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Beyond the eye: The neural signature of cerebral visual processing in children with cerebral palsy

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BEYOND THE EYE: THE NEURAL SIGNATURE OF CEREBRAL VISUAL PROCESSING IN CHILDREN WITH CEREBRAL PALSY

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Cerebral palsy (CP) is a permanent, non-progressive neuromuscular disorder diagnosed early in childhood. Frequently the lesion that causes the motor impairments in individuals with CP concurrently disrupts the visual networks, placing them at a high risk of cerebral visual dysfunctions. Cerebral visual impairment (CVI) often remains unrecognized or misdiagnosed in people with CP. Despite the crucial role of visual function in the development of movement and cognition, the neurophysiological basis of the cerebral visual dysfunctions is almost entirely unknown. This investigation aimed to examine the neurophysiological mechanisms underlying cerebral visual dysfunction in children with CP. Specifically, this research used magnetoencephalographic brain imaging techniques to evaluate the cortical processing of visual motion, spatial contrast, and spatial attention. The first study identified aberrant oscillatory activity in the motion-sensitive MT/V5 cortex, while participants viewed horizontal movement. These visual processing deficits were linked with delayed motor responses and errors in perceptual judgments. The outcomes of this study suggest that the uncharacteristic neural oscillations in the visual MT/V5 cortical area may partially account for the abnormal perceptions and motor decisions seen in children with CP. The second study targeted the processing of basic perception, independent of visual motion, by using a high-contrast spatial-grating known to elicit gamma oscillations and associated with visual acuity. This study found that children with CP have deficits in the frequency-specific occipital oscillations involved in the processing of contrast. The third study probed the cortical oscillations serving visuospatial attention,

arguably the most prevalent cerebral visual dysfunction reported in children with CP. The outcomes from this study showed blunted neural responses serving visual-spatial processing and related the visual dysfunction to performance errors during a visual-spatial discrimination task.

These studies collectively provide neurophysiological evidence for the prominent cerebral visual processing deficiencies in children with CP. Linking these aberrations with perceptual-motor impairments transforms our perception of how small differences in visual processing affect the motor functions of children with CP. Identifying these specific deficiencies in the neurophysiological mechanisms underlying CVI in children with CP should prompt clinicians in new directions for targeted therapeutic interventions.

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
BOLD	Blood-oxygen-level-dependent
CIMT	Constraint induced movement therapy
CNS	Central nervous system
CP	Cerebral palsy
CST	Corticospinal tract
CVI	Cerebral visual impairment
DTI	Diffusion tensor imaging
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
GABA	γ-Aminobutyric acid
GMFCS	Gross motor classification system
MACS	Manual ability classification system
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
MRICS	MRI classification system
MRS	Magnetic resonance spectroscopy
PET	Positron emission tomography
PVL	Periventricular leukomalacia
SPSS	Statistical package for social sciences
SQUID	Superconducting quantum Interference
SSS	Signal space separation

TD	Typically developing
TFC	Time frequency component
TMS	Transcranial magnetic stimulation

INTRODUCTION

Cerebral palsy (CP) describes a group of non-progressive neuromuscular disorders that develop from a prenatal or early brain abnormality or lesion that disrupts brain development and leads to impaired motor control – the hallmark feature of CP (Rosenbaum et al., 2007). The type of tone or movement dysfunction (*i.e.*, spasticity, dyskinesia, or ataxia) and the topographical presentation (*i.e.*, hemiplegia, diplegia or quadriplegia) is dependent on the specific characteristics of the brain abnormality (Rosenbaum, Eliasson, Hidecker, & Palisano, 2014). In the United States, 77% of children with CP have the spastic subtype, and the bilateral presentation is reported most frequently (Christensen et al., 2014).

The brain pathology associated with CP may be classified by the type, presumed timing, extent, and location (Krägeloh-Mann & Horber, 2007). Periventricular white matter lesions account for about half the brain abnormalities found in children with CP and almost all of the brain lesions found in preterm infants (M. Pavlova, Sokolov, & Krägeloh-Mann, 2007). Other types of brain pathology include cortical and subcortical gray matter lesions and miscellaneous lesions (*e.g.*, cerebellar or cerebral atrophy). The extent of brain damage is related to the functional outcomes as children with more substantial damage tend to present with more significant impairment (Krägeloh-Mann, 2004). However, there is not always a direct connection between structure and function. In about 10% of children with CP, there is no observable brain damage (Himmelmann et al., 2017).

In recent years, there has been a growing recognition that visual impairments are a core feature of CP (Ego et al., 2015; Fazzi et al., 2012). Visual dysfunction has been reported in 40 - 90% of children with CP (da Cunha Matta et al., 2008; Dufresne, Dagenais, & Shevell, 2014; Ego et al., 2015; Fazzi et al., 2012; Nikolaos Kozeis et al., 2015), with

one in 10 children having a severe visual impairment or blindness (Novak, Hines, Goldsmith, & Barclay, 2012). The wide discrepancy in incidence is dependent on which aspects of vision are assessed and the method of assessment.

Children with CP present with an extensive spectrum of visual dysfunction that may encompass the peripheral (*i.e.*, eye to the optic chiasm) and central visual systems (Chokron & Dutton, 2016). Within the peripheral visual system, strabismus and refractive errors are the most common visual problem in children with CP (Fazzi et al., 2012; M. J. Park, Yoo, Chung, & Hwang, 2016). Ocular-based impairments are relatively well understood, diagnosed, and have targeted treatments (*e.g.*, prescribing eyeglasses, surgery, low-vision aids). Comparatively, we have a substantial knowledge gap in our understanding of central visual dysfunctions, which likely contributes to clinicians overlooking CVI (Fazzi et al., 2012; Philip & Dutton, 2014) and lacking effective interventions when CVI is identified (Novak & Honan, 2019; Novak et al., 2020).

Central visual problems are broadly categorized as cerebral visual impairments (CVI). These impairments cannot be explained by any ocular pathology and can be present despite normal eye conditions (Chokron & Dutton, 2016; Philip, Guzzetta, Chorna, Gole, & Boyd, 2020). CVI occurs when a brain abnormality disrupts a portion of the visual processing pathway beyond the optic chiasm (*i.e.*, lateral geniculate nucleus, optic radiations, occipital cortex, and visual-associative areas), causing visual dysfunction (Chokron & Dutton, 2016). Briefly, processing the visual scene is a complex and dynamic process that involves interactions between the two visual processing streams, bottom-up processing of visual information coming in, and top-down cognitive and perceptual influences (Gilbert & Li, 2013). Subsequently, disturbing this process may cause a wide range of visual, perceptual, and visuomotor dysfunctions. Dorsal stream (*i.e.*, occipital-parietal or “where” pathway) dysfunctions include problems with visual attention, handling

complex visual scenes and the visual field, motion perception, and visually guided movements like navigation and reaching (Dutton, McKillop, & Saidkasimova, 2006). Ventral stream dysfunctions (*i.e.*, occipital-temporal or “what” pathway) include difficulty recognizing faces, photographs, objects, shapes, routes, and orientation (Dutton et al., 2006).

CVI is most strongly linked with spastic CP and white matter damage (*i.e.*, periventricular leukomalacia), both of which are associated with preterm birth (Philip et al., 2020). Visuospatial impairments are among the most prevalent CVI observed in children with CP (Ego et al., 2015; Pueyo, Junqué, Vendrell, Narberhaus, & Segarra, 2009). Impaired visual functions can further disrupt motor function, communication, socialization, and participation in activities of daily living (*e.g.*, dressing, feeding, bathing) for children with CP (Chokron & Dutton, 2016; Dutton et al., 2006; James, Ziviani, Ware, & Boyd, 2015).

In children with CP, visual dysfunction may be more accurately identified when using electrophysiological methods (Costa & Ventura, 2012). However, what we currently know about CVI is primarily based on behavioral measures and observations (Deramore Denver, Froude, Rosenbaum, Wilkes-Gillan, & Imms, 2016b; Ego et al., 2015; Philip & Dutton, 2014; Philip et al., 2020). Relying on these measures may hamper our understanding of CVI. A recent systematic review of all clinical visual assessments found that there are no valid and comprehensive measures of visual abilities for children with CP (Deramore Denver, Froude, Rosenbaum, Wilkes-Gillan, & Imms, 2016a). Another major problem with current CVI assessments is that they often examine higher-level complex visual processes without considering the lower-level visual processes that are potentially contributing to visual dysfunction. Examining these lower, subcomponents of visual processing may provide insight into the specific visual processes contributing to CVI.

Several studies have used structural MRI data to identify overt brain abnormalities connected to CVI (Philip et al., 2020). However, the pathology of CVI is not always apparent in structural images, and visual function not reliably predicted from structural images (Philip et al., 2020). Children with all subtypes of CP resulting from any brain abnormality may also have CVI (Philip & Dutton, 2014; Philip et al., 2020). Besides a shared etiology, there is no clear correlation between CVI and CP.

A comprehensive understanding of basic visual-perceptual processing mechanisms is required to inform the development of effective assessments and therapies. Research exploring visual cortical processing may reveal insights into the neural signature underlying CVI unrecognized by other methodologies. This dissertation aims to fill this need by systematically evaluating the visual processing networks in children with CP.

Current Study

The current study aims to identify the neural mechanisms that underlie the cerebral visual impairments in children with CP, and to explore how the neural responses identified contribute to the uncharacteristic motor actions in these children. To this end, this dissertation presents a series of studies designed to systematically evaluate basic components of the visual processing networks in children with CP. These studies will utilize the high spatial and temporal resolution of magnetoencephalography (MEG) to quantify the neural activity in a group of older children with CP, and a similar-aged group of typically developing (TD) for comparison, as they process different types of visual information. Significant cortical oscillatory responses in each study will be imaged using beamforming techniques, then statistically compared between groups. The first study directly examines the neural responses that generate visual motion perception by

quantifying the oscillatory activity in the motion-sensitive MT/V5 cortex while viewing a horizontally moving stimulus I hypothesize that children with CP will have a weaker MT/V5 cortical oscillatory response than the TD children. Also, the neural activity will be related to their perceptions of visual motion. Building on this, the second study targets basic perception without visual movement. It does so by analyzing a multi-spectral pattern of occipital responses that are typically generated while processing a high-contrast spatial grating, which is a basic visual acuity stimulus. In this study, I hypothesize that the children with CP will have diminished cortical oscillations in the primary visual cortex. The final study evaluates the visual cortical oscillations serving spatial attention. The hypothesis is that children with CP will have blunted cortical activity related to their performance errors in a visual-spatial discrimination task.

CHAPTER 1: LITERATURE REVIEW

Cerebral Palsy

Cerebral palsy (CP) is a prevalent, non-progressive and permanent neurodevelopmental disorder initially diagnosed by the presence of abnormalities in movement and posture as a result of brain injury occurring during fetal development or early in life (Rosenbaum et al., 2007). One in 323 children in the United States has CP (Christensen et al., 2014). Although the incidence of CP has increased prior to the 1970's, it has remained consistent over the past 25 years and is similar to the prevalence reported in European countries (Christensen et al., 2014; Odding, Roebroeck, & Stam, 2009). Individuals with CP have other co-occurring conditions including speech impairments (80%), cognitive impairments (60%), epilepsy (40%), and feeding problems (50%; Odding et al., 2009).

Factors that increase the risk of a child having CP include a maternal infection, twin pregnancy, low birthweight for gestational age, hyperbilirubinemia, birth depression, and preterm birth (Bax, Tydeman, & Flodmark, 2006; Odding et al., 2009). Preesclampsia may be protective against developing CP (Odding et al., 2009). Demographic factors that may increase the risk of CP include being of black race, male, and low socioeconomic status (Christensen et al., 2014; Odding et al., 2009). There is a higher prevalence of children with CP born with normal birthweight in low social-economic areas compared to affluent areas. Additionally, a greater percentage of children with CP born with low birthweight were from the more deprived areas.

Pathology of Cerebral Palsy

When a concern arises regarding a child's motor development, neuroimaging using magnetic resonance imaging (MRI) to determine etiology is first recommended

(Ashwal et al., 2004). Using the MRI classification system (MRICS), the pathogenic patterns indicative of CP are qualitatively classified into five main groups based on the timing and type of brain injury: maldevelopments, predominant white matter injury, predominant grey matter injury, miscellaneous, and normal findings (Himmelmann et al., 2017).

Brain abnormalities are found on 86% – 89% of MRIs of individuals with CP and occur in the prenatal, perinatal or infant brain (Ashwal et al., 2004; Taylor, Jakobson, Maurer, & Lewis, 2009). Brain abnormalities occurring in the initial stages of fetal brain development through the second trimester include malformations due to proliferation, migration, or organization (Krägeloh-Mann, 2004; Krägeloh-Mann & Horber, 2007). These early maldevelopments are found in only 9% of individuals with CP, and more frequently in children born at term. The origin of these brain abnormalities are frequently syndromes, genetic disorders, viruses, or infections (Krägeloh-Mann & Horber, 2007).

White matter periventricular lesions occur early in the third trimester as the fetal brain continues to grow and differentiate. These type of lesions account for about half of the brain abnormalities in individuals with CP and about 90% of the abnormalities seen in infants born preterm (Krägeloh-Mann, 2004; Krägeloh-Mann & Horber, 2007). Periventricular leukomalacia (PVL), a type of white matter lesion, contributes to significantly larger ventricles in infants. The enlarged ventricular volume has been correlated with the magnitude of the motor impairment (Melhem et al., 2000).

Cortical and subcortical gray matter lesions occur later in the third trimester and are found in 18% individuals with CP (Krägeloh-Mann & Horber, 2007). In about 12% of individuals with CP, brain anomalies are absent on imaging scans. Some authors suggest that genetic or metabolic disorders may account for the presentation of CP characteristics among these cases (Bax et al., 2006). Others have suggested that newer neuroimaging

methods that evaluate the structural fiber tract integrity may identify more nuanced brain damage not observable on traditional MRI scans (Le Bihan & Johansen-Berg, 2012; Son et al., 2007).

Minimally, the lesioned area will affect a cortical or subcortical motor area, but additional areas are commonly involved. The extent may refer to a diffuse or focal event (*e.g.*, stoke). Additionally, many of these brain abnormalities are differentially distributed between groups of CP types and classification levels of function. The clinical presentation and functional deficits of individuals with CP may be attributed to the location, extent, type and timing of the brain abnormality.

Cerebral Palsy Subtypes

In the United States, individuals with CP are grouped by the topographical pattern of limb involvement (*i.e.*, hemiplegia, diplegia or quadriplegia) and by the type of tone or movement pattern (*i.e.*, spasticity, dyskinesia, or ataxia; Rosenbaum, Eliasson, Hidecker, & Palisano, 2014). The European groups use different terminology, grouping first by unilateral or bilateral presentation, then by topographic description of monoplegia, hemiplegia, diplegia, triplegia, or quadriplegia (Surveillance of Cerebral Palsy in Europe, 2000). The topographical pattern is generally dependent on the brain abnormality with lesions in one hemisphere affecting motor function in the opposite hemisphere.

Of the CP subtypes, spastic CP is the most studied. Motor dysfunction of the spastic type is characterized primarily by pyramidal features (Sanger & Kukke, 2007). Individuals with spastic CP demonstrate increased deep tendon reflexes, hypertonia, hyperreflexia, clonus, and a positive Babinski reflex (Sankar & Mundkur, 2005). More than 75% of individuals who have CP have the spastic type, with approximately twice as many reporting bilateral versus unilateral presentation (Christensen et al., 2014). Periventricular

white matter lesions are found in 63% of individuals with spastic CP, and over half of individuals with spastic CP were born preterm (Krägeloh-Mann & Horber, 2007).

The movements in individuals with dyskinetic CP are characterized by extrapyramidal features – abnormal twisted postures and repetitive movements (Sanger, Delgado, Gaebler-spira, Hallett, & Mink, 2003). Between 7% to 16% of individuals with CP have this type and hemiplegic presentation is rare (Bax et al., 2006). Brain lesions affecting the basal ganglia and thalamus are associated with dyskinetic CP (Bax et al., 2006; Himmelmann & Uvebrant, 2011; Krägeloh-Mann & Horber, 2007; Sanger & Kukke, 2007). Many individuals in this group have severe motor problems and severe communication problems, but less cognitive impairment (Himmelmann & Uvebrant, 2011; Krägeloh-Mann, 2004).

Ataxic CP is also an extrapyramidal motor disorder primarily. Movements are characterized by poor balance and coordination, and difficulty with quick, controlled movements (Sanger & Kukke, 2007; Sankar & Mundkur, 2005). This is the most rare type of CP, accounting for approximately 5% of cases (Bax et al., 2006; Himmelmann & Uvebrant, 2011) and almost exclusively found in children of preterm birth (Bax et al., 2006). Most individuals with ataxic CP can walk independently (Himmelmann & Uvebrant, 2011). Attempts to identify predominant patterns of brain abnormalities among individuals with ataxic CP are inconclusive. Over half of individuals with ataxic CP have normal MRI scans. The brain abnormalities identified include brain maldevelopments, periventricular lesions, and cortical-subcortical lesions (Bax et al., 2006; Himmelmann & Uvebrant, 2011; Krägeloh-Mann & Horber, 2007). Cerebellar hypoplasia may account for the clinical presentation in some cases (Krägeloh-Mann & Horber, 2007).

Motor Function in Individual with Cerebral Palsy

By definition, the primary disabling feature of CP is the presence of abnormal gross or fine motor control (Rosenbaum et al., 2007). Classification systems have been developed to consistently describe everyday functional abilities, aiding in communication, goal setting, intervention planning, and translating evidence (Palisano, Avery, Gorter, Galuppi, & McCoy, 2018; Rosenbaum et al., 2014). Each scale is divided into discrete and clinically meaningful levels relevant to the chronological age of the child. The Gross Motor Function Classification System (GMFCS) describes gross motor abilities in movements such as sitting, walking, and climbing stairs. Level I classifications begin performing the activity without limitations, then the levels progress through independent performance with limitations, utilization of assistance and modification (*e.g.,* a hand-held mobility device), partial participation with limitations, and unable. The GMFCS is the most stable of the classification scales with 42% of children under four years and 27% over four years changing levels (Palisano et al., 2018).

Distributions of gross motor functional abilities may differ by CP subtype. Sixty-three percent of individuals with CP are able to walk independently (Christensen et al., 2014). Within the subtypes, approximately 90% of individuals with hemiplegic CP are independent walkers (Bax et al., 2006; Himmelmann & Uvebrant, 2011).

The literature supports a strong association between the severity of brain lesion, motor function impairment and other associated impairments. Larger brain abnormalities are associated with severe motor presentation (Friel, Kuo, Carmel, Rowny, & Gordon, 2014; Himmelmann & Uvebrant, 2011; Smorenburg et al., 2017; Trivedi et al., 2010). Among individuals with CP who have limited walking abilities (GMFCS level IV) or are non-ambulatory (GMFCS level V), a higher prevalence and severity of comorbidities is

found, including communication problems, cognitive impairment, and epilepsy (Bax et al., 2006; Christensen et al., 2014; Himmelmann & Uvebrant, 2011).

Individuals with CP have other gross motor affecting muscles, posture, and gait with muscle weakness reported as a primary element affecting functional mobility. Slower motor unit motor-unit firing rates may make it difficult to recruit sufficient muscle fibers to generate sufficient force (Rose & McGill, 2005). Peripheral changes in the neuromuscular system cause muscle weakness that limits the muscles' ability to produce adequate force. Disuse could cause changes in muscle size, fascicle length and size of sarcomere bundles (Moreau, Falvo, & Damiano, 2012; Moreau, Teefey, & Damiano, 2009).

Upper extremity movements, especially hand functions, may be impaired in individuals with CP. Similarly to the GMFCS, the Manual Ability Classification System (MACS) groups children into levels based on how they handle objects in daily activities (Eliasson et al., 2006). The MACS levels range from handling objects easily and successfully (level I), able to handle most objects but reduced speed (level II), handling objects with difficulty, needing help to prepare or modify activities (level III), handling a limited selection of easily managed objects in adapted situations (level IV), and not handling or has severely limited ability to perform even simple actions (level V). The MACS is the least stable classification system with 50-70% of individuals with CP changing levels between years (Palisano et al., 2018). Sixty percent of individuals with CP are able to handle most objects (levels I and II), while 24% are unable to handle any objects (Himmelmann & Uvebrant, 2011). Diminished grip strength, sensation, and manual abilities are related to hand use in individuals with CP. Grip strengths are diminished in children with CP (Arnould, Bleyenheuft, & Thonnard, 2014; Klingels et al., 2012; Rich et al., 2017).

Somatosensory Impairments in Individuals with Cerebral Palsy

The brain lesion attributed to the motor system dysfunction may have jointly disrupted the somatosensory system. Literature suggests injury to the sensorimotor cortex, white matter somatosensory tracks, and reduced functional connectivity in the sensorimotor cortex may contribute to widespread somatosensory deficits in individuals with CP (Burton, Dixit, Litkowski, & Wingert, 2009; J. D. Lee et al., 2011; Papadelis et al., 2019; Trivedi et al., 2010; Wingert, Sinclair, Dixit, Damiano, & Burton, 2010).

Somatosensory impairments are prevalent in individuals with CP. All extremities may be affected, albeit the deficit is more pronounced in the affected limb (Wingert et al., 2010). Somatosensory function in most commonly measured with behaviorally-based clinical assessments measuring two-point discrimination, touch-pressure detections, and stereognosis (*i.e.,* identification of forms by haptic manipulation; Auld, Boyd, Moseley, & Johnston, 2011; Krumlinde-Sundholm & Eliasson, 2002). Proprioceptive integrity is measured with matching limb positions between bilateral extremities or estimating the position of one limb (Hedberg-Graff, Granström, Arner, & Krumlinde-Sundholm, 2019; Wingert, Burton, Sinclair, Brunstrom, & Damiano, 2009)

Pure sensory impairments in both perceiving and detecting somatosensory information have been reported using these methods (Arnould et al., 2014; Auld, Boyd, Moseley, Ware, & Johnston, 2012; Klingels et al., 2012; Riquelme & Montoya, 2010; Sanger & Kukke, 2007). Problems with tactile registration may contribute to problems with tactile perception (Auld et al., 2012). Individuals with CP commonly demonstrate poor stereognosis (Auld et al., 2012; Klingels et al., 2012) and a diminished joint position sense (Burton et al., 2009; Ickx et al., 2018; Riquelme & Montoya, 2010).

The cortical processing of somatosensory information may be different compared to similarly aged peers. Studies have provided neurophysiological evidence supporting

aberrant cortical responses to tactile stimulation in children with CP (Kurz, Becker, Heinrichs-Graham, & Wilson, 2015; Kurz, Wiesman, Coolidge, & Wilson, 2017; Kurz & Wilson, 2011; Nevalainen et al., 2008; Sanger & Kukke, 2007). Interestingly, one study reported divergent cortical responses given different intensities of tactile stimulation. Youth with CP had diminished responses to light touch and exaggerated responses to painful when measuring somatosensory evoked potentials with EEG (Riquelme & Montoya, 2010). Evidence suggests that these somatosensory deficits may be contribute to degraded task-based motor performance (Kurz, Heinrichs-Graham, Becker, & Wilson, 2015).

Current interventions for individuals with CP focus on decreasing motor impairments with the goal of improved functional motor performance (Novak et al., 2013). Interventions assume that improved movements will translate to better skills. Somatosensory function is fundamental to everyday hand use, however dexterity, stereognosis, and manual abilities appear to have a greater contribution to functional hand use compared to pure impairments in sensation (*e.g.,* touch registration; Arnould et al., 2014).

Individuals with CP and their families frequently seek occupational therapy and physical therapy services to improve motor activities and self-care function (Novak & Honan, 2019; Novak et al., 2020). Interventions that are activity based, contextually relevant, and goal-directed are highly recommended. For example, there continues to be strong support for therapies focused on the individual actively learning to move the affected arm or hand by increasing usage in functionally relevant activities. Constraint induced movement therapy (CIMT) and bimanual therapy have consistently demonstrated improved hand function in the affected limb in individuals with hemiplegic CP (H. -h.

Huang, Fetters, Hale, & McBride, 2009). These interventions provide an opportunity to examine neuronal responses to functional changes.

Cortical Plasticity and Reorganization

The timing of the lesion impacts further brain development and influences the potential for reorganization. Earlier lesions maybe provide more opportunity for compensation and reorganization compared to later lesions (Krägeloh-Mann, 2004). In the motor system, previous research has used transcranial magnetic stimulation (TMS) pulses to determine hemispheric motor control of the affected limb in individuals with hemiplegic CP. This research has established three types of (re)organization of the corticospinal tract (CST) following a unilateral lesion. The affected limb can be controlled by the typical contralateral projections from the lesioned hemisphere, maintained ipsilateral projections from the nonlesioned hemisphere, or by a mixture of contralateral and ipsilateral projections (Eyre et al., 2007; Eyre, Taylor, Villagra, Smith, & Miller, 2001).

Individuals with ipsilateral, uni-hemispheric corticospinal tract control tend to have more impaired hand function, however improvement after intensive, activity-based therapy is not depend on corticospinal tract projection type (Friel et al., 2014; Holmström et al., 2010; Islam et al., 2014; Kuhnke et al., 2008). Children with all corticospinal tract project types may improve hand function, as only the baseline hand function measures tend to correlate with corticospinal tract dysgenesis (Friel et al., 2014; Islam et al., 2014; Smorenburg et al., 2017). The ability to maintain a typical pattern of contralateral corticospinal tract organization may still be advantageous. Despite both groups improving function, the contralateral group improved speed. The ipsilateral group became slower (Kuhnke et al., 2008).

When the motor function is reorganized following brain damage, the somatosensory function may be altered additionally. In individuals with contralateral corticospinal control have more pronounced somatosensory deficits (Wilke et al., 2009). Evidence for modified somatosensory functions reflect functional reorganization and altered topographical representation in the somatosensory cortex (A. Guzzetta et al., 2007; J. J. Lee et al., 2013; Papadelis et al., 2018; Staudt et al., 2006; Wilke et al., 2009). There appears to me more evidence for somatosensory reorganization when the brain lesion occurs early (*e.g.,* periventricular white matter lesion in preterm infants). In this case the growing somatosensory projections could bypass the lesion and reach the sensorimotor cortex (Eyre et al., 2007; Staudt et al., 2006).

Vision and Visual Function

The basic anatomy of the visual pathway is well understood. Beginning with low-level visual processing in the retina, the pathway continues through the optic nerve, optic chiasm, optic tract, lateral geniculate nucleus (LGN), and optic radiations to the primary visual cortex. Higher levels of visual processing continue as the pathway diverges through the cerebral cortex. Including oculomotor and prefrontal areas, almost half of the cerebral cortex is involved with visual processing (Gilbert, 2013).

Visual processing is divided between two separate yet highly interconnected streams. The model of a dorsal and ventral processing streams was first proposed as two hierarchical pathways that process different information about an object (Gilbert, 2013). The ventral pathway connects the primary visual cortex to the ventral portion of the temporal lobe and processes information about object recognition or “what” an object is. The dorsal pathway connects the primary visual cortex to the parietal and frontal lobes and processes information about “where” an object and is used for guiding movement.

Support for these pathways initially came from animal studies showing that discrete areas of the cortex responded selectively to object features (*e.g.,* color, shape, direction, movement). Other authors have proposed a pathway that reflects parallel processing through separate parvocellular (P) and magnocellular (M) pathways to the primary visual cortex (Liu et al., 2006). The P pathway is a slower, ventral pathway that processes static object properties such as form and color. The M pathway is a faster, dorsal pathway that processes dynamic object properties such as movement and spatial relationships (Gilbert, 2013). More recently a revised model was proposed to reflect the role of vision in actions by dividing the pathways between a vision-for-action (*i.e.,* dorsal) stream and vision-for-perception (*i.e.,* ventral) stream (Goodale, 2011). These models provide a template for understanding where visual processing may become disrupted and what visual functions may be affected.

The development of visual functions begin at birth, and the cortical processing of visual information soon emerges. In a newborn, visual function is under subcortical control, and the visual functions present are more reflexive (Braddick & Atkinson, 2011). As the newborn matures, the cortex takes increasing control of these visual functions and continues to develop visual functions through divergent visual processing streams. Changes in ocular structures (*e.g.*, increasing eye size, changes in rods and cones) account for 25% of the differences in higher visual processes that develop from infancy to maturity (Braddick & Atkinson, 2011), suggesting that changes in functional visual skills may be attributed to the development of cortical visual processing skills. Behavioral and neurophysiological research indicates that cortical visual processing skills develop sequentially, with the cortical visual functions of orientation and spatial frequency tuning emerging first, followed by direction selectivity and binocular disparity (Braddick &

Atkinson, 2011). Although these cortical visual processing skills are not present at birth, there is evidence to support their emergence in the first year of life.

The cortical processing of many visual functions have been explored using functional neuroimaging methods in healthy adults. Specific characteristics of visual stimuli are reflected by different changes in cortical oscillations. For example, viewing a high-contrast square-wave grating (*i.e.,* a basic visual acuity measure) induces a sustained increase in strength of the gamma (> 30 Hz) oscillations and decrease in strength of the alpha-beta (8-25 Hz) oscillations in the primary visual cortices (Adjamian et al., 2004; S. D. Hall et al., 2005; Swettenham, Muthukumaraswamy, & Singh, 2009). Only the strength of the gamma response is dependent on the properties of the contrast stimulus (Swettenham et al., 2009).

Task related changes in cortical oscillations may reflect different brain functions, such as perception or awareness. Alpha and beta (8 – 18 Hz) visual-cortical oscillations have been associated with top-down processing of visual feedback (Bastos et al., 2015; Popov et al., 2017; Van Kerkoerle et al., 2014). These oscillations are thought to influence the neural computations early in the visual stream that are involved in the perception of a visual stimulus (Li, Piëch, & Gilbert, 2004; Piech, Li, Reeke, & Gilbert, 2013). Gamma band neural activity (ERS) in the visual cortex has been associated with the bottom-up thalamocortical processing of visual information (Saleem et al., 2017; Takesaki et al., 2016).

Visual Disorder in Cerebral Palsy

Types of Visual Disorders

Type of visual disorder can be categorized by the portion of the visual pathway where the dysfunction occurs. Ocular impairments occur due to a problem in the initial

segment of the pathway, from the eye structures (*e.g.,* lens, cornea) and optic nerve through the optic chiasm. Examples of ocular impairment found in individuals with CP include refraction errors (*e.g.,* myopia, hyperopia) and fundus oculi abnormalities (*e.g.,* optic disc pallor, disc cupping; Fazzi et al., 2012; Nikolaos Kozeis et al., 2015; Nikos Kozeis et al., 2007; Lew et al., 2015; Park et al., 2016). Ocular impairment occurs in up to 90% of individuals with CP, with refractive errors reported most frequently (Fazzi et al., 2012; H. Lew et al., 2015; M. J. Park et al., 2016).

Oculomotor dysfunction occurs when there is a disturbance of vision involving the ocular muscles affecting eye movement and function. These include problems with fixations, smooth pursuits, saccades, and strabismus and occur in up to 90% of individuals with CP (Costa & Ventura, 2012; Fazzi et al., 2012; Nikolaos Kozeis et al., 2015; M. J. Park et al., 2016). Strabismus and abnormal saccadic movements are the most prevalent oculomotor dysfunction found in individuals with CP (Fazzi et al., 2012; H. Lew et al., 2015; M. J. Park et al., 2016).

Cerebral visual impairment (CVI) occurs from damage to the central visual pathway. CVI is broadly defined as disruption in the central visual pathway including the lateral geniculate nucleus, optic radiations, primary visual cortex, and visual association areas that causes a deficit in visual function that cannot be explained by an ocular pathology (Good, Jan, Burden, Skoczenski, & Candy, 2001). CVI encompasses a broad range of visual disorders dependent on the specific visual area damaged. CVI include low-level visual processes (*e.g.,* visual acuity, visual field, contrast sensitivity) and intermediate-level visual processes (*e.g.,* stereopsis, optokinetic nystagmus; Ego et al., 2015; Fazzi et al., 2012; Stiers et al., 2002). High-level visual processing disorders resulting from visual association area damage are sometimes classified separately as visuocognitive or visuoperceptual disorders (Fazzi et al., 2012; Good et al., 2001; Pueyo

et al., 2009). These disorders involve difficulty with the perception and integration of visual information (*e.g.,* object identification, perception of moving targets, recognizing faces). Cerebral VIs occur in 60 – 90% of individuals with CP (Fazzi et al., 2012; Pueyo et al., 2009).

Visual Disorder and CP Subtype

Specific visual disorders are prevalent among different subtypes of spastic CP. Each subtype has a slightly different neuro-ophthalmological profile that includes all types of visual disorders (Fazzi et al., 2012). A more district profile has been noted in individuals with hemiplegic CP. These individuals have more visual field deficits (Fazzi et al., 2012) and a lower incidence of CVI (da Cunha Matta et al., 2008; Fazzi et al., 2012). Refractive errors, strabismus, stereopsis, or visuoperceptual dysfunction are equally represented across types of CP (Dufresne et al., 2014; Ego et al., 2015; Fazzi et al., 2012; Nikos Kozeis et al., 2007; Stiers et al., 2002). Similarly, the few studies that have explored differences between types of CP (*i.e.,* spastic, mixed and dyskinetic), have not found distinct neuro-ophthalmological profiles (Dufresne et al., 2014; Pueyo et al., 2009).

The incidence of oculomotor dysfunction increases with increasing presentation (*i.e.,* diplegia, hemiplegia, tetraplegia; da Cunha Matta et al., 2008; Fazzi et al., 2012). Differences with gradations with respect to visual acuity were significant when measured using electrophysiological methods, but not with behavioral methods (Costa & Ventura, 2012). A few studies reported no differences in visual acuity by presentation used only behavioral assessments (Fazzi et al., 2012; Nikos Kozeis et al., 2007; Stiers et al., 2001). Behavioral methods may be less reliable when assessing individuals with severe motor and cognitive disorders.

Motor Function and Visual Disorder

Several studies highlight a strong relationship between motor function and the prevalence and severity of visual disorder. The level of motor function as measured by a standardized, gross motor assessment was inversely correlated with the level of refractive error in young children with CP (H. Lew et al., 2015). Additionally, visual acuity loss measured by sweep visual evoked potential was highly correlated with GMFCS level (da Costa, Salomão, Berezovsky, De Haro, & Ventura, 2004). This relationship is further supported by numerous studies reporting the highest prevalence of visual disorders among individuals with tetraplegic CP (Costa & Ventura, 2012; da Cunha Matta et al., 2008; Fazzi et al., 2012; Pueyo et al., 2009). However, this may reflect the extent of the underlying brain lesion more than motor function.

Pathology of Visual Disorders in Individuals with Cerebral Palsy

Despite a strong correlation between motor function and CP motor presentation with visual disorder, many studies have failed to discover a strong relationship between the type of brain lesion and ocular impairments, oculomotor dysfunction, and lower-level visual processing impairments in individuals with CP (Dufresne et al., 2014; Andrea Guzzetta, Fazzi, et al., 2001). As with other areas of function, the clinical consequence of the brain lesion on visual function is dependent on the severity and topography of the lesion.

As a large area of the cortex is involved with visual processing, many different brain pathologies are associated with CVI. Lesions that cause significant developmental delay are associated with poor visual outcomes (*e.g.,* cortical blindness) in cerebral visual impairment (Krägeloh-Mann, 2004). Brain maldevelopments occurring both early (*e.g.,* lizenecephalies) and late (*e.g.,* periventricular lesions) in gestation have also been

associated with CVI. Cortical and subcortical lesions only present in frontal or parietooccipital areas contribute the development of CVI, even when motor function is spared. Basal ganglia and thalamus involvement appears especially sensitive to disrupting visual function (Andrea Guzzetta, Fiori, Scelfo, Conti, & Bancale, 2013; Mercuri et al., 1997), even in the absence of cortical damage (Mercuri et al., 1997).

Among individuals with CP, the highest percentage who have visuocognitive disorders were reported in children with gray matter abnormalities (Pagnozzi, Dowson, Doecke, et al., 2016; Pagnozzi, Dowson, Fiori, et al., 2016; Schenk-Rootlieb, Nieuwenhuizen, van Waes, & van der Graaf, 1994). Patients who had CVI and were without identifiable brain abnormalities (36% of patients) demonstrated more difficulty with visual tasks involving the presentation of everyday objects from different perspectives.

The higher-level visual processing disorder (*i.e.,* CVI, visuocognitive and visuoperceptual impairments) may reflect a sophisticated visual disorder associated with subtle differences in brain structures detected by functional or newer structural processing methods. For example, using the shape of the primary visual cortex as a proxy for cortical volume, the shape of the ipsilesional primary visual cortex was predictive of level of visuocognitive deficit in children with hemiplegic CP (Pagnozzi, Dowson, Fiori, et al., 2016). Additionally, several studies using diffusion-based imaging identified a reduction in the integrity of the superior longitudinal fasciculus, which connects the occipital and parietal-frontal cortices, in patients with similar visuocognitive impairments and CP (Bauer et al., 2014; Galli et al., 2018; Ortibus et al., 2012).

Interestingly, several studies argue that the visual disorders observed in individuals with CP may be more strongly associated with gestational age at birth than with a specific brain lesion. Among children with CP born preterm, studies report a higher incidence of refractive error and ocular impairments potentially attributable to retinopathy of prematurity

(Dufresne et al., 2014; Nikolaos Kozeis et al., 2015). Preterm birth may also have a stronger, negative impact on visuomotor impairment and visuoperceptual disorders (Ego et al., 2015; Pagliano et al., 2007), and increase the risk of CVI (Ortibus, De Cock, & Lagae, 2011).

Visual Disorders in Individuals with Cerebral Palsy

Individual with CP may be at risk for other visual deficits. Studies have noted impairments in processing biological motion and faces (Lange et al., 2009; M. Pavlova, Staudt, Sokolov, Birbaumer, & Krägeloh-Mann, 2003). Visuospatial neglect is frequently identified in children with hemiplegic CP, and may be a consequence of left-hemispheric language functions reorganization to the right hemisphere in children with left-lesioned hemiplegic CP (Lidzba, Staudt, Wilke, & Krägeloh-Mann, 2006). However visuospatial deficits may be more prominent among children with CP (Ickx et al., 2018). By using multiple behavioral test to identify visuospatial deficits, Ickx and colleagues (2018) found that visuospatial deficits are present in 64% of children with hemiplegic CP, more common in those with cortical/subcortical lesions compared to periventricular lesions.

Visuocognitive and visuoperceptual deficits appear to manifest separately from cognitive impairments. Several studies have controls for IQ or nonverbal intelligence and found that the visual perceptual deficits persist (Ego et al., 2015; Ortibus, Lagae, Castees, Demaerel, & Stiers, 2009; Stiers et al., 2002; van den Hout et al., 2004). Only prematurity places a child with CP at higher risk for these higher-level visual disorders (Ortibus et al., 2009).

Plasticity of Visual Functions

The visual system appears to have less benefit from cortical plasticity compared to other systems (Krägeloh-Mann, 2004; Lidzba et al., 2006). Evidence from functional

MRI (fMRI) suggests that the left-hemispheric language functions can reorganize to the right hemisphere in children with left-lesioned hemiplegic CP (Lidzba et al., 2006). However, this appears to come at a cost to right-hemispheric visual functions. However, there is emerging evidence of recovery of visual function following earlier brain injury in children with hemiplegic CP. A group of children with hemiplegic CP were identified with visual field loss at one year of age. When the same children were assessed at five years, only one had a visual field deficit (Mercuri et al., 2003). The cortical visual function of a 12-month-old infant with a prominent left hemispheric lesion was evaluated using fMRI and diffusion tractology. At 12 months of age the infant demonstrated no visual induced activation and absent optic radiation fiber only in the affected hemisphere (Seghier et al., 2004). When the infant was reevaluated at 20 months, the left hemisphere showed visually induced activations and the presence of optic radiations (Seghier et al., 2005).

Better visual outcomes may be associated with earlier lesions. The presence of a specific visual field can be reliably predicted using diffusion tensor imaging (DTI) to measure the asymmetry of the optic radiations in children who had a perinatal arterial ischemic stroke (Koenraads et al., 2016). However, predicting visual field loss is highly inconsistent in children with earlier periventricular hemorrhagic infarction (Andrea Guzzetta et al., 2013). The visual field sparing of the early focal brain lesions are attributed to cortical plasticity. When the damage occurs early, the track can be “rewired” around the lesioned optic radiations and still connect to the visual cortex. In individuals who had thalamus or basal ganglia damage, or who had brain lesions occur late in gestation, the thalamo-cortico pathway cannot rewire and the visual field loss remains.

Effect of Visual Disorders on Function and Quality of Life

Visual function is crucial for participation in everyday activities. Higher-level visual processing abilities are strongly associated with the ability of an individual with CP to perform activities of daily living (ADL) and the academic learning (Critten, Campbell, Farran, & Messer, 2018; Critten, Messer, & Sheehy, 2019; James et al., 2015). The presence of a visual disorder significantly contributes to lower gross motor function, higher need for caregiver assistance, and lower quality of life compared to individual with CP compared to those with CP who do not have a visual disorder (Salavati, Rameckers, Steenbergen, & Van Der Schans, 2014; Tseng et al., 2016).

Methods for neuroimaging: Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a noninvasive functional brain imaging technique that measures the magnetic fields created by neurons' electrical activity. MEG offers both high spatial (3 – 5 mm) and temporal resolution (< 1 ms; Wilson, 2015), which makes it uniquely suited for examining the neural dynamics of underlying many sensory and cognitive processes. MEG sensors record the changes in the magnetic fields that occur during the experimental paradigm. Through magnetic source imaging, the MEG data is matched with separate structural information obtained from magnetic resonance imaging (MRI) to reconstruct the brain source generating the neural signal observed in the MEG sensors.

Neuromagnetic Signal

The neuronal activity generated by groups of active neurons can be recorded on the cortical surface (*e.g.*, with electrocorticography or intracranial electroencephalography, EEG), on the scalp (*e.g.*, EEG), or above the scalp (*e.g.*, MEG).

One advantage of MEG is that the magnetic fields are not distorted by the conductive properties of the tissues between the source activity and the sensors (*e.g.,* brain, CSF, scalp, skull), unlike the ionic current (Hansen, Kringelbach, & Salmelin, 2010).

Previous research has demonstrated that the neuromagnetic signal recorded by MEG is more similar to recordings of local field potentials than to multi-unit activity recordings (Zhu et al., 2009). The local field potential is thought to be dependent on the architectural organization and the synchrony of the neuronal sources (Buzsáki, Anastassiou, & Koch, 2016). Hence, the primary neural source contributing to the MEG signal likely originates from the dendritic activity in groups of cortical pyramidal cells. Their uniform arrangement closer to the cortical surface would allow for sufficient temporal summation for registration on the MEG sensors.

The spatial and temporal characteristics observed in the evoked and induced oscillatory responses are intrinsic to the neurons and thought to represent functionally-relevant cortical processes that are important for communication throughout the central nervous system (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001; Van Dijk, Van Der Werf, Mazaheri, Medendorp, & Jensen, 2010). The exact range of the canonical frequency bands that are reported in the literature varies. Theta-band oscillations (4 – 8 Hz) are likely important for the initial perception of objects (Busch, Dubois, & VanRullen, 2009; Makeig et al., 2002). Alpha-band (8 – 12 Hz) and beta-band (13 – 30 Hz) oscillations have been shown to modulate task performance and engagement (Bastos et al., 2015; Ikkai, Dandekar, & Curtis, 2016; Li et al., 2004; Van Dijk et al., 2010). Gamma-band (>30 Hz) oscillatory changes in the MEG signal appear to code specific stimulus features, such as contrast, spatial frequency, and motion (Adjamian et al., 2004; Swettenham et al., 2009).

MEG research probes these functional responses primarily by recording the evoked and induced cortical activity during event-related experimental designs (Wilson,

2015). The experimental design takes into account the number and type of stimulus; type, timing, and duration of anticipated evoked and induced responses; and the number of trials required to improve the signal-to-noise ratio. This information is used to build adequate intervals between stimuli and trials to avoid neural activity contaminating the baseline period or other neural responses. Using MEG to examine the oscillatory responses to specific sensory or cognitive events can provide insight into the neural mechanisms supporting cognitive (*e.g.*, attention, learning, memory) and sensory (*i.e.*, registration, perception, integration) processes that underlie health and dysfunction.

Several lines of research have compared the recorded signals of MEG and functional magnetic resonance imaging (fMRI) to understand how these different imaging methods relate to each other and brain activity. Although more common, fMRI is an indirect method of functional imaging that detects changes in the blood-oxygen-level-dependent (BOLD) response. The electrophysiological functions of active neurons (*e.g.*, action potentials, neurotransmitter cycling, post-synaptic potentials) create a higher demand for energy, which causes changes in blood flow and the local ratio of oxygenated – deoxygenated blood. Differences between the paramagnetic deoxygenated hemoglobin and the slightly diamagnetic oxygenated hemoglobin provide a contrast that is “coupled” to the neuronal activity (Wilson, 2015). While fMRI's spatial resolution is excellent (~3 mm), the temporal resolution of fMRI is limited by the physiology of the vascular response. The hemodynamic changes may lag several seconds and be influenced by vascular differences in the brain (E. L. Hall, Robson, Morris, & Brookes, 2014; Salmelin & Parkkonen, 2010).

Research suggests that fMRI and MEG have similarities that indicate that they are capturing similar, yet slightly different aspects of neural functions in their recorded signal. The BOLD hemodynamic response correlates with local field potential recordings, similar

to MEG (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Studies using similar paradigms have found that the BOLD response and MEG signal are found in the same cortical areas (Brookes et al., 2005; Muthukumaraswamy & Singh, 2008, 2009; Singh, Barnes, Hillebrand, Forde, & Williams, 2002; Zumer, Brookes, Stevenson, Francis, & Morris, 2010). However, differences between these methods have been discovered by examining gamma-band changes in response to specific visual stimulus features. These studies have shown that the hemodynamic response appears insensitive to the properties of spatial frequencies (*e.g.*, type of grating, tuning for specific frequency; Muthukumaraswamy & Singh, 2008, 2009). Additionally, there is a negative correlation between the BOLD response and the MEG recorded signal in the lower frequencies (*i.e.*, alpha and beta frequency band power decreases)(Singh, Barnes, & Hillebrand, 2003; Singh et al., 2002; Zumer et al., 2010). These studies suggest that different physiological processes may be contributing to divergent signals. Furthermore, the MEG signal may capture the intrinsic properties that are not reflected in the BOLD signal.

MEG Experimental Methods and Data Acquisition

The electrical activity of active neurons generates tiny magnetic fields on the order of 10^{-15} Tesla (Hari & Salmelin, 2012; Wilson, 2015). The amplitude of the MEG signal is dependent on the magnitude of neural activity, and the distance between the neural source and sensors and (A. Hillebrand & Barnes, 2002). Although the magnetic field may pass through the head relatively undistorted, the signal attenuates exponentially upon leaving. For MEG to successfully detect the magnetic flux produced by the active cortical neurons, several considerations are put into place during MEG acquisition and processing. MEG recordings are usually completed in magnetically shielded rooms with active or passive shielding that helps to filter non-brain signals (*i.e.*, noise) coming from the

environment (*e.g.*, electrical equipment, street traffic). Inside the shielded room, all equipment and persons should be free from ferromagnetic materials that would disturb the MEG sensors (*e.g.*, orthodontics, wristwatch, cell phone, keys).

MEG studies typically use event-related experimental designs, as opposed to the block-designs common in fMRI research (Wilson, 2015). The MEG research design takes into account the number and type of stimulus; type, timing, and duration of anticipated evoked and induced responses; and the number of trials required to improve the signal-to-noise ratio. This information is used to build adequate intervals between stimuli and trials to avoid task-related neural activity contaminating the baseline period or other neural responses. Paradigms exploring complex or higher cognitive processes will likely require a larger number of trials.

Before the experiment, four coils are placed on the participant's head, three fiducial points are marked, and the scalp surface is digitized to provide their three-dimensional position. The participant is in a seated or supine position with the head placed inside the MEG helmet that contains the MEG sensors. During the recording, a small electrical current with a unique frequency label (*e.g.,* 322 Hz) runs to each of the coils. This produces a measurable magnetic field that will allow the participant's head position within the helmet to be localized in reference to the sensor array throughout the experiment.

Each sensor contains two gradiometers and one magnetometer that records the magnetic flux (Parkkonen, 2010). The magnetometers have one pick-up coil that measures the changes in the magnetic flux and is sensitive to deeper structures and environmental noise. The gradiometers also use a pick-up coil but additionally have a compensation coil that is wound in opposition and primarily measures the interfering signal (Parkkonen, 2010). Axial gradiometers measure radial gradients are sensitive to close sources just peripheral to the sensor. Planar gradiometers measure the tangential

gradients and are sensitive to close sources directly below (Wilson, 2015). The sensors are immersed in liquid-helium to reduce the electrical interference and output the sum of the magnetic flux in each coil. The MEG sensors output the magnetic signal to a paired superconducting quantum interference device (SQUID). The SQUID converts the magnetic flux into an amplified electrical signal that is recorded and further processed outside of the MEG recording room.

MEG Processing

The raw MEG signal contains interference (*i.e.*, noise) that was generated by non-neural sources. There are different noise-canceling methods that can be applied post-recording to minimize the effect that noise on the MEG data. The spatiotemporal signal space separation (SSS, Taulu & Simola, 2006) method divides the space into two subspaces, one that contains all the sources generating the signal inside the MEG helmet and the other that contains all the sources that generate signal outside the helmet. The outside of helmet interference is suppressed from the signal (Parkkonen, 2010). Physiological artifacts (*e.g.*, heartbeat, eye blink) are removed using signal-space projection (Uusitalo & Ilmoniemi, 1997). In this method, the spatial pattern of the artifact is visually identified in the MEG data, then subsequently subtracted. Finally, trials that contain artifacts are rejected using a fixed amplitude and gradient threshold that is participant-specific, which is necessary given the variance across participants in MEG-sensor-to-brain distance and neural response strength.

The artifact-free sensor level data is transformed into time-frequency domains using complex demodulation to extract the evoked and induced neural responses related to the MEG experiment. The resulting spectral power estimations are averaged over trials for each sensor. The sensor level data is normalized by the pre-stimulus neural activity in

a defined time-frequency window (*i.e.,* baseline). This is completed by dividing the power value of each time-frequency bin by the respective bin's baseline power. This results in a relative time-frequency component (TFC) plot of the spectral power at a given frequency and time for each sensor.

Time-frequency windows are selected for further processing from a TFC plot averaged across all participants. Each data point in this grand-averaged spectrogram is initially evaluated using a mass univariate approach based on the general linear model in a two-stage process. First, one-sample t-tests are conducted on each data point, and the output spectrogram of *t*-values is thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants. In stage two, time-frequency bins that survived the threshold are clustered with temporally and spectrally neighboring bins that are also above the ($p < 0.05$) threshold and a cluster value is derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing is then used to derive a distribution of cluster-values, and the significance level of the observed clusters (from stage one) are tested directly using this distribution (Ernst 2004; Maris and Oostenveld 2007). Significant clusters are then selected to be analyzed in source space.

The source of the neural signal is reconstructed through beamforming or spatial filtering for each individual, which involves solving the forward and inverse problems. The forward problem is data-free and centers on how the neural activity would look on the MEG sensors if the location, orientation, and amplitude of the neural source was known (Wilson, 2015). The inverse problem asks what pattern (*i.e.*, location, orientation, and amplitude) of neural activity would create the signal recorded on the MEG sensors. As there is an infinite number of solutions to the inverse problem, there will not be one definitive answer. Beamformers are used to address these problems. For the forward

problem, brain-space is modeled as a single sphere divided into equally sized voxels (*i.e.*, cubes of brain tissue). For each voxel, the beamformer derives an equation that reflects what the neural signal from the target voxel would look projected to each sensor if the target voxel's signal did not attenuate and the signal from all other voxels was suppressed. Each sensor is weighted based on its distance and depth to the target voxel (Wilson, 2015). Some of the unique properties of the MEG sensor, such as the sensitivity of the gradiometers to neural activity at the cortical surface, can be considered when selecting the best solution to the inverse problem. The result is individual beamformer images referred to as pseudo-*t* maps, with units (pseudo-*t*) that reflect noise-normalized power differences (*i.e.*, stimulus vs. baseline) per voxel.

Purpose of Dissertation

This literature review has identified that visual dysfunctions are overwhelmingly present in individuals with CP, the pathology of the visual impairment is not apparent or predictable, and a limited amount of cortical plasticity may exist for visual functions. Visual function is typically identified through clinical-behavioral measures, although neurophysiological methods are more accurate and clinical measures are deficient. Research has primarily focused on exploring potential relationships between types of visual impairments and type of CP, brain abnormality, or structural integrity. Separate visual functions contributing to cerebral visual impairments are commonly grouped when interrogated, which hinders the ability to identify the source of the impairment.

The knowledge gaps identified in this literature review include understanding the neurophysiological mechanisms underlying visual functions and how potential visual processing deficiencies relate to motor function. These areas are essential for successful participation in everyday activities. Therefore, the primary purpose of this dissertation is

to gain a gain a deeper understanding of visual processes in individuals with CP. Specifically, this dissertation will examine the neural underpinnings of basic visual processes and the relationship of cerebral visual processing to task performance in individuals with CP compared to a cohort of typically developing (TD) children of similar age. It is hypothesized that individuals with CP will have degraded visual cortical oscillations. The degraded cortical activity will be related to motor performance deficits in CP. The outcomes from this main purpose will provide foundational information for developing better interventions and assessments targeting visual processing for individuals with CP.

The purpose of this dissertation is to identify the neural responses that underlie basic components of visual-perceptual processing, specifically motion, contrast and spatial attention, and furthermore to explore the relationship of the potentially altered neural responses with behavior.

CHAPTER 2: CHILDREN WITH CEREBRAL PALSY DISPLAY ALTERED NEURAL OSCILLATIONS WITHIN THE VISUAL MT/V5 CORTICES

Introduction

There is a growing consensus that visual dysfunction is possibly a core disorder among children with cerebral palsy (CP; Ego et al., 2015; Fazzi et al., 2012; Guzzetta et al., 2001). This dysfunction may result from an ocular pathology (*e.g.*, acuity, retinopathy of prematurity, strabismus) and/or a brain-based pathology (*e.g.*, visual perceptual impairment; Ego et al., 2015; Guzzetta et al., 2001). These visual perceptual abnormalities likely impact the motor decisions made by children with CP because online monitoring of a motor action involves integrating visual feedback with the other cortical areas (*e.g.*, parietal and motor cortices), and extracting meaningful visual information for functional use (Born & Bradley, 2005).

Prior behavioral studies have identified that children with CP have a decreased sensitivity to visual motion, unrelated to the extent of their motor impairment (M. Pavlova et al., 2003). Several structural imaging studies have shown a possible link between the extent of the damage along the white matter tracts of the visual pathway in these children and their altered visual perceptual abilities (Martín et al., 2016; Schenk-Rootlieb et al., 1994; van den Hout et al., 2004). However, this connection is somewhat controversial given studies have also identified that some children with CP who have poor visual perception on clinical tests do not necessarily have identifiable structural brain abnormalities (Fazzi et al., 2009; Andrea Guzzetta et al., 2013; Schenk-Rootlieb et al., 1994). Potentially, the noted perceptual deficiencies seen in children with CP might be more dependent upon maladaptive neuroplasticity that results in aberrant activation of visual networks rather than the perinatal structural damage that these children may have incurred.

Several electroencephalographic (EEG) and magnetoencephalographic (MEG) studies of healthy adults have shown that the latency and amplitude of the evoked response in the visual MT/V5 cortical area are linked with the speed of the moving visual stimuli (Heinrich, 2007; Kawakami et al., 2002; Maruyama, Kaneoke, Watanabe, & Kakigi, 2002). Specifically, these studies showed that as the speed of the moving visual stimuli increased, the latency of the neural response decreased and the amplitude of the evoked response increased in the visual MT/V5 area. Despite our enhanced understanding of the electrophysiology of these motion-sensitive cortices, these insights have yet to be employed to understand the visual perception deficits seen in children with CP.

Our recent MEG brain imaging results revealed that children with CP have altered cortical beta oscillations in the visual MT/V5 area when completing a visuomotor target force-matching task (Kurz, Proskovec, Gehringer, Heinrichs-Graham, & Wilson, 2017). This implies that the aberrant activity seen in this cortical area could play a partial role in the motor decisions of these children. The purpose of this study was to 1) directly examine visual MT/V5 activity in children with CP while viewing a moving stimulus, and 2) determine if there is a connection between the visual perceptions of these children and the strength of neural activity in the motion-sensitive MT/V5 region.

Methods

Participants

Twenty-one children with CP (age = 15.7 ± 4 yrs.; 13 males; GMFCS levels I-IV; MACS levels I-IV) and 21 TD children (age = 14.0 ± 2 yrs.; 12 males) with no known neurological, developmental, musculoskeletal impairments participated in this study. All participants had normal or corrected to normal vision and no known visual processing impairments reported in their clinical records. In addition, none of the participants were on

medication and none had been previously diagnosed with epilepsy or had an epileptic seizure. All of the parents provided written consent, and the children assented. The University of Nebraska Medical Center Institutional Review Board reviewed and approved this investigation.

MEG Data Acquisition and Experimental Paradigm

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. The children were seated upright in a magnetically silent chair with their head positioned within the helmet-shaped MEG sensor array. A custom-built head stabilization device that consisted of a series of inflatable airbags that surrounded the sides of the child's head and filled the void between the head and MEG helmet was worn during the data collection. This system stabilized the head and reduced the probability of any large medial/lateral and anterior/posterior head movements occurring during the data collections. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers.

During the experiment, the children viewed a visual stimulus that was displayed on a back-projected flat screen at eye-level and approximately one meter away. A custom C++/OpenGL visual MT/V5 stimulus program was created for this investigation. The stimulus consisted of an array of randomly positioned black dots behind a central red dot on a white background for maximum contrast (Figure 1). The children were instructed to fixate their gaze on the stationary red dot and to monitor for motion. The visual stimulus remained stationary for 2000 ms during the baseline period, followed by 1250 ms of fluid, linear visual motion that was created by the black dots cohesively updating their position

every 250 ms. On 12% of trials, the black dots moved vertically, and the children were instructed to press a button with their right index finger as soon as they detected this motion. These vertical movement catch trials were not imaged and were used to behaviorally assess the child's perception of the visual motion. A short practice of the task was completed prior to the recording to ensure all children understood the task and were able to respond correctly. Each child completed a total of 120 horizontal trials to optimize the MEG signal-to-noise ratio. Throughout data acquisition, the children were monitored via real-time audio-video feeds from inside the shielded room.

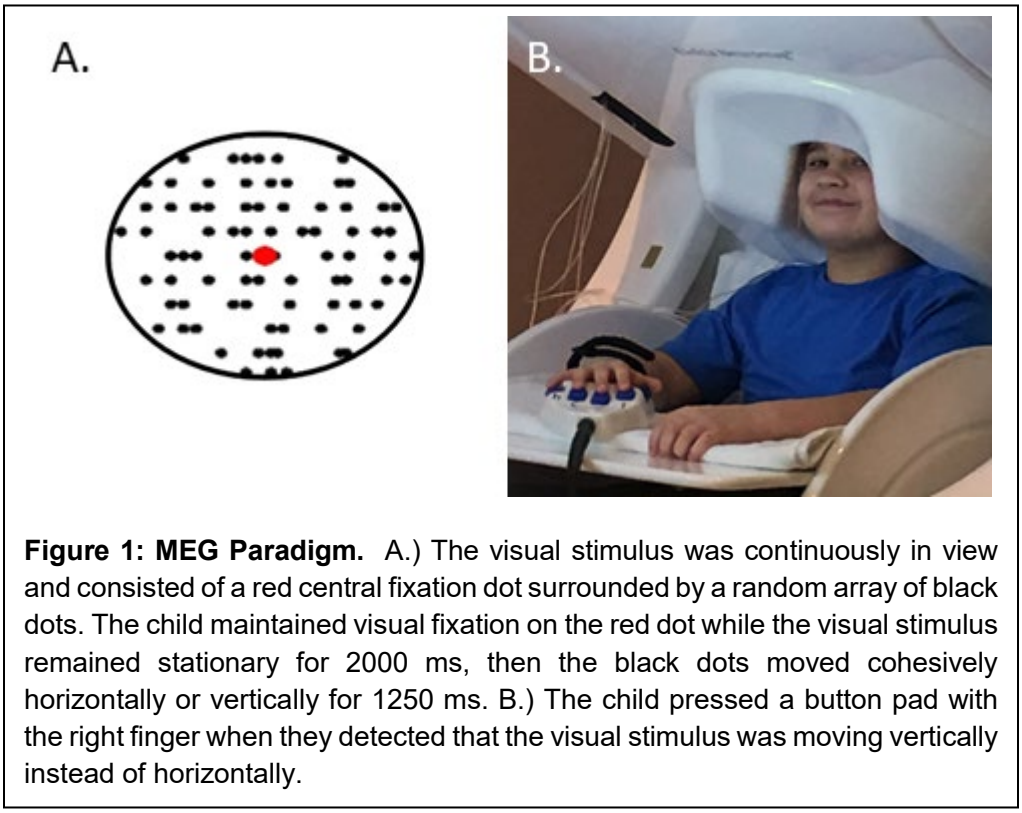

Figure 1: MEG Paradigm. A.) The visual stimulus was continuously in view and consisted of a red central fixation dot surrounded by a random array of black dots. The child maintained visual fixation on the red dot while the visual stimulus remained stationary for 2000 ms, then the black dots moved cohesively horizontally or vertically for 1250 ms. B.) The child pressed a button pad with the right finger when they detected that the visual stimulus was moving vertically instead of horizontally.

MEG Coregistration & Structural MRI Processing

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 x 1.0 X 1.0 mm.

For the MEG experiment, four coils were affixed to the head of the child and were used for continuous head localization. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface was digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). During 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 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 child's MEG data was coregistered with the native space neuroanatomical MRI data using the three external landmarks (*i.e.*, fiducials) and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

MEG Pre-Processing & Time-Frequency Transformation

Each magnetic time series was individually corrected for head motion and was subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Cardio-artifacts from the remaining participants were removed from the magnetic time series using signal-space projection (Uusitalo & Ilmoniemi, 1997). The continuous magnetic time series were divided into epochs of 2100 ms in duration (-600 ms to + 1500 ms, with time 0 defined as the onset of the visual

motion), and the baseline period defined as -500 to -100 ms. Artifact rejection was performed using a fixed threshold method and supplemented with visual inspection. This quality check resulted in three of the participating children being excluded due to notable MEG artifacts. The epoch acceptance rate was 96% (*e.g.*, 95.88 $\pm$ 5.86 epochs) for the remaining children.

Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation and averaged over the respective trials. These sensor-level data were normalized by dividing the power value of each time-frequency bin by the respective bin's baseline power, which was calculated as the mean power during the baseline (-500 to -100 ms). The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Each data point in the spectrogram 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, 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 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 (Ernst 2004; Maris and Oostenveld 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

MEG Source Imaging & Statistics

The dynamic imaging of coherent sources beamformer (DICS) was used to calculate the source power across the entire brain volume using spatial filters in the frequency domain and a single-shell spherical head model (Gross et al., 2001; Arjan Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). The single images were derived from the cross-spectral densities of all combinations of MEG sensors, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Arjan Hillebrand et al., 2005; Van Veen et al., 1997). The resulting beamformer images were 4.0 x 4.0 x 4.0 resolution and, since these were co-registered to each participant's native space T1-weighted anatomical MRI before beamforming, the images could be transformed into standard space by using the transform that was previously applied to the structural MRI volume and spatially then resampled. MEG pre-processing and imaging was performed with the Brain Electrical Source Analysis software (BESA v6.0; Grafelfing, Germany).

After all data were in standard space, neural activity in the visual MT/V5 cortical area was identified by applying a mask of the left and right visual MT/V5 areas using the Juelich Histological Atlas (Malikovic et al., 2007; Wilms et al., 2005) in FSL (Image Analysis Group, FMRIB, Oxford, UK). This mask was applied to the grand averaged beamformer images to identify the coordinates of the peak voxel in the left and right visual MT/V5 cortices. Subsequently, we extracted the time course of these voxels by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector. These "virtual sensor" extractions were completed for each hemisphere and then averaged, as our stimulus presentation was bilateral and we had no laterality

hypotheses. Lastly, permutation testing was employed on the neural time series to identify the time windows where there were significant differences between the respective groups (Maris & Oostenveld, 2007).

Behavioral Data

As stated in the preceding sections, for 12% of trials the visual stimulus moved vertically, and the children were instructed to press a button with their right index finger as soon as they detected this motion. These vertical movement catch trials were not imaged but were used to behaviorally assess the child's perception of the visual motion. Behavioral assessment of the child's visual perception were quantified using the output of a button pad, which was simultaneously collected during the MEG experiment at 1000 Hz. Reaction time was defined as the time difference between stimulus onset and when the button press occurred. Accuracy was calculated as the percentage of trials where the child correctly identified that the visual stimulus moved vertically. Group differences were analyzed with t-tests, and Pearson's correlations were used to determine if there was a relationship between the strength of the cortical oscillations, reaction time and accuracy.

Results

Behavioral results

Compared with the TD children, the children with CP had slower reaction times ($p < 0.001$ Figure 2A) and were less accurate in identifying when the visual stimulus changed from a horizontal to vertical motion ($p = 0.002$; Figure 2B). Together these behavioral results indicate that the children with CP were less able to perceive a change in the visual stimulus. Across all participants there was a strong negative correlation between reaction time and accuracy ($r = -0.71$, $p < 0.001$), suggesting that the children who had slower

reaction times also tended to be less accurate in identifying that the visual stimulus had changed from horizontal to vertical motion.

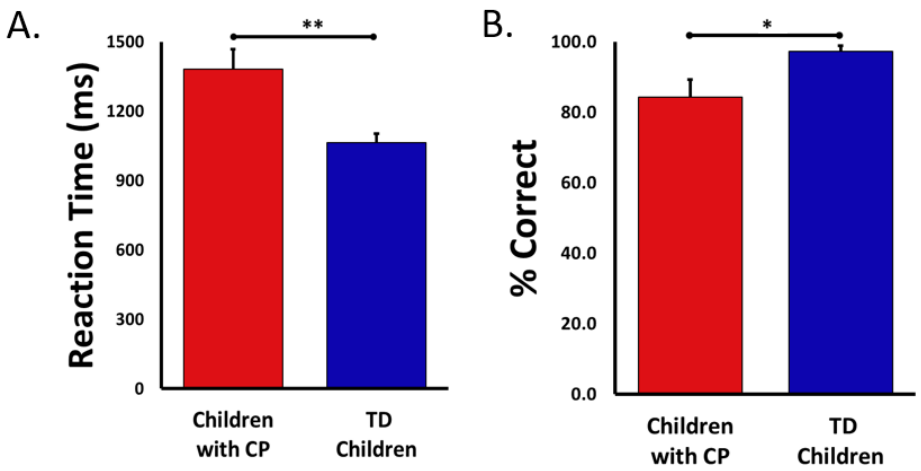

Figure 2: Visuomotor Performance. A.) Reaction time for the children with CP and TD children. Reaction time was calculated as the time difference between the onset of the vertically moving stimulus and the button press. As shown, the children with CP were slower to perceive a change in the motion direction (** indicates $p < 0.001$). B.) Accuracy was determined by the percentage of trials where the visual stimulus was correctly identified when moving vertically. As shown, the children with CP made more errors in their perception of the motion of the visual stimulus (* indicates $p = 0.002$).

Sensor-Level Results

When collapsing the data across the respective groups, the spectrograms showed that there were significant bursts of theta-alpha (5-10 Hz) activity and significant decreases in alpha-beta (8-20 Hz) across a cluster of gradiometers near the occipito-temporal region ($p < 0.001$, corrected; Figure 3). The initial increase in the strength of the theta-alpha oscillations occurred shortly after the onset of the stimulus (50 ms) and was immediately followed by a decrease in the strength of the alpha-beta oscillations between 200-600 ms. In some MEG sensors, these changes in the neural oscillatory activity were repeated about every 250 ms and were time-locked with the updating of the visual

stimulus. For illustrative purposes, we show group-averaged spectrograms for the TD children and children with CP separately in Figure 3, but note that sensor-based statistics were computed by collapsing the data across all of the participants. Qualitative inspection of these figures shows differences in the strength of theta-alpha and alpha-beta oscillations between groups, with notably weaker activity in the children with CP.

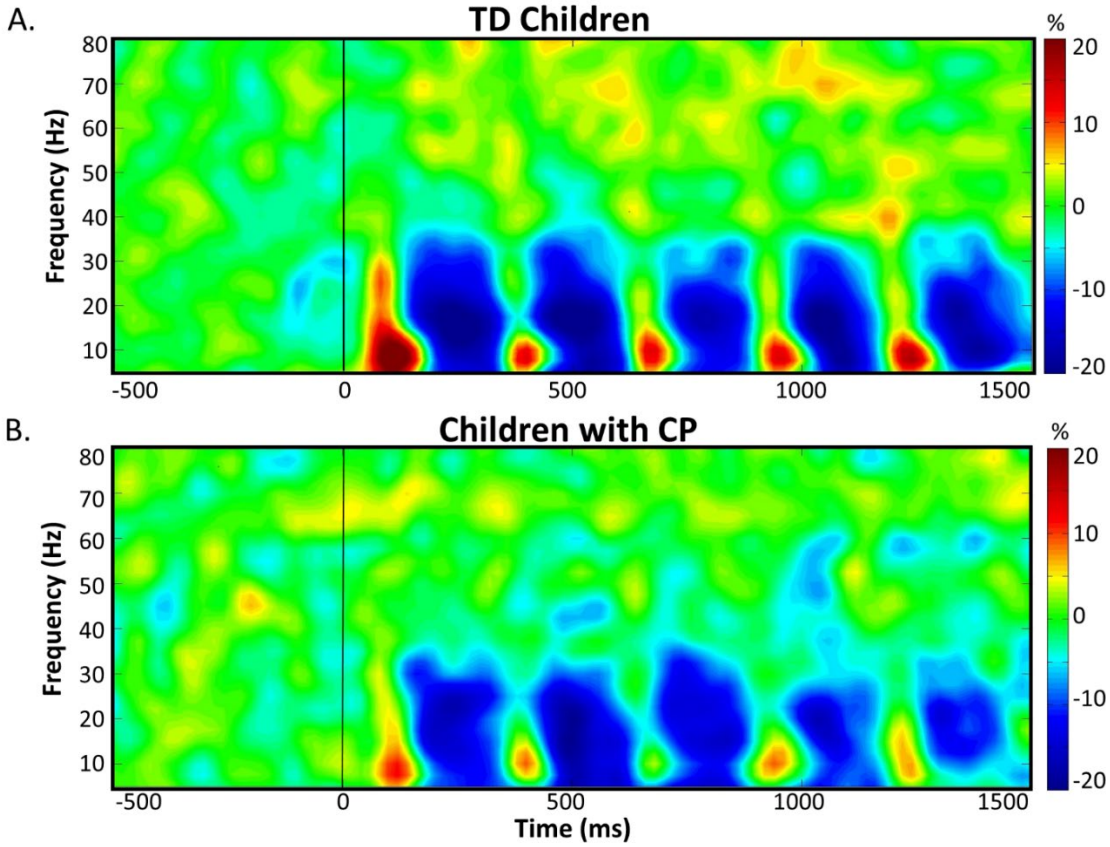

Figure 3: Averaged Time-Frequency Spectrograms for A.) TD children and B.) Children with CP during the visual motion stimulus. These plots were created from a gradiometer sensor located over the occipito-temporal cortical area. Time (in ms) is denoted on the x-axis, with 0 ms defined as the onset of the horizontally moving visual stimulus. Spectral power is expressed as the difference from the baseline period (-500 to -100 ms). As shown, there was a prominent series of increases in the strength of the theta-alpha band (5-10 Hz) oscillations and decreases in the strength of alpha-beta band (8-20 Hz) that occurred throughout the stimulus period and in some sensors were time-locked with the updating of the visual stimulus that occurred every 250 ms. Inspection of the respective figures reveals that the changes in the neural oscillations were weaker in the children with CP compared with the TD children.

Source Level and Neural Time Course Results

Both the increased theta-alpha (5-10 Hz) power within the 0 to 200 ms time window and the decreased alpha-beta (8-20 Hz) power within the 200 to 600 ms time window identified in the sensor-level analysis were imaged using a beamformer and an equal pre-stimulus baseline period between -500 to -100 ms. The resulting images were grand-averaged and revealed that the neural activity was spread bilaterally across the visual cortices. For both the theta-alpha and alpha-beta time-frequency windows, neural time courses were extracted from the peak voxels in the visual MT/V5 cortical areas of each hemisphere per participant and subsequently averaged across hemispheres (Figure 4A). Permutation testing revealed that there were no significant differences ($p > 0.05$) in the strength of the theta-alpha neural time courses of the TD children and children with CP. Conversely, the amount of decrease seen in the alpha-beta neural time course during the 260-340 ms time window were significantly ($p < 0.001$) weaker for the children with CP when compared with the TD children (Figure 4B).

To strengthen the veracity of our results, we examined whether there was differential head movement between groups and the potential impact on our findings. Our results indicated that children with CP had more vertical displacement of the head's position during the experiment compared to TD children (CP =0.3 cm ± 0.2, TD = 0.2 cm ± 0.1, $p = 0.04$). However, the amount of vertical displacement did not correlate with the strength of the alpha-beta oscillations seen in the visual MT/V5 cortical area ($p = 0.5$). The lack of a correlation implies that the vertical displacement of the head during the experiment did not likely influence the results. Of note, we corrected for head movement, and aligned all data to the initial head position of the individual participant (at the start of the MEG session) prior to conducting our MEG sensor-level analyses. Thus, such

differences in motion should be corrected for and not impact the final results, and this is precisely what we found.

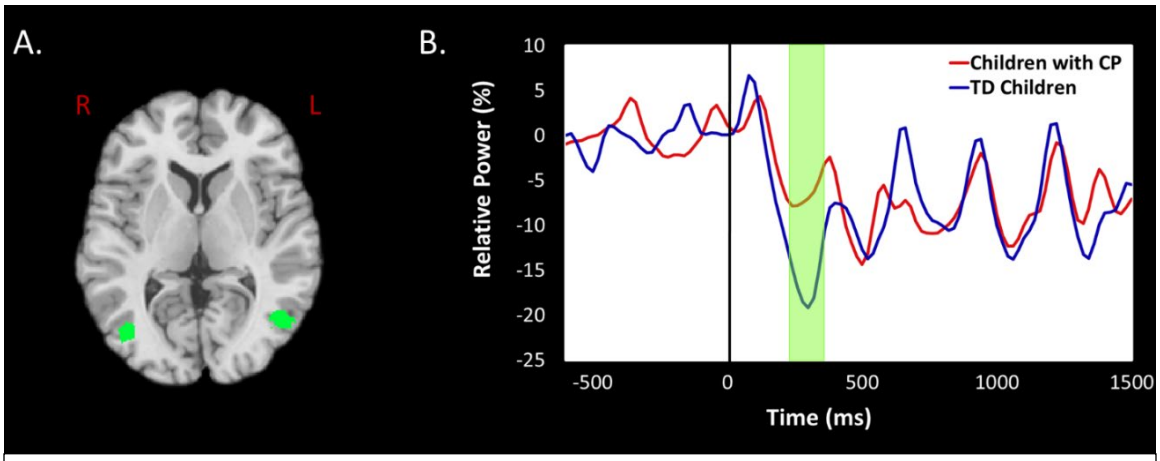

Figure 4: Visuomotion Neural Activity. A.) Beamformer image showing averaged masked visual MT/V5 alpha-beta (8-20 Hz) cortical activity during the 200-600 ms time period of the visual stimulus. This image was used to identify the peak voxel in the visual MT/V5 cortical area across all of the participants. The neural time course in this peak voxel was subsequently extracted from the respective hemispheres and averaged. B.) Neural activity at the alpha-beta frequency within the visual MT/V5 cortical area for the children with CP (red) and TD children (blue). Time (ms) is denoted on the *x*-axis, with 0 ms defined as the onset of visual motion and relative amplitude denoted on the *y*-axis. There were notable changes in the strength of the alpha-beta oscillations throughout the stimulus period that reoccurred every 250 ms. Compared with the TD children, the children with CP had weaker alpha-beta oscillations during the 240-360 ms time window ($p < 0.001$; green shaded area).

Neurobehavioral Correlations

The average of the decreased power in the alpha-beta frequency band across the 260-340 ms time window was subsequently calculated for each participant, and was used to evaluate if the amount of decrease in the alpha-beta cortical oscillations were linked with the child's visual perception. Using the data from all of the participants, there was a positive correlation between the magnitude of the decrease seen in alpha-beta oscillatory activity and reaction time ($r = 0.40$, $p = 0.012$), which suggests that the children who had a smaller decrease in alpha-beta activity also tended to be slower in identifying change in

the movement direction of the visual stimulus. Furthermore, there was a negative correlation between the strength of the decrease in alpha-beta activity and accuracy (r = -0.33; p = 0.046), implying that the children with smaller responses (decreases) tended to be less accurate in identifying the changes in movement direction.

Discussion

Despite the growing recognition that children with CP may have visual dysfunction, there is a significant knowledge gap in our understanding of the neurophysiological aberrations that underlie such perceptual dysfunction. The current study used MEG brain imaging to directly test the integrity cortical processing in the MT/V5 region of children with CP. Our experimental results indicated that compared with TD children, alpha-beta oscillatory activity within the motion-sensitive MT/V5 cortical area was weaker in children with CP. Furthermore, follow-up correlations suggest that these aberrant responses were at least partially linked with the atypical visual perceptions seen in children with CP.

Across both groups, there were prominent changes in the strength of alpha-beta oscillations in the MT/V5 region while viewing the moving visual stimulus. These results are in agreement with prior studies that have demonstrated that this region plays a key role in processing both real and apparent motion (Heinrich, 2007; Kawakami et al., 2002; Maruyama et al., 2002; Zihl & Heywood, 2015). Our results indicate that the decrease in the alpha-beta activity was notably weaker in the early time window (260-340 ms) for the children with CP, which implies that the MT/V5 cortical activity is atypical early in the processing stream. These early deficiencies likely play a prominent role in the visual processing deficits that are being reported in the clinical literature (Ego et al., 2015; Fazzi et al., 2012; Andrea Guzzetta, Mercuri, et al., 2001; van den Hout et al., 2004). Furthermore, they extend our previous findings that have shown children with CP have

weaker beta oscillations within the visual MT/V5 cortical area when performing a visuomotor task (Kurz, Proskovec, et al., 2017). Together with the results presented here, it appears that children with CP likely have visual processing deficits that influence their motor actions.

In the current study, the behavioral data strongly corroborated the brain imaging results by showing that the children with CP took longer to perceive that there was a change in the direction of the visual stimulus (*i.e.*, slower reaction times), and made more errors in deciding if the direction of the visual stimulus had actually changed. In addition, we identified that the children who had a weaker alpha-beta responses (less of a decrease) in MT/V5 during the early time window also tended to be slower in perceiving a change in the visual stimulus, and were less accurate in identifying when a change had occurred. These connections are intriguing because they imply that the uncharacteristic motor decisions seen in children with CP may not be completely dependent on the performance of the musculoskeletal system (Matthiasdottir, Hahn, Yaraskavitch, & Herzog, 2014; Moreau et al., 2012). Rather the motor decisions seen in these children are also partly dependent upon how they process and perceive visual information. This view fuels the emerging perspective that the abnormal motor actions seen in children with CP are fundamentally influenced by top-down processing (Gordon, 2016; Kurz, Proskovec, et al., 2017; Lust, Spruijt, Wilson, & Steenbergen, 2018; Surkar et al., 2018).

None of the children with CP in the current study had a noticeable lesion near MT/V5 on their MRI, and thus no akinetopsia-like presentations were expected (Zihl & Heywood, 2015). However, this observation does not preclude the possibility that the altered cortical activity resulted from damage along the white matter tracks that comprise the dorsal visual pathways that are involved in the transmission of visual feedback. This notion is supported by prior imaging studies that have identified that disruption of the white

matter tracts along the visual pathway in children with CP influences their performance on clinical assessments of visual perception (Martín et al., 2016; van den Hout et al., 2004). However, we are somewhat cautious on this inference because it is just as likely that the altered visual MT/V5 cortical activity might be a maladaptive neuroplastic change that was instigated by a lack of the visual experiences that infants and toddlers typically have through early exploration and mobility (Cole, Robinson, & Adolph, 2016; H. H. Huang, Ragonesi, Stoner, Peffley, & Galloway, 2014). This alternative explanation is supported by prior investigations that have that noted children with CP who have poor visual perception may not have identifiable structural brain abnormalities (Fazzi et al., 2009; Andrea Guzzetta, Mercuri, et al., 2001; M. Pavlova et al., 2003; Schenk-Rootlieb et al., 1994).

Conclusion

The deficient visual perceptions seen in children with CP may in part be related to the uncharacteristic alpha-beta neural oscillations in the motion-sensitive MT/V5 cortical area, and such aberrant oscillations likely impacts the motor decisions of these children. The results of this study further highlight the notion that the atypical motor actions observed in children with CP are not completely musculoskeletal centric, but rather also emerge from improper top-down processing of the ongoing sensory information. Our methodological approach for understanding the nature of the atypical motor actions seen in children with CP is unique because we combine visual motion and somato-motor components in a single experiment (Kurz, Becker, Heinrichs-Graham, & Wilson, 2014; Kurz, Wilson, Corr, & Volkman, 2012; Kurz, Heinrichs-Graham, et al., 2015; Kurz, Proskovec, et al., 2017; Kurz, Wiesman, et al., 2017). This approach is valuable because

it is able to isolate and identify how aberrations in the respective sensory processing influences the motor decisions seen in children with CP.

CHAPTER 3: CORTICAL DIFFERENCES IN PRIMARY VISUAL PROCESSING IN CHILDREN WITH CEREBRAL PALSY

Introduction

Cerebral palsy (CP) is a prevalent neurodevelopmental disorder in which early brain damage results in neuromuscular impairments and sensory-perceptual disturbances (Rosenbaum et al., 2007). While the literature on CP primarily focuses on the sensorimotor impairments, a relatively small body of literature has examined visual dysfunction in children with CP. Despite the paucity of studies, visual dysfunction is now recognized as a core, co-occurring disorder affecting between 50% and 90% of those with CP (Ego et al., 2015; Fazzi et al., 2007, 2012; Pueyo et al., 2009). Visual function is especially important as precise visual information is crucial for understanding our environment and making accurate motor decisions (Krigolson, Cheng, & Binsted, 2015). When the visual system is unable to efficiently process low-level visual information, all other visual computations and processes reliant on this information may be disturbed (Perreault, Habak, Lepore, Mottron, & Bertone, 2015), potentially contributing to diminished motor performance in everyday activities (Denver et al., 2016, Salavati, Rameckers, Steenbergen, & Van Der Schans, 2014).

Several studies have reported that children with CP may have ocular abnormalities such as refractive errors, optic atrophy and optic disc pallor (da Cunha Matta et al., 2008; Fazzi et al., 2012; Ghate, Vedanarayanan, Kamour, Corbett, & Kedar, 2016; Nikolaos Kozeis et al., 2015; M. J. Park et al., 2016). In addition, these children may have oculomotor impairments resulting in difficulty with fixation, smooth pursuits, saccadic movements or strabismus (da Cunha Matta et al., 2008; Fazzi et al., 2012; Nikolaos Kozeis et al., 2015; Nikos Kozeis et al., 2007). Clinical reports also indicate that there may be a high incidence of more nuanced brain-based visual dysfunctions in those with CP,

including basic visual perception deficits (*e.g.*, contrast sensitivity, acuity) and higher-level visual disorders involving perception and integration (*e.g.*, visual-cognitive disorders; Fazzi et al., 2012; Nikolaos Kozeis et al., 2015; Schmetz, Magis, Detraux, Barisnikov, & Rousselle, 2018; Stiers et al., 2002). Given the high prevalence of such visual aberrations in those with CP, it appears likely that the perinatal brain insults that underlie the characteristic sensorimotor impairments seen in CP concurrently affect aspects of the visual processing pathway (*e.g.*, geniculostriate, optic radiations, visual cortex; Chokron & Dutton, 2016; Dutton, McKillop, & Saidkasimova, 2006; Fazzi et al., 2012). Consequently, there is likely a strong connection between the motor presentations seen in those with CP and the degree of the visual processing impairments.

The processing of contrast is a low-level visual processing component that develops early in life and occurs early in the visual processing stream (Braddick & Atkinson, 2011). Adequate processing of visual contrast allows one to determine the edge of a step or discriminate a rock from the background of the sidewalk. Additionally, contrast gratings may be used to determine visual acuity, another fundamental aspect of vision (Braddick & Atkinson, 2011). Several magnetoencephalographic (MEG) brain imaging studies have shown that viewing sinusoidal gratings with high contrast elicits a oscillatory response consisting of a sustained increase in gamma (> 30 Hz) activity in the primary visual (V1) cortices, as well as a decrease in the strength of alpha and beta (8 – 25 Hz) activity in more lateral occipital cortices (Adjamian et al., 2004; S. D. Hall et al., 2005; Swettenham et al., 2009). These spectrally-specific neural responses may serve different visual processes. The strength of the gamma response is dependent upon the contrast properties of the stimulus, while the strength of the alpha-beta power decrease is not contrast dependent (Swettenham et al., 2009). Magnetic resonance spectroscopy (MRS) suggests that individual differences in visual gamma power are likely dependent upon

local γ-Aminobutyric acid (GABA) inhibitory interneuronal connections to pyramidal cells (Muthukumaraswamy & Singh, 2009). Furthermore, structural imaging has suggested that the thickness of local gray matter within visual cortices is closely related to the strength of occipital gamma oscillatory activity (Muthukumaraswamy, Singh, Swettenham, & Jones, 2010). As for the alpha-beta oscillations, the consensuses is that they are central to visual processing and the engagement of visual attention (Ikkai et al., 2016). These responses are generally centered in more lateral occipital visual cortices, bilaterally, and are seen during the processing of almost all visual input (Adjamian et al., 2004; S. D. Hall et al., 2005; Swettenham et al., 2009). Although we currently have in depth knowledge about the cortical oscillations associated with visual processing in healthy controls, no studies to date have determined if such cortical oscillations are altered in children with CP during processing of high-contrast stimuli. Such information will provide key data on the neurophysiological underpinnings of the more nuanced visual processing deficits noted in the clinic for these children. In addition, these data will aide in the development of more precise therapeutic treatments that target the specific neuro-physiological processes that are contributing to the visual deficits.

To date, our MEG investigations have begun to evaluate the potential alterations in cortical visual function seen in children with CP. We initially identified that children with CP have weaker cortical oscillations in the primary visual cortices (V1) while performing a visuomotor knee isometric force production task (Kurz, Proskovec, Gehringer, Heinrichs-Graham, & Wilson, 2017). Given that the task in Kurz et al. (2017) involved components of stimulus tracking, we conducted a follow-up investigation that isolated the cortical oscillations associated with visual motion in the V5/Visual MT cortical area by having children track a series of moving dots (VerMaas, Gehringer, Wilson, & Kurz, 2019). These results showed that the children with CP had weaker alpha-beta (8 – 20 Hz) cortical

oscillations in the V5/Visual MT area during visual motion, implying that visual processing deficits in CP extend beyond the primary visual cortices (VerMaas et al., 2019). Despite the clinical inferences taken away from these investigations, we still have a limited understanding of the neurophysiology underlying most aspects of visual stimulus processing in children with CP. Obviously, the identification of contrasting stimuli plays a prominent role in our visual perception and acuity. Therefore, the primary aim of this investigation was to quantify the strength of visual cortical oscillations induced by a static high-contrast spatial gratings image in children with CP and typically-developing (TD) children. Our systematic evaluation of sub-components of the visual processing networks in children with CP is directed at enhancing the identification and treatment of specific visual problems that may be impacting how children with CP perceive environmental change.

Methods

Participants

A total of 46 children participated in this investigation. In this study, the term “children” is defined as anyone under 18 years-old at the time of enrollment. Twenty-one children had been diagnosed with CP (age = 13.4 ± 2.8 yrs.; 12 females) and twenty-five were TD (age = 14.5 ± 3.1 yrs.; 11 females). Visual inspection of the MR images of the participants showed no visible signs of atrophy or damage to the occipital cortices. All participants were free of metal implants that could interfere with the MEG or be a MRI safety hazard. The TD participants had no known visual, neurological, developmental, or musculoskeletal impairments. The demographics of the children with CP are shown in Table 1. The children with CP that participated in this study were referred from the staff occupational and physical therapists at the Munroe-Meyer Institute who provide

educational services in the school setting. As part of their educational services, all of the children undergo a vision screening to determine if they have visual deficits that need to be addressed. This visual screening includes near (40.6 cm) and far (6 m) distance visual acuity in right/left eye, and pass/fail tests for amblyopia, strabismus, and internal/external eye health. The children that were referred for this study were listed as having normal or corrected to normal visual acuity when using both eyes and could focus at a distance of 1 meter. None of the participants were identified as having challenges with functional vision that impacted their activities of daily living or access to educational materials. All of the parents provided written consent that their child could participate in the investigation, and the children assented. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation.

Table 1. Demographics of the participating children with spastic cerebral palsy (CP). GMFCS = Gross Motor Function Classification Score. Children with a level I walk independently, level II walk with some limitations, level III primarily use crutches or a walker while walking, and level IV primarily use power mobility.

Child with CP	Age (years)	Sex	GMFCS Level	CP subtype
1	16.7	F	I	Diplegia
2	16.7	M	III	Diplegia
3	11.6	M	II	Right Hemiplegia
4	15.4	F	III	Diplegia
5	11.0	F	II	Diplegia
6	14.9	F	III	Diplegia
7	16.8	M	II	Diplegia
8	11.5	M	I	Diplegia
9	15.8	M	I	Diplegia
10	13.8	F	I	Diplegia
11	10.6	F	II	Right Hemiplegia
12	9.3	F	I	Right Hemiplegia
13	11.8	F	II	Diplegia
14	17.8	M	III	Diplegia
15	11.3	F	III	Diplegia
16	10.7	M	II	Right Hemiplegia
17	10.1	M	II	Left Hemiplegia
18	12.0	M	I	Left Hemiplegia
19	13.4	F	IV	Diplegia
20	12.3	F	II	Right Hemiplegia
21	18.9	M	II	Diplegia

MEG Data Acquisition and Experimental Paradigm

Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. For the experiment, the participants were seated upright in a magnetically silent chair with their head positioned within the helmet-shaped MEG sensor array. A custom-built head stabilization device that consisted of a series of inflatable airbags that surrounded the sides of the head and filled the void between the head and MEG helmet was worn during the data collection in order to stabilize the head and reduced the probability of any large head movements. To assess the neural processing of primary visual information, the participant viewed a series of vertical, stationary, square wave gratings (3 cycles per degree) that have been previously shown to evoke robust power changes in the alpha (8 – 16 Hz range) and gamma (40 – 56 Hz range) bands (Adjamian et al., 2004; S. D. Hall et al., 2005; Swettenham et al., 2009; Wilson, McDermott, Mills, Coolidge, & Heinrichs-Graham, 2017). Images were displayed on a back-projected flat screen at eye-level and approximately one meter away. The participants were instructed to fixate on a central red square that remained present throughout the paradigm. Each visual presentation trial began with the appearance of the stationary gratings that remained visible for 500 ms before disappearing. The inter-stimulus interval varied between 2.2 and 2.6 seconds, and 120 visual stimulations were presented (Figure 5).

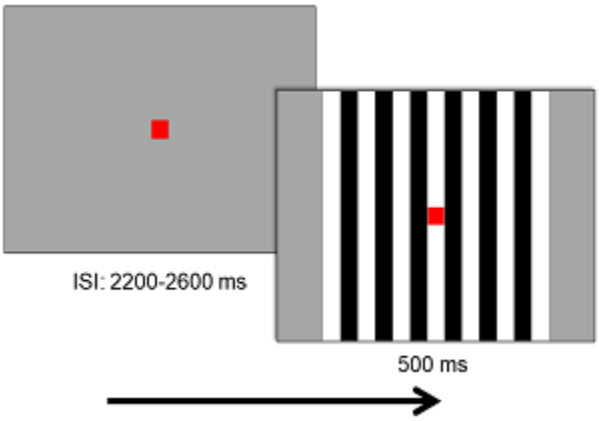

Figure 5: MEG Visual Task. Participants were positioned upright one meter from the stimulus screen and maintained visual fixation on the central red square throughout the task. A static spatial-grating stimulus was presented for 500 ms, with an interstimulus interval (ISI) of 2200–2600 ms. Each participant viewed 120 spatial-grating trials during the experiment.

MEG Coregistration

For the MEG experiment, four coils were affixed to the head of each participant and were used for continuous head localization. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface was digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). During 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 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 their neuro-anatomical MRI data using the three external landmarks (*i.e.*, fiducials) and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were

aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

MEG Pre-Processing & Time-Frequency Transformation

Using the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion that may have occurred during the visual processing experiment and was subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Cardiac and blink artifacts were removed from the data using signal-space projection (SSP), which was accounted for during source reconstruction (Uusitalo & Ilmoniemi, 1997). The continuous magnetic time series was divided into epochs of 1300 ms in duration (-400 ms to + 900 ms; time 0 ms defined as the onset of the first visual grating), with the baseline period defined as -350 to -50 ms. Artifact rejection was performed using a fixed threshold method and supplemented with visual inspection. This quality check resulted in four of the participants (CP = 1, TD = 3) being excluded due to notable MEG artifacts. The epoch acceptance rate was 82% (98 ± 4 epochs) for the remaining participants, with no statistical difference in acceptance rate between groups (p = 0.86).

The artifact-free epochs were transformed into the time-frequency domain using complex demodulation (Kovach & Gander, 2016), and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of the mean spectral density. These sensor-level data were normalized using the respective bin's baseline power (-350 ms to -50 ms time window). The specific time-frequency windows used for imaging were determined by a fully data-driven approach that began with a statistical analysis of the sensor-level spectrograms across the entire array of gradiometers across all participants. Each data point in the spectrogram 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 (baseline vs. visual presentation) 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 across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and spectrally 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 (Maris & Oostenveld, 2007). 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 contained significant oscillatory events across all participants (described in the Results section) were subjected to a beamforming analysis.

MEG Source Imaging & Statistics

A minimum variance vector beamforming algorithm was employed to calculate the source power across the entire brain volume (Gross et al., 2001; Arjan Hillebrand et al., 2005). The single images were derived from the cross-spectral densities of all combinations of MEG sensors, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Arjan Hillebrand et al., 2005; Van Veen et al., 1997).

Such images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences (*i.e.*, visual presentation vs. baseline) per voxel. The resulting beamformer images were 4.0 x 4.0 x 4.0 resolution and were transformed into standard space by using the transform that was previously applied to the structural MRI volume and then spatially resampled. MEG pre-processing and imaging was performed with the Brain Electrical Source Analysis software (BESA v6.0; Grafelfing, Germany).

We imaged the statistically-defined time-frequency windows in each participant using a beamformer and then averaged all output pseudo-t maps across participants to identify the peak voxels, which were used to identify group differences in the cortical oscillations of interest. To examine the dynamics, the virtual sensor (*i.e.*, voxel time series) for the peak voxel per response were computed by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series for each source vector centered in the voxel of interest (Cheyne, Bakhtazad, & Gaetz, 2006; Heinrichs-Graham, Arpin, & Wilson, 2016; Heinrichs-Graham & Wilson, 2016). An average of the respective time courses was subsequently created to qualitatively evaluate the changes seen in each frequency band of interest.

Results

Sensor Space Analysis

Presentation of the visual stimulus was associated with strong oscillatory power changes across a large number of gradiometers over the occipital cortices (Figure 6). These grand-averaged sensor-level spectrograms showed a robust increase in power that began 50 ms after the visual stimulus and stretched across a broad frequency band (20 – 72 Hz), and was sustained in the high-gamma (60 – 72 Hz) frequency range for about 300 ms. Statistical analyses revealed separate components of increased power within the beta

(20 – 36 Hz, 50 – 100 ms), low-gamma (40 – 56 Hz, 50 – 100 ms), and high-gamma (60 – 72 Hz, 50 – 350 ms) frequency ranges ($p < 0.001$, corrected; Figure 6). Concurrently, a significant decrease in the power was detected in the alpha-beta (10 – 20 Hz) frequency range during the 175 to 475 ms time window ($p < 0.001$, corrected; Figure 6). To identify the brain regions generating these oscillatory responses, we beamformed each of these respective time-frequency windows.

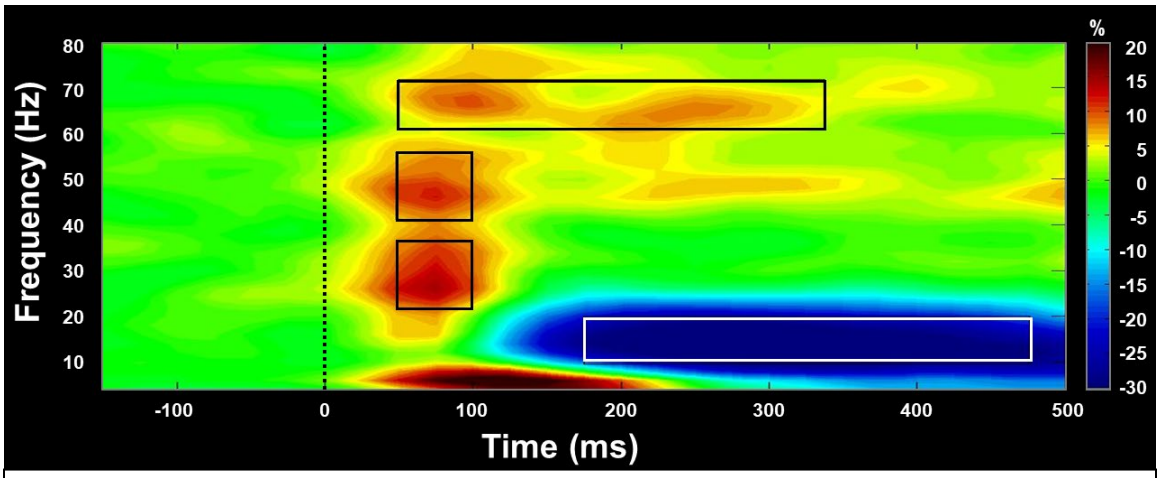

Figure 6: Time-Frequency Spectrogram from a gradiometer sensor located over the occipital cortex averaged across all participants. Time (in ms) is denoted on the *x*-axis, with 0 ms defined as the onset of the spatial grating. Spectral power is expressed as the difference from the baseline period (-350 to -50 ms). Separate components of significantly increased power were seen across the beta (20 – 36 Hz, 50 – 100 ms), low-gamma (40 – 56 Hz, 50 – 100 ms) and high-gamma (60 – 72 Hz, 50 – 350 ms) frequency bands. In addition, there was a significant decrease in power in the alpha-beta (10 – 20 Hz) frequency band during the latter time window (175 to 475 ms). Permutation testing indicated that all components were significant relative to baseline, $p < 0.001$, corrected.

Alpha and Beta Cortical Oscillations

The beamformer images for the power increase seen in the beta (20 – 36 Hz) band during the 50 – 100 ms time window (baseline = -100 to -50 ms) revealed activity bilaterally in the occipital cortices. The individual pseudo-t values from the peak voxels of the respective hemispheres were subsequently extracted for each participant and averaged,

as we did not have hemisphere-specific hypotheses. Group-wise statistical testing indicated that the strength of the beta increase did not differ between groups (TD = 4.2 $\pm$ 1.3; CP = 2.9 $\pm$ 0.7; p = 0.36).

The beamforming images for the decrease in alpha-beta (10 – 20 Hz) power during the latter 175 – 475 ms time window (baseline = -350 to -50 ms) indicated that these neural oscillatory responses extended across the occipital cortices (Figure 7). The pseudo-t value from the peak voxel in each hemisphere was extracted and averaged per participant, as again we had no hemisphere-specific hypotheses. Group-wise statistics indicated that the strength of the alpha-beta decrease seen in the occipital cortices was significantly stronger for the TD group compared to the group with CP ($p < 0.001$). To determine the temporal dynamics, we extracted the neural time course from the peak voxel from each hemisphere and averaged the respective time courses. These time courses showed that the strength of the alpha-beta decreases were stronger for the TD group beginning at 75 ms and continued to be stronger throughout the presentation of the visual stimulus.

Lastly, to inform future studies, we performed an exploratory analysis by dividing groups based on type of CP (hemiplegic and diplegic) and GMFCS level to examine a potential relationship with the strength of the cortical oscillations. The strength of the beta response did not differ between children with hemiplegia and diplegia forms of CP (p = 0.96) or by GMFCS levels (p = 0.40).

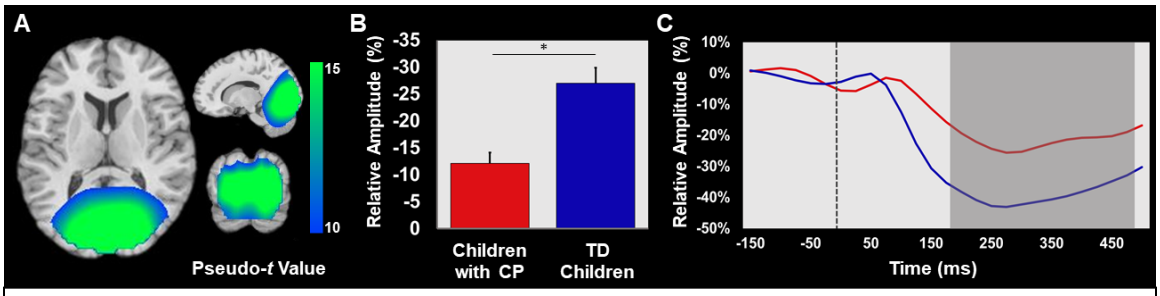

Figure 7: Alpha-Beta (10-20 Hz) occipital cortical oscillations during the 175 to 475 ms time window. A) The grand-averaged beamformer image shows that the alpha-beta oscillations were centered on the occipital cortices. The pseudo-*t* color bar is shown to the right of the image. B) Relative response values (pseudo-*t*) averaged across participants per group, with * indicating $p < 0.001$. C) The neural time course was extracted from the peak voxel of each hemisphere, and then averaged across hemispheres for each group. The time series of the children with CP are plotted in red, while the TD participants are plotted in blue. Time (ms) is denoted on the *x*-axis with relative amplitude (%) shown on the *y*-axis. The visual stimulus was presented at 0 ms (dotted line), and the time-frequency window imaged is shown in the grayed area. The TD group demonstrated a stronger decrease in the alpha-beta occipital cortical oscillations throughout the stimulus presentation compared to the group with CP.

Gamma Cortical Oscillations

The low-gamma (40 – 56 Hz) during the 50 to 100 ms time window (baseline -100 to -50 ms; Figure 8) and high-gamma (60 – 72 Hz) oscillations during the 50 to 350 ms time window (baseline -350 to -50 ms; Figure 9) were generated by the occipital cortices bilaterally. The pseudo-*t* values from the peak voxels of the respective frequency bands were subsequently extracted and averaged across hemispheres per response. The results indicated that the stimulus induced a significantly weaker gamma responses in both the low ($p = 0.01$) and high-gamma range ($p = 0.01$) in those with CP compared to the TD children. The neural time courses from the peak voxels were subsequently extracted to evaluate these differences. These time courses showed that the children with CP had notably weaker low and high-gamma oscillations compared with the TD children throughout the stimulus duration.

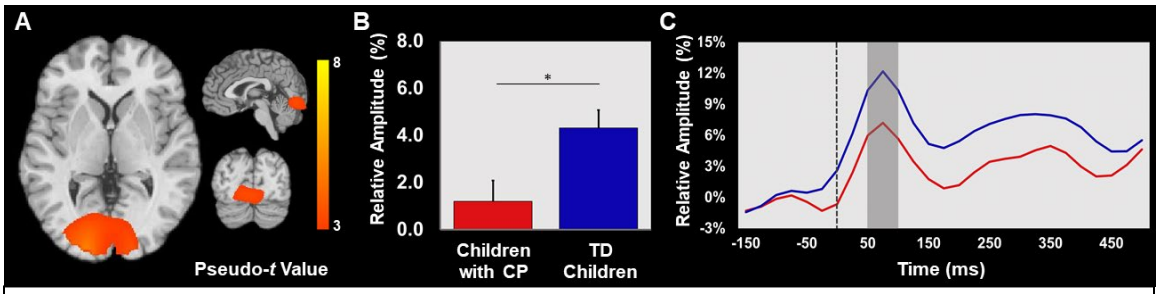

Figure 8: Low-Gamma (40–56 Hz) occipital responses during the 50 to100 ms time window. A) The grand-averaged beamformer image shows that the gamma increase was centered on the occipital cortices. B) Relative response values (pseudo-*t*) averaged across participants per group, with * indicating $p = 0.01$. C) The neural time course was extracted from the peak voxel of each hemisphere, and then averaged across hemispheres for each group. The time series for the group with CP are plotted in red, while the TD group are plotted in blue. Time (ms) is denoted on the *x*-axis with relative amplitude (%) shown on the *y*-axis. The visual stimulus was presented at 0 ms (dotted line), and the time-frequency window imaged is shown in the grayed area. The TD group had consistently stronger neural activity when compared with the group with CP.

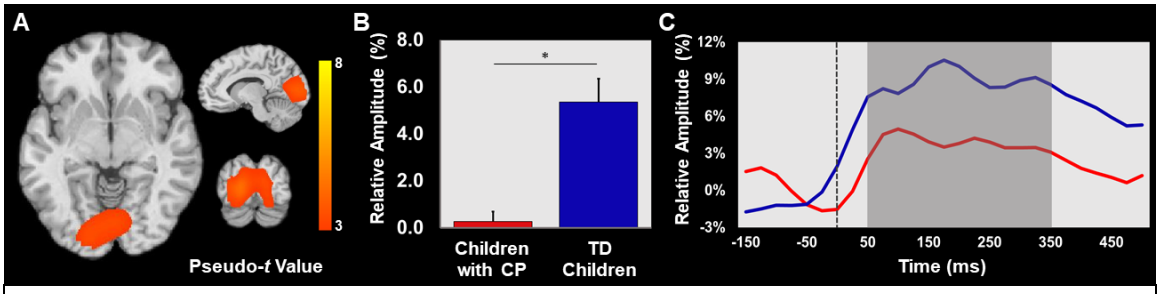

Figure 9: High-Gamma (60–72 Hz) occipital responses during the 50 to 350 ms time window. A) The grand-averaged beamformer image shows that the induced change in high-gamma oscillations was centered on the occipital cortices. B) Relative response values (pseudo-*t*) averaged across participants per group, with * indicating $p = 0.01$. C) The neural time course was extracted from the peak voxel of each hemisphere, and then averaged across hemispheres for each group. The time series of the children with CP are plotted in red, while the TD children are plotted in blue. Time (ms) is denoted on the *x*-axis with relative amplitude (%) shown on the *y*-axis. The visual stimulus was presented at 0 ms (dotted line), and the time-frequency window imaged is shown in the grayed area. The TD group had consistently stronger neural activity when compared to the group with CP.

Analogous to our approach for alpha and beta oscillations, the children with CP were further divided into groups based on type of CP (hemiplegic and diplegic) and

GMFCS level to examine a potential relationship with the strength of the low- and high-gamma cortical oscillations. The strength of both gamma responses did not differ between children with hemiplegia and diplegia forms of CP (low-gamma, $p = 0.34$; high-gamma, $p = 0.44$) or by GMFCS levels (low-gamma, $p = 0.30$; high-gamma, $p = 0.86$).

Discussion

A number of studies have begun to establish visual processing impairments in children with CP using behavioral-observational methodologies (Ego et al., 2015; Fazzi et al., 2007, 2012; Pueyo, Junqué, Vendrell, Narberhaus, & Segarra, 2009). Yet, the neural mechanisms that underlie these deficits remain, for the most part, completely unknown. This study used MEG and beamforming methods to quantify the occipital cortical oscillations while TD children and children with CP viewed stationary high-contrast stimuli. Our results showed that the induced changes in the strength of the alpha-beta and gamma cortical oscillations were weaker in the children with CP. These results indicate that the altered alpha-beta and gamma cortical oscillations likely play a role in the aberrant visual processing frequently observed clinically. Further discussion of the implication of these results are detailed in the following sections.

Compared with the TD participants, those with CP had weaker gamma oscillatory activity in the occipital cortices while viewing the spatial gratings. Prior research has suggested that such gamma oscillations are linked with bottom up processing of visual information (Bastos et al., 2015; Pelt et al., 2016; Saleem et al., 2017; Takesaki et al., 2016). This may indicate that the initial cortical processing of fine visual features are degraded in those with CP. A previous MRS and PET study has also shown that gamma oscillations are dependent upon the interconnection between the pyramidal cells and GABAergic inhibitory interneurons (Kujala et al., 2015; Muthukumaraswamy & Singh,

2009). This relationship might explain the weaker gamma results presented here since prior PET studies have also shown that participants with CP tend to have increased GABA receptor binding potential within the cortices (J. D. Lee et al., 2011; H. J. Park et al., 2013). Hence, we suspect that the weaker gamma responses seen in this investigation is to some degree a result of altered GABA activity. Conceptually, aberrant gamma oscillations would result in more downstream errors in the higher-level integration of the incoming visual information.

The children with CP also had weaker decreases in their alpha-beta activity within the occipital cortices while viewing the gratings. Such alpha and beta cortical oscillations have been associated with top-down processing of the visual feedback (Bastos et al., 2015; Van Kerkoerle et al., 2014), and are thought to influence the neural computations early in the visual stream that are involved in the perception of a visual stimulus (Li et al., 2004; Piech et al., 2013). Hence, it is possible that the perceptual errors seen in children with CP may be related to top-down visual processing. A prior MEG study has also shown that the alpha-beta oscillations are central to the engagement of visual attention (Ikkai et al., 2016). Hence, it is alternatively feasible that the weaker alpha-beta oscillations seen in the children with CP might be linked with their inability to sustain attention on the visual stimuli.

Despite the high prevalence of visual processing impairments in children with CP recognized in the literature and in the definition of CP, these aberrations continue to be overlooked in the medical and educational communities. Frankly, many of the perinatal brain lesions that cause the characteristic motor impairments in CP are also implicated in the etiology of visual dysfunction (Jacobson, Rydberg, Eliasson, Kits, & Flodmark, 2010). Hence, the visual dysfunction and the motor dysfunction may be intricately linked. For example, individuals with CP may have periventricular leukomalacia, which frequently

affects the development of the optic radiations (Hoon et al., 2009). Periventricular leukomalacia has been associated with visual (Fazzi et al., 2009; Lennartsson, Nilsson, Flodmark, & Jacobson, 2014), as well as motor dysfunction. Additionally, the basal ganglia may contribute to the motor dysfunction in those with CP (Hoon et al., 2009) along with affecting basic visual processes such as visual acuity, fixation shifting, visual attention, and visual evoked potentials (Mercuri et al., 1997). Hence, there is likely significant overlap in the etiology of the motor and visual deficits seen in those with CP. Therefore, it is plausible that those with greater motor impairments may also have visual processing deficits that synergistically affect the fidelity of their motor actions. Historically, the motor impairments in these children have been primarily seen as resulting from a musculoskeletal origin. This perception might not be completely accurate, as they might just as likely be related to perceptual processing of the environmental constraints.

Before closing, several possible limitations should be considered. While the experimental paradigm used in this investigation allowed us to explore the visual processing of contrast stimuli in children with CP, we were limited in our abilities to probe higher-level neural processes. Secondarily, our experimental data does not provide a full clinical picture of the visual disturbances in the participants, as a detailed neuro-ophthalmological evaluation was not performed. That being said, it should be recognized that the MEG assessments used here do provide a reliable and unbiased measure of visual cortical function in children with CP since they do not rely on self-report. It is also important to note that all of our participants with CP had the spastic subtype and caution should be made when expanding these results to children with non-spastic CP. Finally, we were unable to evaluate if there is a possible connection between the structural aberrations seen in children with CP and the strength of the occipital oscillations. It is

possible that specific brain maldevelopments and/or white/grey matter injuries may moderate the strength of the occipital cortical oscillations.

Conclusion

Our experimental outcomes suggest that specific neurophysiological processes may be abnormal in the visual processing network of children with CP. Overall, our results showed deficient cortical activity serving visual processing, including weaker alpha-beta and gamma neural oscillations following high-contrast visual stimuli. Identifying deficiencies in specific neural processes may provide a target for intervention and an unbiased neurophysiological marker for evaluation. We foresee that therapeutic strategies that enhance lower-level visual processes may have cascading beneficial effects on higher-level visual-perceptual processes.

CHAPTER 4: CHILDREN WITH CEREBRAL PALSY HAVE ALTERED OCCIPITAL CORTICAL OSCILATION DURING A VISUOSPATIAL ATTENTION TASK

Introduction

Cerebral palsy (CP) is a neurodevelopmental disorder that is primarily characterized by impaired motor functions resulting from brain lesions or anomalies that occur early in life (Rosenbaum et al., 2007). Although the treatments for CP are primarily motor centric, there is a growing body of literature that suggests visual impairments are also central to this disorder (Ego et al., 2015; Fazzi et al., 2009; VerMaas et al., 2020, 2019). The specific visual deficits that emerge are heterogeneous, potentially reflecting dysfunction of the ventral and dorsal visual pathways (Fazzi et al., 2009; Galli et al., 2018; van Genderen, Dekker, Pilon, & Bals, 2012) that are involved in bottom-up sensory and top-down attention processes (Smith & Chatterjee, 2008). Deficits in visuospatial insufficiencies are among the most common visual-processing impairment reported in individuals with CP (Ego et al., 2015; Fazzi et al., 2009; Ortibus et al., 2009; Pueyo et al., 2009), and may be present despite normal or near-normal visual acuity (Akhutina et al., 2003; Ego et al., 2015).

Visuospatial dysfunctions noted in children with CP include deficits in attention to visual stimuli in specific areas of space and errors judging the relationship between spatial elements. Visuospatial impairment is frequently attributed to white matter lesions commonly observed in children born premature (Belmonti, Fiori, Guzzetta, Cioni, & Berthoz, 2015; Ego et al., 2015; Fazzi et al., 2009, 2004; Ortibus et al., 2011; van den Hout et al., 2004). The magnitude of these deficits have been linked to the extent of the brain lesion (Fazzi et al., 2009, 2004; Galli et al., 2018; Andrea Guzzetta, Mercuri, et al., 2001; M. A. Pavlova & Krägeloh-Mann, 2013; M. Pavlova et al., 2007), and the severity of

the accompanying motor-function impairment (Hawe, Kuczynski, Kirton, & Dukelow, 2020; M. Pavlova et al., 2007). Visuospatial abilities appear to be unrelated to the subtype of CP (*i.e.*, spastic, athetoid, ataxic, mixed), intellectual disability, side of motor impairment, or history of seizures (Ego et al., 2015). Furthermore, some children with normal MRIs also present with visuospatial deficits (Fazzi et al., 2009; Ortibus et al., 2011, 2009; Schenk-Rootlieb et al., 1994; van Genderen et al., 2012).

Visuospatial functioning is often associated with spatial neglect and visual field dysfunction. In adults, these impairments occur contralateral to the lesion and primarily following a right hemispheric injury (Cassidy, Bruce, Lewis, & Gray, 1999). Since the brain lesion occurs earlier, visuospatial abilities may develop differently. In some children, language reorganizes to the right hemisphere when a lesion is incurred in the left hemisphere. The consequence of this reorganization is that the extent of the visuospatial dysfunction is proportional to the gain in new language representation in the contra-lesion hemisphere (Lidzba et al., 2006). Ickx and colleagues (Ickx et al., 2018) not only found non-lateralized visuospatial attentional deficits in children with right and left hemiplegic CP (HCP), but also found that children with left HCP tended to have a greater egocentric visuospatial impairment (lateralized neglect in reference to their body), while right HCP had greater allocentric impairment (lateralized neglect in reference to an object). Similar visuospatial deficits have been reported in children with bilateral brain injuries (Fazzi et al., 2009; Pueyo et al., 2009; Schmetz, Magis, Detraux, Barisnikov, & Rousselle, 2019). One study found that children with CP had difficultly shifting their eye gaze to attend to a new spatial target (Maioli et al., 2019). While these collective studies highlight the significance of visuospatial impairments, the underlying neural mechanisms generating this dysfunction remains unclear.

Several magnetoencephalographic (MEG) studies with neurotypical controls have begun to uncover how changes in the frequency specific cortical oscillations reflect the encoding and decoding of information during tasks that require visuospatial attention (B. J. Lew, Wiesman, Rezich, & Wilson, 2020; Wiesman, Mills, et al., 2018; Wiesman, O'Neill, et al., 2018; Wiesman & Wilson, 2019). These studies have revealed that there is an early increase in the occipital theta (4-8 Hz; 40-540 ms) cortical oscillations that is tied to object perception and the initial encoding of visual information. In the later time window (190-540 ms), a decrease in the strength of the alpha (8-14 Hz) occipital oscillations occurs processing of the visual stimulus. Lastly, a concurrent increase in the occipital gamma (54-86 Hz; 140-540 ms) oscillations has been attributed attending to the visual stimulus. Although these multispectral changes have been well catalogued across several studies, it is currently unknown if these cortical oscillations are disturbed in children with CP. If this is the case, then these aberrant oscillations would partly explain the uncharacteristic visuospatial processing seen in children with CP. The objectives of this study were to 1) determine if the occipital cortical oscillations differ between children with CP and typically developing (TD) controls while performing a visuospatial attention task, and 2) investigate the potential link between the strength of the frequency specific cortical oscillations and the visuospatial task performance.

Methods

Participants

A total of 42 children participated in this study, including 21 diagnosed with spastic CP (age = 13.5 ± 3.0 yrs.; 10 males) and 21 TD controls (age = 14.7 ± 3.2 yrs.; 11 males). All participants had normal or corrected to normal binocular visual acuity and could focus at a distance of one meter, the distance of the stimulus screen. The children with CP

presented with spastic diplegia (n = 15) or hemiplegia (n = 6, left-side affected = 2), and had minimally impaired hand function as categorized by the Manual Abilities Classification System (MACS Levels I-II). Most participants with CP had mild to moderate motor impairments as categorized using the Gross Motor Functional Classification System (GMFCS). Five participants were classified as level I (walks independently), nine as level II (walks with some limitations), six as level III (walks using crutches or walker), and one was level IV (limited walking, uses wheelchair). The TD controls had no known neurological, developmental, or musculoskeletal impairments. All of the parents provided written consent and the children assented. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved the protocol for this investigation.

MEG Experimental Paradigm

Participants completed a visuospatial attention task during MEG data acquisition that is known to elicit spectrally-specific neural responses (Wiesman, Heinrichs-graham, Proskovec, McDermott, & Wilson, 2017). Briefly, the participants were seated upright in a magnetically shielded room with their head positioned within the helmet-shaped MEG sensor array. The stimulus images were displayed on a back-projected flat screen at eye-level and approximately one meter away. The participants were instructed to fixate on a centrally located crosshair that remained present throughout the paradigm. After a variable amount of time (ISI: 1900 ms – 2100 ms), an 8 x 8 high-contrast grid appeared for 800 ms in one of four locations: offset to the right or left, and above or below the fixation cross (Figure 10). The left/right orientations were defined by a lateral offset of 75% of the grid from the center of the fixation. The participants were instructed to respond with a right-hand button press as soon as they determined whether the checkerboard was positioned more to the left (index finger) or right (middle finger) of the center cross. Prior to the task,

each participant practiced the task to ensure comprehension. Each participant completed 240 trials, balanced across positions in a pseudo-randomized order.

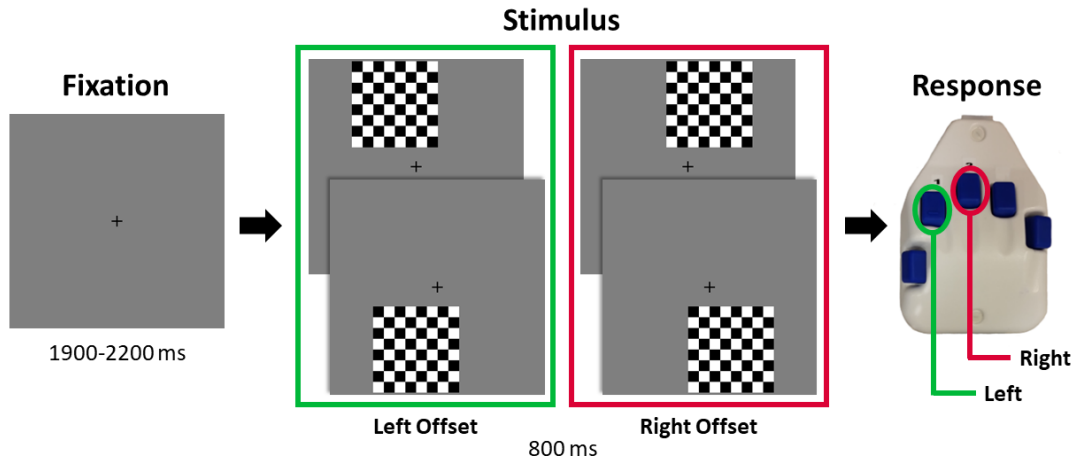

Figure 10: Visuospatial Attention Paradigm. Each trial began with a fixation period lasting about 2000 ms (variable interstimulus interval: 1900 – 2200 ms), with the final 400 ms of fixation (prior to the stimulus onset) serving as the baseline period. The high contrast stimulus appeared for 800 ms in one of four positions. Participants attended to and indicated the lateralized position of the of the stimulus relative to the central fixation cross by pressing a button with their index (left) or middle (right) finger.

MEG Data Acquisition and Coregistration

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for environmental noise compensation. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz using an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers. During the data collection, the participants were monitored via real-time audio-video feeds from inside the shielded room. Each participant wore a custom-built head-stabilization device that consisted of inflatable airbags that surrounded the sides of the head and filled the void between the head and MEG helmet. This system stabilized the head and reduced the probability of any large head movements occurring during the data collections.

Prior the MEG experiment, four coils were affixed to the head of each participant and were used for continuous head localization. The location of these coils, three fiducial points, and the scalp surface was digitized to determine their three-dimensional position (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). During 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 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 fiducial and scalp surface points), each participant's MEG data was coregistered with the structural T1-weighted MRI prior to source space analyses. The structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany). Following source analysis (*i.e.*, beamforming), each subject's 4.0 mm^3 functional images were also transformed into standardized space using the transform that was previously applied to the structural MRI volume and spatially resampled.

MEG Pre-Processing & Time-Frequency Transformation

Using the MaxFilter software (Elekta), each MEG dataset was individually corrected for head motion that may have occurred during the visual processing experiment, and was subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006). Cardiac and blink artifacts were removed from the data using signal-space projection (SSP), which was accounted for during source reconstruction (Uusitalo & Ilmoniemi, 1997). The continuous magnetic time series was divided into epochs of 2700 ms in duration, from -500 ms to + 2200 ms, with

the onset of the high contrast stimulus being defined as 0 ms and the baseline period defined as -400 to 0 ms. Artifact rejection was performed using a fixed threshold method and supplemented with visual inspection. Since only correct trials were used in the analysis and the children with CP had fewer correct responses, trials were randomly removed from the TD controls to achieve similar signal-to-noise ratios between the groups. This resulted in an average of 150 trials per participant that were used for further analysis, and the mean number of trials per participant did not significantly different between groups (CP = 147 ± 57, TD = 154 ± 57; $p = 0.71$). The artifact-free epochs were transformed into the time-frequency domain using complex demodulation (Kovach & Gander, 2016), and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of the mean spectral density. These sensor-level data were normalized using the respective bin's baseline power (*i.e.*, mean power during the -400 ms to 0 ms time window).

The specific time-frequency windows used for imaging were determined by a fully data-driven approach that began with a statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Each data point in the spectrogram 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 (baseline vs. visual presentation) 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 across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and spectrally 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 (Maris & Oostenveld, 2007). For each comparison, at least 1,000 permutations were computed to build a distribution of cluster values. Based on these analyses, only the time-frequency windows that contained significant oscillatory events across all participants (described in the Results section) were subjected to a beamforming analysis.

MEG Source Imaging & Statistics

The Dynamic Imaging of Coherent Sources (DICS) beamformer was employed to calculate the source power across the entire brain volume for the statistically-defined time-frequency windows of interest (Gross et al., 2001; Arjan Hillebrand et al., 2005). The single images were derived from the cross-spectral densities of all combinations of MEG sensors, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per participant using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Arjan Hillebrand et al., 2005; Van Veen et al., 1997). Such images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences per voxel. The resulting beamformer images were 4.0 mm^3 resolution and were transformed into standard space by using the transform that was previously applied to the structural MRI volume and then spatially resampled. MEG pre-processing and imaging was performed with the Brain Electrical Source Analysis software (BESA v6.0; Grafelfing, Germany). We subsequently averaged all output pseudo-t maps across participants to identify the peak voxels, which were used to identify group differences in the cortical oscillations of interest. Independent t-tests were used to discern

differences in the frequency specific pseudo-t values of the respective groups. To qualitatively examine the neural dynamics, the virtual sensor (*i.e.*, voxel time series) for the peak voxel per response were computed by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded a time series for each source vector centered in the voxel of interest (Cheyne et al., 2006; Heinrichs-Graham et al., 2016; Heinrichs-Graham & Wilson, 2016).

Visuomotor Behavioral Data

Behavioral assessment of the visuospatial task performance was quantified using the output of a button pad. Reaction time was defined as the time difference between stimulus onset and when the button press occurred. To account for spurious reaction times, reaction times 2.5 standard deviations (SD) above or below the participant's mean were excluded prior to averaging. The reaction times of the remaining trials were then averaged for each participant and across the group. The accuracy was calculated as the percentage of trials where the participant correctly identified the visual stimulus position. Independent *t*-tests were used to discern between group differences, and Spearman Rho correlations were used to determine if there was a relationship between the strength of the cortical responses with reaction time and accuracy.

Results

Sensor-Level Analysis

Analysis of the sensor spectrograms collapsed across all participants revealed multiple, spectrally-distinct oscillatory responses in sensors located over the occipital cortices (Figure 11A; *ps* < 0.001, corrected). These included a power increase in the theta (4 – 8 Hz, 50 – 300 ms) and gamma (64 – 80 Hz, 400 – 550 ms) bands, along with a power

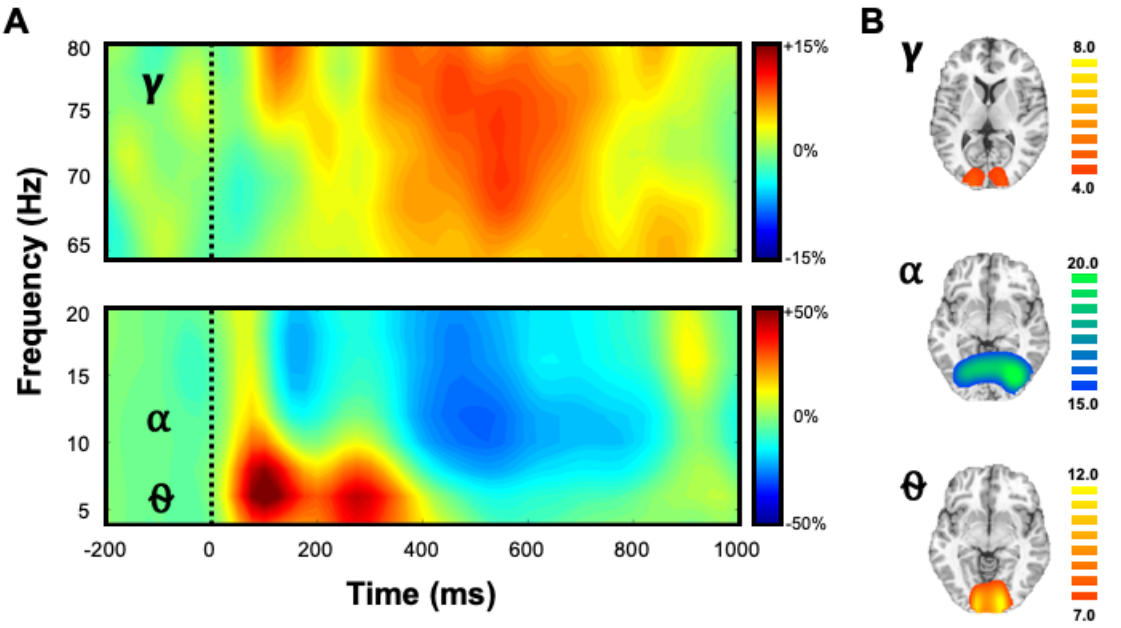

Figure 11: Time-Frequency Spectrogram & Beamformer Images of visuospatial task-related neural responses, averaged across all participants. A) Each representative plot displays the significant oscillatory responses from a gradiometer sensor over the occipital cortex that was representative of the significant neural responses. Time (in ms) is denoted on the x-axis, with 0 ms defined as the onset of the visual stimulus. Spectral power is expressed as the difference from the baseline period (-400 to 0 ms). Separate components of significantly increased power were seen across the gamma (64 – 80 Hz, 400 – 550 ms; top spectrogram) and theta (4 – 8 Hz, 50 – 300 ms; bottom spectrogram) frequency bands. A strong decrease in power was seen in the alpha band (8 – 14 Hz, 350 – 550 ms; bottom spectrogram). Permutation testing indicated that all components were significant relative to baseline, $p < 0.001$, corrected. B) The grand-averaged beamformer images show that the neural oscillations were centered in the occipital cortices. The pseudo-*t* color bar is shown to the right of the gamma (64 – 80 Hz; top image), slightly more lateralized alpha (8 – 14 Hz; middle image), and theta (4 – 8 Hz; bottom image) occipital cortical responses.

decrease in the alpha-band (8 – 14 Hz, 400 – 550 ms). Additionally, a significant power decreased emerged in the beta band (18 – 24 Hz) that was strongest in sensors over the left fronto-parietal region. Prior studies have identified that the sensorimotor cortices is the source of the beta power decrease (B. J. Lew, O'Neill, et al., 2020; Wiesman, Mills, et al., 2018; Wiesman, O'Neill, et al., 2018; Wiesman & Wilson, 2019). Hence, we did not further

examine the beta oscillations since the production of the motor action was not the primary interest of this study.

Beamformed Images

To identify the brain regions generating the responses noted in the sensor analysis, a beamformer was applied to each participant's responses using an equal pre-stimulus baseline period (theta: -300 ms to -50 ms; alpha and gamma: -250 ms to -100 ms) and frequency range. The resulting output images were averaged across all participants for each time-frequency window. The images of the theta response (4 – 8 Hz, 50 – 300 ms) and gamma response (64 – 80 Hz, 400 – 550 ms) identified bilateral peaks of neural activity in the primary visual cortices (Figure 11B). While the alpha activity (8 – 14 Hz, 400 – 550 ms) showed bilateral peaks in more lateral visual association cortices (Figure 11B). We subsequently extracted the pseudo-t values from the peak voxel of the respective cortical oscillations. As we did not have hemisphere-specific hypotheses, the respective pseudo-t values from the each hemispheres were averaged. The neural time courses were also extracted from the same peak voxels, and averaged across hemispheres to qualitatively evaluate the temporal dynamics of each response.

Our statistical analysis revealed that the children with CP exhibited weaker theta occipital cortical oscillations ($p = 0.008$; Figure 12A). Inspection of the neural time course for this response shows that the children with CP had weaker theta oscillations shortly after stimulus presentation and this difference lasted about 350 ms (Figure 12B). The children with CP also had weaker gamma occipital cortical oscillations compared to the TD group ($p < 0.001$; Figure 12C). Evaluation of the neural time course reveals that the gamma activity appeared to be weaker throughout the stimulus (Figure 12D). In contrast,

the alpha occipital cortical oscillations were not significantly different between the respective groups (CP = 14.8 ± 15.2, TD = 25.1 ± 19.0; $p = 0.06$).

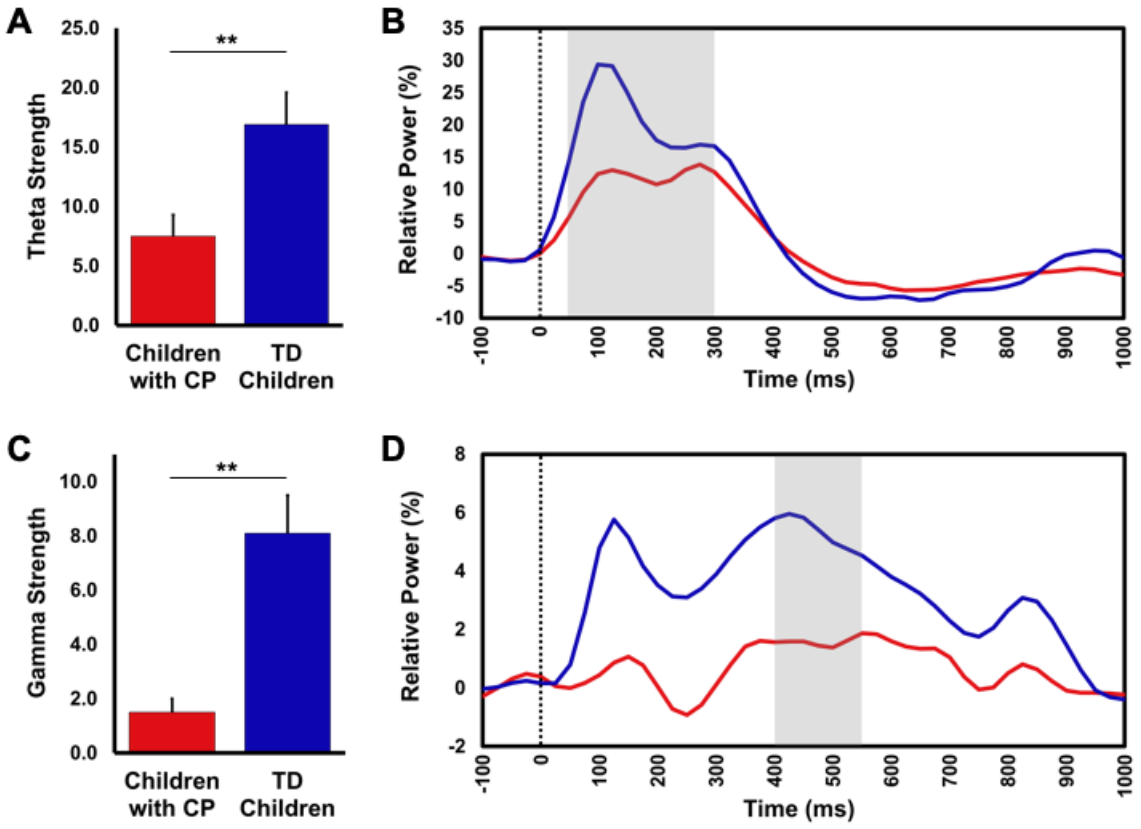

Figure 12. Theta and Gamma Oscillatory Responses. A) Theta (4 – 8 Hz, 50 to 300 ms) occipital cortical oscillations. The relative response values (pseudo-*t*) show a weaker response in children with CP ($p = 0.008$). B) Theta peak voxel neural time course. The time series of the children with CP are plotted in red, while the TD participants are plotted in blue. Time (ms) is denoted on the *x* – axis with relative amplitude (%) shown on the *y* – axis. The visual stimulus was presented at 0 ms (dotted line), and the time-frequency window imaged is shown in the grayed area. C) Gamma (64 – 80 Hz; 400 to 550 ms) occipital cortical oscillations. Relative response values (pseudo-*t*) show a weaker response in children with CP ($p < 0.001$). D) Gamma peak voxel neural time course. The time series of the children with CP are plotted in red, while the TD participants are plotted in blue. Time (ms) is denoted on the *x* – axis with relative amplitude (%) shown on the *y* – axis. The visual stimulus was presented at 0 ms (dotted line), and the time-frequency window imaged is shown in the grayed area.

Visuospatial Task Performance

There were significant differences in the visuospatial-motor performance generated by the children with CP and the TD group. The children with CP had a higher percentage of incorrect responses (TD = 96 ± 8%, CP = 70 ± 26%, $p < 0.001$; Figure 13A) and slower reaction times (TD = 0.54 ± 0.12 s, CP = 0.74 ± 0.16 s, $p < 0.001$; Figure 13B). Together these results suggest that the children with CP had more difficulty deciphering the spatial location of the high-contrast stimulus relative to the crosshairs. Additionally, there was a negative relationship between accuracy and reaction time (r_s = -0.51, p = 0.001; Figure 13C) across all children, suggesting that children who were more accurate tended to respond more quickly.

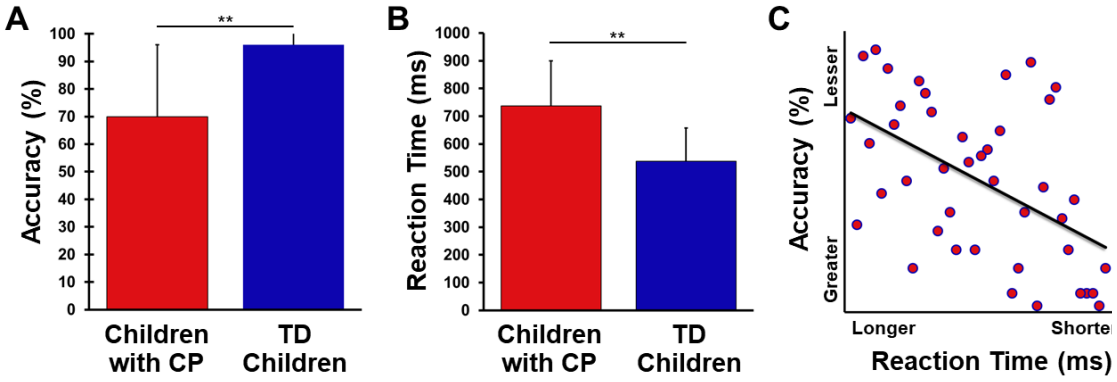

Figure 13: Visuospatial Task Performance. A) Behavioral results for task accuracy (in % correct) on the y – axis with groups denoted on the *x* – axis. As shown, children with CP made more errors identifying the directional shift of the high-contrast stimulus. B) Behavioral results for task reaction time (in ms) on the *y* – axis with groups denoted on the *x* – axis and responses. As shown, children with CP took longer to determine the directional shift of the high-contrast stimulus. C) Relationship between accuracy (in % correct) denoted on the *y* – axis and reaction time (in ms) on the *x* – axis (r_s = -0.51; p = 0.001). Children who took longer to decide the spatial location of high-contrast stimulus were also less accurate. ** p < 0.001.

Relationship between Cortical Oscillations and Task Performance

Our analysis of all participants identified a relationship between the strength of the neural activity in the occipital cortices and the performance components. Specifically, the strength of the theta and gamma oscillations were shown to have a positive association with accuracy (theta: $r_s = 0.57$, $p < 0.001$, Figure 14A; gamma: $r_s = 0.53$, $p < 0.001$; Figure 14B). This indicates that children who had stronger theta and gamma occipital cortical oscillations also tended to make less errors in their visual perception of the stimulus' spatial location. A negative rank order relationship was also found between response time and the strength of the theta ($r_s = -0.48$, $p = 0.001$; Figure 14C) and gamma ($r_s = -0.41$, $p = 0.006$; Figure 14D) cortical oscillations. This suggests that the children who were quicker to identify the spatial location of the high-contrast stimulus had stronger theta and gamma occipital cortical oscillations.

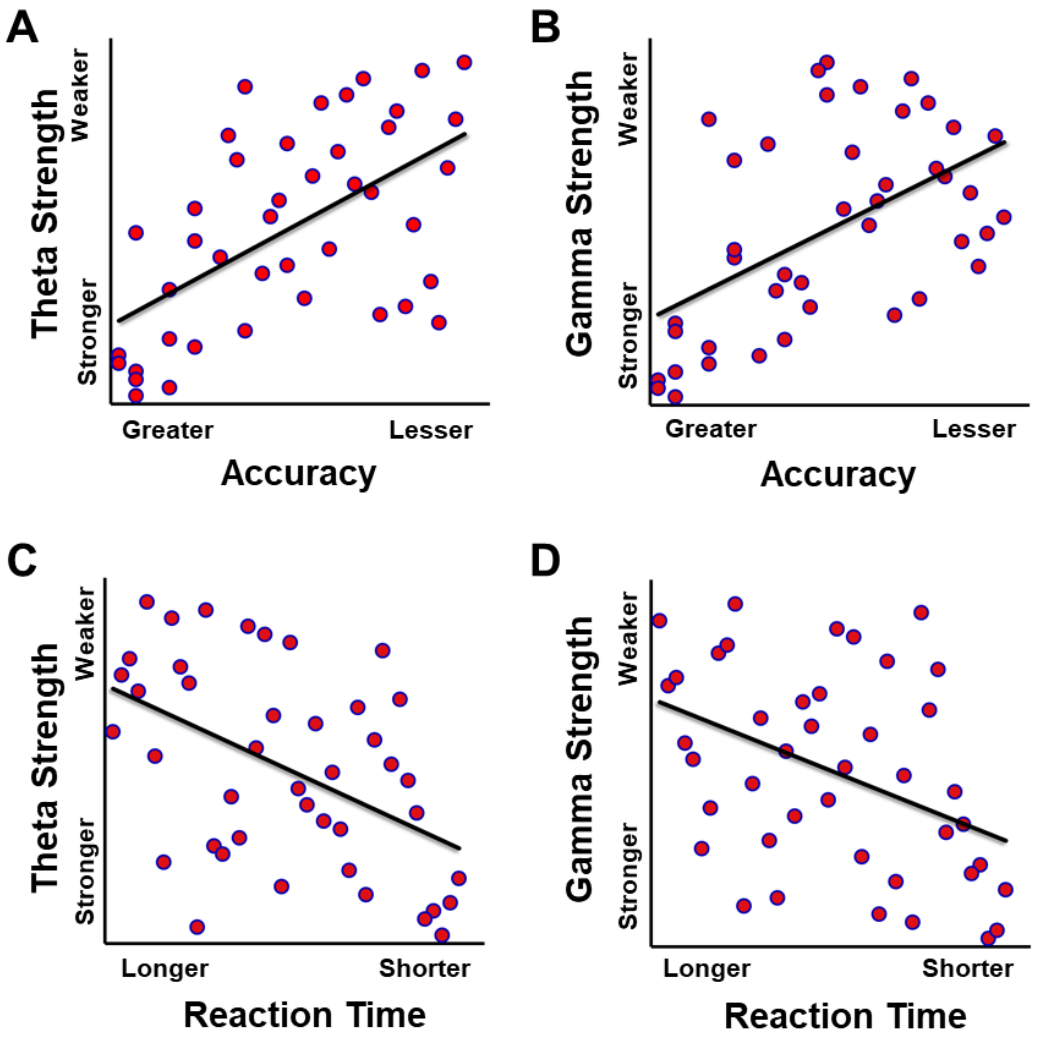

Figure 14: Rank-Order Correlations. Rank-order correlations between the strength of the occipital cortical oscillations (peak relative response in pseudo-*t*) and the task performance of the participants. Stronger gamma-band (64 – 80 Hz) and theta-band (4 – 8 Hz) oscillations within the occipital cortices were associated with (A, B) more correct responses and (C, D) faster decisions in determining the spatial location of the high-contrast stimulus.

Discussion

Impairments in visuospatial processes are the most common visual-processing deficits found in children with CP (Ego et al., 2015; Fazzi et al., 2009; Ortibus et al., 2009; Pueyo et al., 2009). Nonetheless, we have little understanding of the neural dynamics responsible for the altered visuospatial functions seen in the clinic. This study is the first

study to use MEG to evaluate the oscillatory responses during a visuospatial attention task in children with CP. Our results showed that the theta and gamma cortical oscillations in the primary visual cortices were weaker in children with CP. Furthermore, the weaker theta and gamma cortical oscillations were linked with a degraded perception of the spatial location of the high-contrast stimulus. Altogether, these results indicate that the altered theta and gamma cortical oscillations likely play a role in the altered visuospatial attention seen in children with CP.

The increase in the occipital theta and gamma cortical oscillation seen in this investigation were consistent with other studies that have used a similar visuospatial attention task (B. J. Lew, O'Neill, et al., 2020; Wiesman, Mills, et al., 2018; Wiesman, O'Neill, et al., 2018; Wiesman & Wilson, 2019). Prior research has suggested that such oscillations are linked with bottom up processing of visual information (Bastos et al., 2015; Pelt et al., 2016; Saleem et al., 2017; Takesaki et al., 2016), and likely play fundamental roles in CNS communication, perception and cognition (Başar et al., 2001). The theta activity is presumed to be representative of object perception and the initial coding of basic visual information (Başar et al., 2001; Busch et al., 2009; Makeig et al., 2002), while the gamma oscillations are thought to be important for attending to the stimulus and perceptual binding (Edden, Muthukumaraswamy, Freeman, & Singh, 2009; Muthukumaraswamy & Singh, 2013).

Compared with the controls, our results identified that the seminal occipital theta and gamma cortical oscillations that are associated with visuospatial attention were markedly blunted in the children with CP. The altered theta oscillations implies that the neural generators involved in the perception and initial encoding of visual information were aberrant in the children with CP. Furthermore, the weaker gamma oscillations fuels the impression that the neural generators involved with visual attention were also insufficient.

Based on these results, we contend that these aberrant occipital cortical oscillations play a prominent role in the visuospatial deficiencies that have been identified in the clinical literature (Ego et al., 2015; Fazzi et al., 2009; Ortibus et al., 2009; Pueyo et al., 2009). This impression is supported by the behavioral results that showed the children with CP had slower reaction times and a larger percentage of errors when perceiving the spatial location of the high-contrast visual stimulus. Furthermore, our correlational analysis enhances this argument as results the participants with weaker theta and gamma occipital oscillations also tended be less accurate and took longer to discriminate the spatial location of the visual stimulus.

Visual processing plays a crucial role in movement planning, control and evaluation (Krigolson et al., 2015). Individuals with CP need precise information from their visual environment to adapt their movement patterns in order to complete functional activities such as reaching (Savelsbergh, Ledebt, Smorenburg, & Deconinck, 2013). If the bottom-up processing of the spatially relevant visual environment is aberrant, the downstream visual computations and motor planning decisions based on this degraded visual information are likely to result in visuomotor performance errors. In our study, we expected slower reaction times in the children with CP given the motor impairments. However, their task accuracy was also markedly reduced compared to the control group and both behavioral responses were linked to weaker theta and gamma oscillations occurring during stimulus presentation. This finding is consistent with previous studies reporting a similar relationship between theta and gamma neural activity and improved visuospatial tasks performance (Busch et al., 2009; Edden et al., 2009; Wiesman et al., 2017; Wiesman, O'Neill, et al., 2018), and suggests that deficits in visuospatial neural functions contribute to the motor performance impairments observed in children with CP. Of note, it is also conceivable that both the motor and visual impairments are hindering

visuospatial functioning (Belmonti et al., 2015; Hawe et al., 2020). The motor impairment may disrupt the process of visuospatial development by limiting physical exploration of the visual space (M. A. Pavlova & Krägeloh-Mann, 2013; Smith & Chatterjee, 2008; Thébault et al., 2018). This may also account for the growing gap in visuospatial abilities that is observed younger and older children with CP compared to TD controls (Schmetz et al., 2019).

The results shown here add to the growing number of MEG studies that have shown the occipital cortical oscillations are uncharacteristic in children with CP. For example, these investigations have identified children with CP have aberrant alpha (8-14 Hz) and beta (16-24 Hz) occipital cortical oscillations while performing a visuomotor target matching task (Kurz, Proskovec, et al., 2017). Studies have also identified the V5/MT alpha-beta (8-20 Hz) oscillations are weaker while children with CP view a moving stimulus (VerMaas et al., 2019). Likewise, the occipital alpha-beta (10-20 Hz) and gamma (40-72 Hz) oscillations are uncharacteristic while viewing high-contrast spatial gratings (VerMaas et al., 2020). We contend that the likelihood of children with CP having visual processing impairments deserves greater attention when evaluating the potential cognitive and motor difficulties seen in the clinic. Furthermore, we stress that therapeutic approaches that are directed at improving visual processing in children with CP will likely have cascading beneficial effects on their motor actions.

DISCUSSION

Main Outcomes

The overarching goal of this dissertation was to discover the neural mechanisms underlying the brain-based visual impairments in children with CP and probe the potential contribution of aberrant visual processes to the uncharacteristic motor actions that are a hallmark of this disability. Specifically, this dissertation research used magnetoencephalographic brain imaging techniques to systematically evaluate the specific cortical oscillatory responses during the processing of basic, low-level components of vision. Understanding these visual processing mechanisms is essential for the accurate identification of visual processing impairments and the development of targeted interventions for children with CP.

The series of studies is this dissertation emerged from an unexpected finding – altered oscillatory activity in the visual cortices during a task designed to probe impaired motor actions. The first study isolated visual motion perception from motor actions and quantified the neural activity in the motion-sensitive visual MT/V5 cortices while children with CP viewed a horizontally moving stimulus. The central hypothesis was that children with CP would have an altered V5 cortical oscillatory response, which would be related to their visual perceptions. This study found a unique pattern of alternating theta-alpha (5-10 Hz) and alpha-beta (10-20 Hz) neural responses that were time-locked with the positional shifts of the dots that created the visual stimulus. The children with CP had slower reaction times, which may be partly expected from their motor impairments; however, they were also less accurate in identifying the direction of the visual motion stimulus. This miscalculation was surprising given the substantial directional change (*i.e.*, horizontal or vertical) and highlighted the notion that CVI in children with CP may be more profound

and unexpected than realized. The children with CP demonstrated blunted alpha-beta neural activity in the visual MT/V5 cortical area that was related to the delayed motor responses and the directional visual-perception errors. This result suggests that children with CP have weaker neural mechanisms in the visual MT/V5 cortical area that likely contribute to the delayed perception of directional changes and more visual-perceptual judgement errors. These findings increase our understanding of how small, potentially undetectable differences in visual processing may influence the motor decisions of children with CP.

The second study of this dissertation specifically targeted the neurophysiology underlying basic visual perception independent of motion. This study hypothesized that viewing a high-contrast, square-wave grating stimulus, comparable to a visual acuity stimulus, would evoke weaker oscillatory changes in children with CP. The high-contrast stimulus is known for producing multi-spectral responses that are thought to represent different bottom-up and top-down visual processes occurring in the occipital cortex. The results of study two supported the hypothesis, and the children with CP produced weaker neural responses in the alpha-beta band (10-20 Hz) and the low- and high-gamma bands (40-56 Hz, 60-72 Hz). Diminished gamma response may reflect that children with CP have difficulty processing visual information as it initially enters the visual cortex. The weaker alpha-beta cortical activity may indicate discrepancies in top-down visual processing, such as problems with integrating visual feedback or visual attention. These results provide additional neurophysiological support for the presence of deficits in basic visual perception. These low-level processing differences are likely to affect subsequent visual computations and integration that is essential for higher-level functions. Understanding which visual processes are deficient may direct the development of interventions targeting these deficits.

The final dissertation study focused on spatial attention by quantifying the differences in the visual cortical oscillations that underlie visuospatial discrimination in children with CP. The ability to covertly lateralize one's attention is fundamental to making accurate motor decisions in everyday life activities like searching for items or safely navigating down the street. This study hypothesized that the children with CP would have weaker cortical oscillations when processing the laterality of a visual stimulus that relate to performance errors in a visuospatial discrimination task. The results from this study revealed multiple, spectrally distinct oscillatory responses in the occipital cortex that partially supported the hypothesis. The theta- (4-8 Hz) and gamma-band (64-80 Hz) power increases were weaker in children with CP; however, group differences in the alpha-band (8-14 Hz) power decrease failed to reach significance. In regards to their visuospatial task performance, the children with CP demonstrated prolonged reaction times and profound accuracy errors. This result is similar to the first study and equally surprising given the simplicity of the visual discrimination task. Additionally, the strength of the theta and gamma visual responses had a negative relationship with the task performance deficits. Together, the blunted theta and gamma activity seen the children with CP may relate to problems with the initial coding and feature binding of visual information entering the visual processing stream. These impairments in visuospatial attention likely lead to difficulty perceiving salient features in the environment and further contribute to motor performance problems in children with CP.

Collectively, the results from these studies expose the neural signature of CVI in children with CP. They provide evidence that the neural mechanisms responsible for generating vision are aberrant at the lowest-level of visual processing in the occipital cortex. Moreover, these deficits might play a prominent role in the uncharacteristic motor actions in children with CP.

Limitations

Before concluding, several limitations of this dissertation should be acknowledged. Although the children who participated in this study were reported to have normal functional vision, MEG data revealed disturbances in the cortical processing of visual information. The extent to which the neural oscillatory responses correspond with current neuro-ophthalmological assessments is unknown, though I would suspect they would not be strongly related. Some studies suggest that CVI is not dependent on good visual acuity (Fazzi et al., 2009; Pueyo et al., 2009). However, other areas, such as contrast sensitivity and visual field perimetry, have not been examined may have different effects on visual functions. Electrophysiological assessment methods are more sensitive to visual deficits (Costa & Ventura, 2012), which implies that MEG tasks may reveal more visual disturbances than behavioral measurements. Future studies that include a full neuro-ophthalmological examination could provide insight into how specific clinical measures of visual functions are related to the uncharacteristic neural dynamics observed in the dissertation studies.

Specifically, in regards to CP, all of the participants had the spastic subtype with mild-moderate motor impairment. CVIs affect individuals with all types of CP. How the dissertation study results would extend to other CP subtypes or individuals with a higher degree of motor impairment is unknown. Additionally, this dissertation was unable to probe a potential relationship between brain lesion characteristics and function. Most studies have found that the size and location of the lesion are related to the degree of impairment, although not absolutely. The link with brain injury or structural differences may be less informative given early plasticity and the heterogeneity of visual functions in children with similar lesions.

Current research suggests that approximately 50% of children with CP have an intellectual impairment, yet mild cognitive deficits may be under-recognized (Fluss & Lidzba, 2020). The direct impact of cognitive levels on visual processing performance is unclear. Several studies have found that visual-perceptual impairments are not directly related to cognitive levels, especially when using non-verbal or performance IQ (Fazzi et al., 2009; Galli et al., 2018). Although the simplicity of the visual tasks used in these dissertation studies likely placed little demand on cognitive functions, future studies may consider incorporating neuropsychological testing, especially when probing higher, visual-cognitive functions. Additionally, while using a simple visual stimulus allowed all participants to complete these tasks, it limits the ability to extend these findings to higher, visual-cognitive processes and participation.

Finally, the visual oscillatory responses in studies one and three were linked to functional performance through reaction time measurements. It is unclear to what extent the variation in reaction times relate specifically to motor skills (*e.g.*, selection and execution of the motor plan) and visual function. Incorporating a baseline, visual-perception reaction time measurement (*e.g.,* the time between visual stimulus presentation and button press indicating conscious awareness of the visual stimulus) could help understand the unique contribution of visual cortical processes. Interpreting motion direction (study one) or spatial laterality (study three) should take longer. The resultant reaction time differences would directly reflect visual processing.

Conclusions

The studies in this dissertation have systematically discovered the uncharacteristic neural dynamics underlying components of basic visual processes in children with CP. These results collectively provide neurophysiological evidence supporting the presence of impaired neural processes serving the subcomponents of vision function. Moreover, these low-level visual components appear to significantly contribute to the motor performance deficits that characterize the disability. The results of the studies build on the current literature that now recognizes the vast presence of brain-based visual impairments in children with CP. Accurately identifying these abnormal neural mechanisms provides clinicians a specific target for intervention and a marker to evaluate the intervention's success. Clinicians implementing therapeutic strategies that enhance these lower-level visual components or adjust and appropriately challenge the level of visual function may improve the underlying processing. These strategies could create a cascading benefit to motor abilities and higher-level visual processes, potentially enhancing academic achievement and social participation. Ultimately, understanding the aberrant neurophysiology in fundamental components of vision could lead to individuals with CP and their families living more productive and meaningful lives.

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