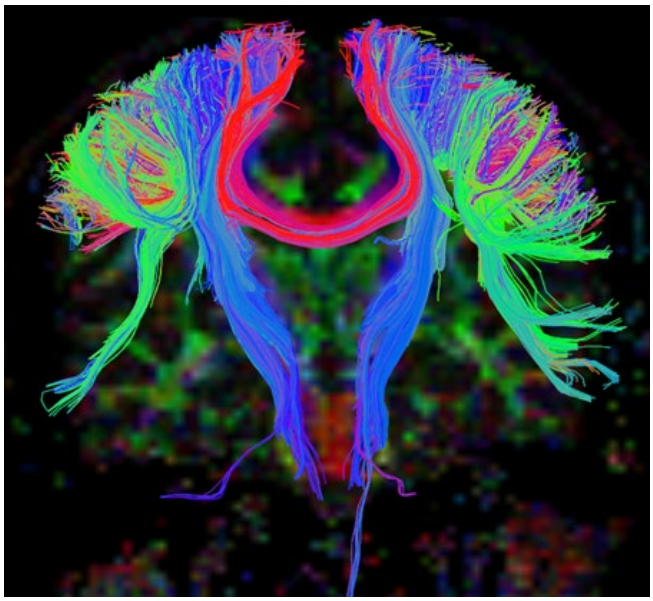

Figure 3: *Mapping of the white matter fibers in the brain of a 16-year-old TD child using DTI. The different colors represent the directionality of the water diffusion. Adapted from 'Diffusion tensor imaging demonstrated radiologic differences between diplegic and quadriplegic cerebral palsy', by Chang et al., 2012, American Journal of Neuroradiology.*

Significance/Rationale

CP is associated with the highest lifetime costs of any childhood disorder. The Center for Disease Control and Prevention (CDC) estimates that the lifetime cost to care for an individual with CP is ~$1M[9]. HCP causes serious motor impairments often accompanied by disturbances of sensation[10,11,12,13] and has substantial effects on the function and health-related quality of life for children and their families[14].

Current standards for CP therapy include occupational & speech therapy and adaptive equipment; there is a need to diversify therapeutic avenues. There is continuing evidence that interventions during the first two years of life in HCP can be more influential than later in life. If we can better understand the brain parenchyma and the mechanisms in which they change during HCP, we can make significant improvements in treatment and therapeutics. New strategies and targets can be developed to improve the lifestyle and lessen the impact of the childhood disorder for both the patient and their support network. This study has the potential to improve our understanding of both motor and sensory organization in children with HCP as well as further the literature on the feasibility of neuroimaging studies of patients with HCP within their developing years.

Materials and Methods:

Database collection

Utilizing the Cook's Children Medical Center patient database, we collected data on all patients with a diagnosis of HCP and could be stratified based on: (i) previous neuroimaging findings/underlying pathology; and (ii) associated clinical symptoms. The database was utilized to correlate the imaging findings to the clinical outcomes.

Study Participants and Setting

Six children with spastic HCP (six males; mean age: 12.3±2.2 years) and ten age-matched typically developing (TD) children (six males; mean age: 11.5±1.7 years) participated in this study.

MEG imaging with HD-EEG

To determine the functional relationships in patients with HCP, MEG with simultaneous HD-EEG will be utilized.

Recording

We recorded simultaneous 256-channels HD-EEG and 306-sensors MEG recordings while participants were performing a visuomotor integration task. Participants were instructed to tap their left index after a cartoon cat image presented and to tap their right index after a cartoon dog image presented (Go trials), and not to tap when a red-light bulb image followed the cat or dog image (NoGo trials) **(Fig.6)**. Go and NoGo trials were randomly scattered (75% Go and 25% NoGo trials). MEG and HD-EEG data analysis was performed with Brainstorm. Recordings were firstly filtered (band-pass: 1-100 Hz; notch: 60 Hz), then epoched into trials time-locked to the visual-Go cues and tapping onset as detected from electromyography (EMG) that was collected at the first dorsal interosseous muscle of both hands. Cortical source waveforms were reconstructed with dynamic Statistical Parametric Mapping (dSPM) source inversion to individual specific boundary element model. Event-related desynchronization (ERD) and synchronization (ERS) in alpha (8-13 Hz) and beta (14-30 Hz) frequency bands were assessed at sensor level, then localized to cortex by computing whole cortex activity time-frequency maps.

Data Collection

Data analysis was performed using Brainstorm[15]. Magnetic evoked fields (MEFs) elicited by finger movements was estimated. Somatosensory evoked fields (SEFs) was estimated for each stimulation site. Time frequency analysis for both MEFs and SEFs was estimated for each trial and averaged. As time-lock triggers, we used the movement onset from the accelerometer for the MEFs, and the tactile stimulus onset for the SEFs. Source localization of M1 was performed with a beamformer[16]. Source localization of S1 was performed at the peak of the first response after stimulation. The activity of M1 and S1 was mapped onto the source volume.

Diffusor Tensor Imaging (DTI)

DTI is an imaging technique that utilizes MRI to detect specific changes in location, orientation, and anisotropy of white matter tracts in the brain[17]. It is used to map the diffusion of water through the tracts, providing the spatial location. We tracked the CST and the TST for all participants using DSI studio[18]. For these tracts, we estimated the following DTI measures: mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (Dr), and axial diffusivity (Da). MD is a measure of rotationally invariant magnitude of the diffusion of a substance and FA is a measure of the total directional movement of water [19]. While Dr and Da measure the magnitude of water diffusion independent of the directional movement [20]. Out of these indices, FA is the most sensitive to microstructural changes in the white matter, while Dr and Da are can delineate the specific changes[21]. These measurements can give insight into axonal degeneration/integrity as well myelination/demyelination.

Statistical Analysis

To correlate the functional changes in M1 and S1 and the structural changes of the CST and TST in children with PV-WMI, with their hand motor performance assessed by the AHA test[22-23] The AHA scores were transformed to equal interval unit logits by a Rasch-analysis. Functional MEG measures included the LI for M1 and the Euclidean distances between the cortical responses in S1. Structural DTI measures included MD, FA, Dr, and Da of the CMT and TST. Associations between categorical and continuous variables were analyzed using nonparametric Mann-Whitney U tests. Correlations between MEG and DTI measures and AHA score was assessed using

Spearman correlation. To evaluate the relationship between MEG and DTI variables and AHA score, univariate linear regressions were performed. Multivariate general linear regression were performed for candidate measures that are associated with AHA score ($p<0.05$).

Results:

Initial Data:

A study performed in 2014, by Papadelis et al., was the first study to successfully use multiple neuroimaging techniques on the same group of CP patients. Additionally, it showed that both motor and sensory divisions of the brain can lead to different clinical outcomes for CP patients, as well as the importance of the connectivity in the motor and sensory tracts, respectively, in the pathophysiology of the disease, illustrated in **Figure 4** below. Another study performed in 2018 by Papadelis et al., further advanced our knowledge on the ascending sensory tracts or connectivity of the sensory pathway. Through different neuroimaging modalities, such as MEG and DTI, Papadelis et al., was able to correlate the degree of sensory tract injury to sensor deficits in the contralateral hand. The DTI results are shown in **Figure 5** below, illustrating the amount of neuronal damage.

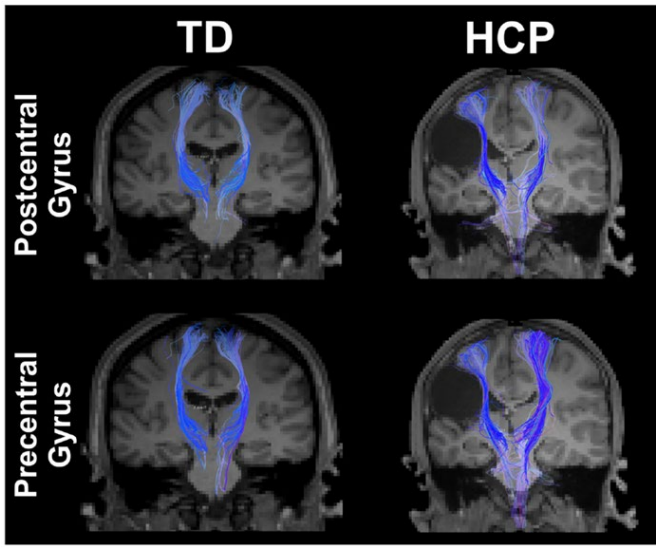

Figure 4. *Thalamocortical white matter fiber tract projections in TD and HCP, patients captured via DTI and MRI imaging. Thalamocortical tract project to the primary somatosensory cortex. Adapted from 'Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study' by Papadelis et al., 2014, Frontiers in Human Neuroscience*[6]

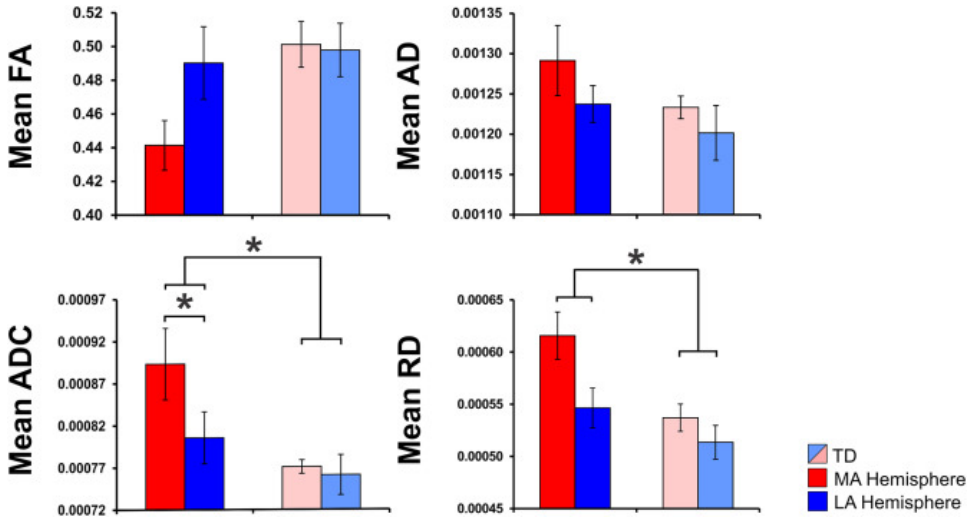

Figure 5. *DTI measurements of the ascending sensory tracts (thalamocortical) of HCP and TD children. Each graph is an average of the digits (thumb, middle finger, and pinky finger) of both the more affected (MA) in red, and least affected (LA) in blue, hemispheres. The measurements of fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and apparent diffusion coefficient (ADC) all represent different characteristics of water diffusion through the brain. The values represent axonal characteristics and can show the amount of neuronal damage. The error bars are indicated the standard error of the mean and the asterisks show the statistically significances between each group ($p<0.05$). Adapted from 'Reorganization of the somatosensory cortex in hemiplegic cerebral palsy associated with impaired sensory tracts' by Papadelis et al., 2018, Neuroimage: Clinical*[24].

Data:

As stated above, we defined different trial types Go or No-Go, while associating them with a cue **(Fig. 6).** Utilizing EMG data, we marked when the initial onset of the cue began, and then the time of onset of when the patients activated their first dorsal interossei muscle or index finger. Utilizing MEG and HD-EEG, we could correlate these findings to the cortical centers of the brain. By using sensor level time-frequency analysis we showed that children with HCP had weaker alpha and beta ERD **(Fig. 7; $p<0.05$)** and ERS **(Fig. 8; $p<0.05$)** than TD children. Source localization of alpha beta ERD and ERS revealed that cortical oscillation differences between children with HCP and TD children mainly exist in the sensorimotor cortex, superior parietal cortex, V1 and V5 visual areas.

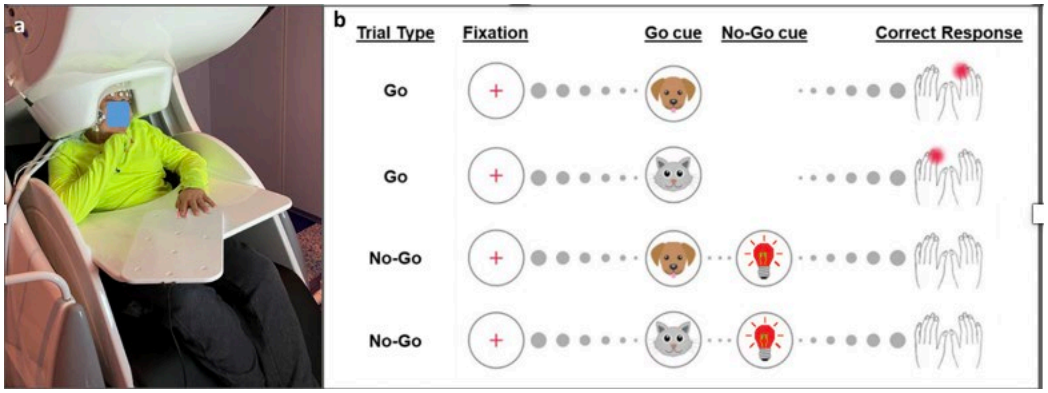

Figure 6. *Go trials were defined by when the patient saw either a cat or a dog as the image. If a dog was seen, they were instructed to tap their R index finger, if a cat was seen, their L index finger. No-go trials were defined by when the patient saw either a cat or dog plus a red light and were instructed to not tap any finger.*

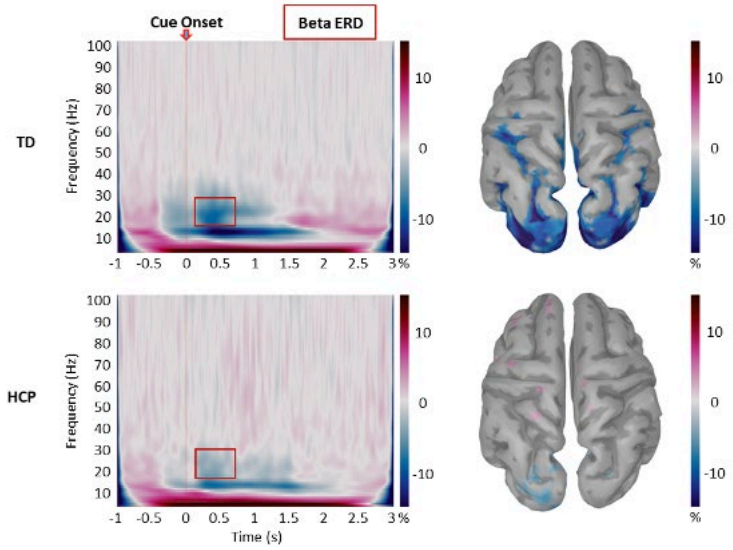

Figure 7: *Source Level beta ERD. ERD refers to event-related desynchronization or the short-lasting attenuation signal in the cortices of the brain prior to a visual stimulation. The image of the brain on the right illustrates the stronger signal in typically developing children as compared to children with HCP. The graph onf the left of the image correlates with the image. Additionally, the brain image shows the localization of the signal.*

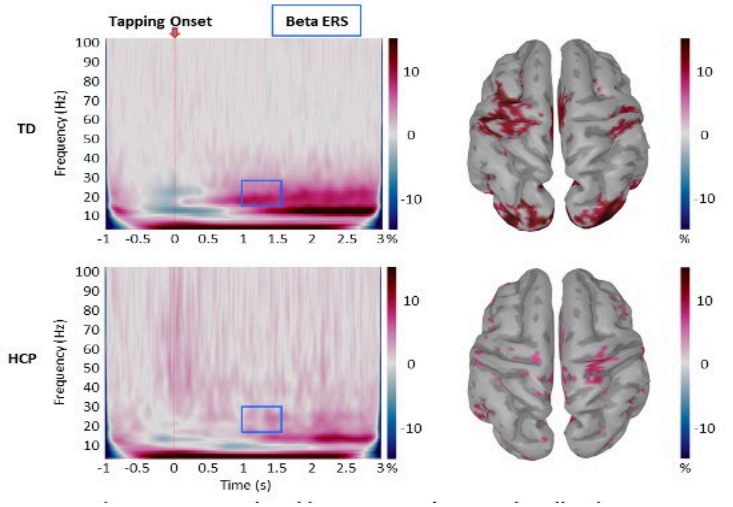

Figure 8: *Source level beta ERS and source localization. ERS refers to event-related synchronization or the power of the increase or decrease in the EEG waveform of a specific frequency during motor execution. The image of the brain on the right illustrates that there the stronger signal in typically developing children as compared to children with HCP. The graph on the left of the image correlates with the image. Additionally, the brain image shows the localization of the signal.*

Discussion:

As CP continues to plague many children and families worldwide, there is a strong need to improve rehabilitation and therapeutic strategies. The motor and sensory deficits that result can leave an everlasting impact on many. Science has advanced our knowledge on functional and structural changes that occur, using novel imaging techniques and statistical analysis. However, there is still more that needs to be done, as it can have a significant impact on the quality of life of many patients. CP not only impacts motor and sensory function but has can also have a negative social impact. For instance, those with severe damage due to CP could be paralyzed and in a wheelchair. This can lead can be debilitating not only in a physical sense, but also a mental burden. Additionally, parent's mental health and quality of life can be negatively impacted, by having to pay expensive medical bills, and having to see their child go through such grueling conditions. These multiple factors that can be addressed and alleviated by better targeted therapy.

With the use of novel brain imaging techniques: DTI, MEG, and HD-EEG we have better defined the brain plasticity changes that are seen in hemiplegic cerebral palsy patients. We can now better understand not only the localization of the white matter tract injury, but also the extent of the injury.

Through DTI previous studies have found that the fractional anisotropy (FA) in the most affected region of the brain, or where the initial anoxic brain injury occurred was significantly decreased. Fractional anisotropy represents the total directional movement of water[19], and as water diffuses through an axon it should increase. In fact, a decrease in FA is regarded as a sensitive early detection of change in white matter infrastructure[27]. Therefore, with the use of DTI to detect FA we can estimate the extent of white matter damage seen in HCP but comparing it to a typically developing child.

Additionally, a common deficit in patients with HCP is upper motor functioning. Children with hemiplegic cerebral palsy tend to have abnormal motor function in their upper limbs, and it has been thought to be primarily due to muscle deformations. Patients with CP suffer from spasticity, which is defined as velocity-dependent changes in muscle tone, leading to functional impairments. Cortical oscillations or alterations in neuronal activity are a possible contributing factor that is poorly understood. We recruited six patients with HCP and ten typical developing children with similar age groups to perform the visuomotor task described above. Using a visuomotor task and integrating MEG, HD-EEG and EMG we found that patients with HCP had weaker brain activation than typical developing children. Furthermore, after performing source localization analysis we found that this primarily occurred in sensorimotor, superiorparietal cortices, and the V1 and V5 visual areas. The sensorimotor cortex is responsible for the execution of movements on the contralateral side of the body[25]. While the superiorparietal cortex and the V1 and V5 visual areas have a role in visuospatial processing[26]. Thus, our findings indicate that patients with HCP may have difficulty in both planning and executing visuomotor tasks due to not only muscle deformations, but also wavering neuronal activity in these specific areas of the brain.

As we continue to further our knowledge the specific structural changes that occur during the initial anoxic brain injury, that ultimately develops into cerebral palsy, there is a growing need to further define these changes. Our study was able to add another piece to the puzzle by defining changes in neuronal activity that are evident in patients who suffer from HCP. By localizing the delays in cortical signaling, we now have potential targets for therapies.

Future Directions:

With the ability to measure neuronal activity and compare it to controls, we now have a measurement or capability to assess visuomotor rehabilitation methods in patients with cerebral palsy. Additionally, we have specific cortices that we can target, such as the superiorparietal and V1 and V5 visual areas. Rehabilitation methods are continually advancing and improving. Robotic rehabilitation will play a crucial role in improving patients' functional outcomes with cerebral palsy. The Amadeo Robot has shown clinical improvements in patients who have suffered from a first-time stroke, with resulting hemiparesis. Performing three hours of neuro physiotherapy, which included skill and gait training, clinical outcomes improved for all seven subjects in a study conducted by Sale et al.[28] Despite the success of studies, there continues to be a need to perform further studies to help reduce the disease burden of cerebral palsy.

Conclusion:

In summary, through novel brain imaging techniques, cerebral palsy, an increasingly common neuromotor brain disease can be better characterized. In our study, we were able to further map the brain plasticity changes seen in HCP. We found that there were differing changes in the white matter tracts that were dependent on the initial brain injury and correlated them to impairments in visuomotor tasks. Patients who suffer from cerebral palsy can benefit from focused rehabilitation on cortical planning. With the further use of robotics in the future, we could help train children in simple visuomotor tasks, such as the one defined above. We can now successfully map changes in activity. Therefore, here is a continued need define the exact brain changes that occur after intensive rehabilitation. This study further increased the knowledge and feasibility of HD-EEG, MEG, DTI, and EMG as a marker for rehabilitation success in patients with HCP. Additionally, it allowed us to localize changes in neuronal activity to certain areas of the brain, meaning the future rehab can be more targeted.

Compliance:

This research study was conducted under the supervision and guidance of my mentor, Dr. Papadelis who is the Director of Research at the Jane and John Justin Neurosciences Center of Cook Children's Health Care System, a Professor of Pediatrics in TCU Burnett School of Medicine, an Adjunct Associate Professor in the University of Texas at Arlington, and an Assistant Professor of Pediatrics at Harvard Medical School. All patients who were evaluated in this study were followed by a pediatric physician at Cook’s Children Medical Center. All data was collected at Cook’s Children Medical Center.

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