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Reorganization of the somatosensory cortex in hemiplegic cerebral palsy associated with impaired sensory tracts

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ABSTRACT

Functional neuroimaging studies argue that sensory deficits in hemiplegic cerebral palsy (HCP) are related to deviant somatosensory processing in the ipsilesional primary somatosensory cortex (S1). A separate body of structural neuroimaging literature argues that these deficits are due to structural damage of the ascending sensory tracts (AST). The relationship between the functional and structural integrity of the somatosensory system and the sensory performance is largely unknown in HCP. To address this relationship, we combined findings from magnetoencephalography (MEG) and probabilistic diffusion tractography (PDT) in 10 children with HCP and 13 typically developing (TD) children. With MEG, we mapped the functionally active regions in the contralateral S1 during tactile stimulation of the thumb, middle, and little fingers of both hands. Using these MEG-defined functional active regions as regions of interest for PDT, we estimated the diffusion parameters of the AST. Somatosensory function was assessed via two-point discrimination tests. Our MEG data showed: (i) an abnormal somatotopic organization in all children with HCP in either one or both of their hemispheres; (ii) longer Euclidean distances between the digit maps in the S1 of children with HCP compared to TD children; (iii) suppressed gamma responses at early latencies for both hemispheres of children with HCP; and (iv) a positive correlation between the Euclidean distances and the sensory tests for the more affected hemisphere of children with HCP. Our MEG-guided PDT data showed: (i) higher mean and radian diffusivity of the AST in children with HCP; (ii) a positive correlation between the axial diffusivity of the AST with the sensory tests for the more affected hemisphere; and (iii) a negative correlation between the gamma power change and the AD of the AST for the MA hemisphere. Our findings associate for the first time bilateral cortical functional reorganization in the S1 of HCP children with abnormalities in the structural integrity of the AST, and correlate these abnormalities with behaviorally-assessed sensory deficits.

1. Introduction

Cerebral palsy (CP) is defined as a group of non-progressive disorders of movement and posture due to a defect or lesion in the developing brain (Rosenbaum et al., 2007). The most common form of CP is hemiplegic CP (HCP) that impairs the use of one hand and disrupts bimanual co-ordination. More than 95% of children with CP suffer from sensory deficits in their upper extremities, such as limited proprioception, stereognosis, and tactile discrimination (Lesný et al., 1993; Sanger and Kukke, 2007; Wingert et al., 2008; Riquelme and Montoya, 2010). The neurophysiological mechanisms underlying these sensory deficits remain unclear. Yet, it has been proposed that abnormal and limited movements of CP contribute to repetitive, aberrant sensory inputs to the immature brain, resulting in abnormal sensory feedback and altered cortical organization (Coq et al., 2008). The development of fine motor skills depends heavily on the somatosensory system (Cascio, 2010), and tactile feedback from mechanoreceptors in the skin and joints is critical to the online modulation of fine motor skills, such as the pinch grip (Soechting and Flanders, 2008; Papadelis et al., 2016). Therefore, it is not surprising that motor dysfunction in children with CP strongly

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correlates with somatosensory impairments (Kinnucan et al., 2010; Auld et al., 2012).

Converging evidence from neurophysiological, behavioral, and functional neuroimaging studies supports altered somatosensory processing in the brains of children with CP. Electroencephalography (EEG) and magnetoencephalography (MEG) studies of CP have reported abnormal amplitude, latency, morphology, and/or somatotopy of cortical somatosensory evoked potentials or fields. These were in response to electrical stimulation of the median nerve, tibial nerve, or tactile stimulation of the hand digits (Wilke and Staudt, 2009; Teflioudi et al., 2011; Kurz and Wilson, 2011; Guo et al., 2012; Nevalainen et al., 2012; Papadelis et al., 2014). Furthermore, the magnitude of the somatosensory cortical activity was found to be related to the mobility and strength impairments seen in children with CP (Kurz et al., 2015b). Few previous MEG studies also reported changes in the oscillatory activity of CP in response to the application of peripheral somatosensations (Guo et al., 2012; Pihko et al., 2014; Kurz et al., 2014, 2015a, 2015b; Becker, et al. 2015). Except Guo et al. (2012) and Kurz et al. (2017), these studies focused their attention on lower frequency bands (i.e., alpha and beta), which are traditionally considered to be closely tied to the activation of the sensory cortex (van Ede et al., 2011). Nevertheless, frequencies in the gamma band are of particular importance since they are more spatially discrete and somatotopically specific than lower frequency oscillations (Crone et al., 1998). Synchronization in gamma frequencies might characterize 'skillful' cortical representations, as for example, the thumb representation in the primary somatosensory cortex (S1) (Tecchio et al., 2003). Gamma activity in the S1 has been previously reported in the brain of healthy adults after the delivery of painful (Gross et al., 2007) and non-painful somatosensory stimuli (Tecchio et al., 2003, 2008; Bauer et al., 2006; Fukuda et al., 2008; Witzel et al., 2011). In a recent work by Kurz and colleagues (2017), MEG cortical oscillations, between 10 and 75 Hz, in response to paired-pulse electrical stimulation of the tibial nerve were found to be weaker in children with CP compared to TD children. Our previous MEG study (Papadelis et al., 2014) revealed evidence of functional reorganization in the S1 of children with CP; S1 cortical activations in response to tactile stimulation of the first, third and fifth digits were farther apart in children with CP than in typically developing (TD) children. Functional abnormalities observed in the event-related potentials, evoked by tactile stimulation of the hands, have been further correlated with deficits in two-point discrimination as assessed by neurobehavioral tests (Maitre et al., 2012). In line with these findings, smaller response magnitudes and constricted spatial extents were observed with functional magnetic resonance imaging (fMRI) in the primary and secondary somatosensory cortexes of individuals with mild spastic CP compared to TD individuals during tactile stimulation of the hands (Wingert et al., 2010). Resting-state fMRI studies also showed abnormalities in the functionally connected networks in the somatosensory cortex of individuals with CP (Burton et al., 2009; Papadelis et al., 2014). Altogether, these functional neuroimaging studies suggest a direct association between abnormalities in the somatosensory cortex and diminished somatosensory function in CP.

Altered somatosensory function may not be due to abnormalities in the somatosensory cortex alone. In fact, a growing body of evidence from diffusion tensor imaging (DTI) and tractography studies has demonstrated that the ascending thalamocortical tracts (AST) have more influence on the motor and somatosensory function than the corticospinal motor tracts in CP (Hoon et al., 2002, 2009; Thomas et al., 2005; Trivedi et al., 2010; Rose et al., 2011; Tsao et al., 2015). Hoon et al. (2002, 2009) demonstrated that the severity of injury in the AST was directly linked to deficits in the sensorimotor function, while injury to the corticospinal tracts did not relate to measures of strength or sensation. Reduced fractional anisotropy, reduced tract volume, and increased mean diffusivity of the thalamocortical projections were also reported in the ipsilesional hemisphere of children with congenital hemiplegia (Tsao et al., 2015). The aforementioned findings from anatomical neuroimaging studies indicate that the behaviorally-observed sensory deficits in children with CP – and possibly the functional abnormalities seen with functional neuroimaging in the somatosensory system – could be due to damage to the AST. However, a direct link between the anatomical and functional findings is still missing, possibly because the same individuals with CP are rarely examined with multimodal neuroimaging. Such an attempt to integrate findings from different neuroimaging techniques that assess the structural and functional aspects of the somatosensory system was made in our previous multimodal neuroimaging study (Papadelis et al., 2014). Preliminary data from a small cohort of children with CP were presented showing evidence of abnormal functionality in the S1 and damaged thalamocortical pathways in the more affected (MA) hemisphere of children with CP. However, the cohort of patients was inhomogeneous consisting of both diplegic and hemiplegic patients with CP. More importantly, the neuroimaging findings from the different techniques were evaluated in isolation.

In the current study, we aim to integrate functional and structural lines of evidence to assess the integrity of the somatosensory system in the same cohort of children with HCP. Our main hypothesis is that functional somatosensory deficits in children with HCP are related to abnormal functional processing in the ipsilesional S1 as a result of damaged AST. Based on preliminary data from our previous study (Papadelis et al., 2014), we specifically hypothesize that somatosensory magnetic fields elicited by the tactile stimulation of the hand digits will present abnormal amplitude, latency, oscillatory activity, and somatotopy in the MA hemisphere of children with HCP. These functional abnormalities will be correlated to the severity of damage in the AST and to the behaviorally-assessed sensory deficits. To test our hypothesis, we integrate findings from MEG and probabilistic diffusion tractography (PDT) using a MEG-guided tractography technique. Unlike traditional anatomy-based DTI methods, this approach does not make assumptions about structure-function relationships that may not hold after cortical reorganization (Reid et al., 2016). It is thus expected to provide new information on the altered structure-function relationships arising during brain development in children with HCP. By using this approach, we provide here a direct association of measures of functional cortical organization in the S1 of HCP children with measures of structural integrity of the AST and measures of the severity of sensory deficits.

2. Material and methods

2.1. Participants

Neuroimaging data were assessed from 10 children with spastic HCP (age = 12.3 ± 3.9 years; 4 females) and 13 age-matched TD children (age = 12.5 ± 3.5 years; 8 females). The clinical characteristics of participants with HCP are shown in Table 1. Inclusion criteria were: (i) Gross Motor Function Classification System (GMFCS) level I or II (Palisano et al., 1997), (ii) Manual Abilities Classification Scale (MACS) I or II (Eliasson et al., 2006), (iii) asymmetrical motor impairment assessed by a physiatrist (D.N.), and (iv) ability to follow verbal instructions. Exclusion criteria were: (i) metallic implants, devices, or pumps, (ii) history of brain operation, or (iii) any genetic syndrome or severe intellectual developmental disability. The TD children were right-handed and had no history of neurological disorder or brain injury. Handedness in children with HCP was determined based on the higher functioning hand. The Institutional Review Board at Boston Children's Hospital reviewed and approved this investigation. Informed consent was acquired from the parents and the children assented to participate in the study.

2.2. Somatosensory testing

Touch sensitivity was measured at the tip of the thumb (D1), middle