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Regional vulnerability of longitudinal cortical association connectivity Associated with structural network topology alterations in preterm children with cerebral palsy

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ABSTRACT

Preterm born children with spastic diplegia type of cerebral palsy and white matter injury or periventricular leukomalacia (PVL), are known to have motor, visual and cognitive impairments. Most diffusion tensor imaging (DTI) studies performed in this group have demonstrated widespread abnormalities using averaged deterministic tractography and voxel-based DTI measurements. Little is known about structural network correlates of white matter topography and reorganization in preterm cerebral palsy, despite the availability of new therapies and the need for brain imaging biomarkers. Here, we combined novel post-processing methodology of probabilistic tractography data in this preterm cohort to improve spatial and regional delineation of longitudinal cortical association tract abnormalities using an along-tract approach, and compared these data to structural DTI cortical network topology analysis. DTI images were acquired on 16 preterm children with cerebral palsy (mean age 5.6 ± 4) and 75 healthy controls (mean age 5.7 ± 3.4). Despite mean tract analysis, Tract-Based Spatial Statistics (TBSS) and voxel-based morphometry (VBM) demonstrating diffusely reduced fractional anisotropy (FA) reduction in all white matter tracts, the along-tract analysis improved the detection of regional tract vulnerability. The along-tract map-structural network topology correlates revealed two associations: (1) reduced regional posterior–anterior gradient in FA of the longitudinal visual cortical association tracts (inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, optic radiation, posterior thalamic radiation) correlated with reduced posterior–anterior gradient of intra-regional (nodal efficiency) metrics with relative sparing of frontal and temporal regions; and (2) reduced regional FA within frontal–thalamic–striatal white matter pathways (anterior limb/anterior thalamic radiation, superior longitudinal fasciculus and cortical spinal tract) correlated with alteration in eigenvector centrality, clustering coefficient (inter-regional) and participation co-efficient (inter-modular) alterations of frontal–striatal and fronto-limbic nodes suggesting re-organization of these pathways. Both along tract and structural topology network measurements correlated strongly with motor and visual clinical outcome scores. This study shows the value of combining along-tract analysis and structural network topology in depicting not only selective parietal occipital regional vulnerability but also reorganization of frontal–striatal and frontal–limbic pathways in preterm children with cerebral palsy. These finding also support the concept that widespread, but selective posterior–anterior neural network connectivity alterations in preterm children with cerebral palsy likely contribute to the pathogenesis of neurosensory and cognitive impairment in this group.

1. Introduction

One of the most common types of cerebral palsy is spastic diplegia, which is thought to be related to perinatal preterm white matter injury or periventricular leukomalacia (PVL). The topography of the neuropathology of PVL includes both a focal and diffuse component, with regional vulnerability of the parietal–occipital white matter and crossing fibers of the deep cerebral white matter. In conjunction with these motor abnormalities, these patients are also known to have a host of neurocognitive problems including visual-motor and visual perception disabilities, which are associated with various types of frontal executive-attention deficits. The distribution of the neural network substrate that underlies this neurocognitive phenotypic disability is poorly

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understood and is likely related to regional vulnerability of cortical association pathways and compensatory brain reorganization.

Diffusion weighted imaging techniques, including Diffusion Tensor Imaging (DTI) and diffusion tensor tractography (DTT), can be used for the detection of white matter microstructural changes (Mori and Zhang, 2006; Gerig et al., 2004) that likely underlie the disability associated with cerebral palsy. In the last several years, numerous groups have reported DTI-based white matter differences in this population. The majority of studies have predominately focused on regions of the brain associated with putative sensorimotor function and demonstrate variable deficits (Scheck et al., 2012; Hoon et al., 2002; Murakami et al., 2008; Ludeman et al., 2008; Chang et al., 2012; Trivedi et al., 2010; Rose et al., 2007) (for systematic review see Scheck et al., 2012). For the most part, these studies use similar approaches and typically measure diffusivity and anisotropy within a priori selected white matter (WM) regions of interest (ROIs) related to sensorimotor function. Additional studies utilizing deterministic based tractography methods, mainly Fiber Assignment by Continuous Tracking (FACT), are likewise focused on the identification of a priori sensorimotor tracts as ROIs for quantification of diffusivity measurements (Rose et al., 2011; Thomas et al., 2005; Yoshida et al., 2010; Rha et al., 2012). More recently there have been descriptive reports of structural network topology alterations in children with cerebral palsy. However, there is relatively less information about correlating regional vulnerability of longitudinal cortical association tracts with structural network topology changes in this population.

There are a few DTI studies investigating more global WM deficits, also demonstrating changes in mean diffusivity and fractional anisotropy measures in children with CP (Rai et al., 2013; Lee et al., 2011). In a tractography study, Nagae et al. found multiple and wide-spread differences in a qualitative assessment of 26 manually defined fiber tracts (Nagae et al., 2007). These studies suggest a more diffuse pattern of white matter injury, and indicate the need for a more comprehensive whole brain characterization of white matter damage in CP. The technique of DTI has been used to study both cortical spinal tract and cortical association white matter in survivors of prematurity with cerebral palsy (Nagae et al., 2007; Pandit et al., 2013; Hoon et al., 2009; Counsell et al., 2007), but these studies have typically relied only on tractography post-processing methods based on the FACT algorithm. These more traditional tractography methods typically collapse each tract's diffusion data into a single numeric mean average, resulting in loss of visualization and analysis of regional variation in diffusion metrics along the tracts. Diffusion measurements can vary along the course of a tract for multiple reasons. First, certain axons within a fascicle of a white matter tract do not necessarily follow the course of the entire tract, as groups of axons arising of a common neuronal cell group may enter the white matter fascicle at one point and then eventually exit the same fascicle at a different point. Second, there is regional decrease in fractional anisotropy in areas of crossing fibers, in which a segment of most of the longitudinal cortical association fibers in the brain will travel through. Third, both normal developmental processes and pathological conditions have been recently shown to have regional tract variation using different types of along the tract trajectory analysis. Combining more refined tractography analysis with structural topology analysis may help us understand how regional vulnerability of specific cortical association tracts can be interrelated to more global dynamics in the alteration of neural networks that can underlie the more complex neurocognitive phenotypes observed in these patients.

In this study, we tested the hypothesis that there would be selective regional vulnerability of cortical association tracts in preterm children with PVL that would correlate with structural network topology differences. We first delineate the degree of diffuse microstructural abnormalities using both standard averaged measurements from probabilistic tractography data, Tract-Based Spatial Statistics (TBSS) and template based voxel-based morphometry (VBM) analysis. We then delineated regional cortical association longitudinal tract variation using probabilistic tractography and along tract analysis, supplemented by population distribution maps. We targeted our primary tractography analysis to study cortical association longitudinal fiber tract including the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) (intrahemispheric pathways and ventral visual stream correlates), superior longitudinal fasciculus (intrahemisperic pathway with integration of visual pathways with the posterior frontal regions), the posterior thalamic radiations (cortical thalamic including connection from pulvinar to the parietal cortex), the anterior thalamic radiation (including both frontal–thalamic and frontal–striatal pathways) and the optic radiation (primary visual relay). Next, we calculated structural network topology measurements in this same preterm cerebral palsy cohort and compared to a healthy control group, to determine if there was any compensatory regional reorganization that was associated with regional vulnerability of the longitudinal cortical association fiber tracts. Lastly, we correlated both along tract and global structural network topology measurements with motor and visual outcome measurements.

2. Methods

2.1. Subjects

The cohorts analyzed in this study have been previously described (Nagasunder et al., 2011). The inclusion criteria for the preterm survivors with cerebral palsy were: 1) prematurity (<37 gestational weeks at birth); 2) confirmed cerebral palsy by medical history and neurological examination; and 3) evidence for the sequelae of periventricular leukomalacia on conventional MRI performed during childhood. These sequelae were defined as periventricular volume loss and signal hyperintensities on FLAIR as previously described (Nagasunder et al., 2011; Panigrahy et al., 2001). Additionally, preterm children with retinopathy of prematurity were excluded from our study as a subset of these preterm children was originally recruited as part of a neonatal visual functional MRI study (Ceschin et al., 2015). The controls were children born at term (37–42 gestational weeks) with normal conventional MRI performed in the same age range in childhood as the preterm cohort.

Written consents for use of their child's clinically acquired MRI data and for participation in additional neurodevelopmental and neuroimaging studies were obtained from parents on behalf of the prospectively recruited patients by a research coordinator. The ethics committee approved this consent process. Additionally, as this study involved a retrospective review of all clinically-acquired neuroimaging data for the period between 2005 and 2009, which included subjects who were not enrolled into prospective studies, approval was also obtained for the retrospective use of all clinically acquired MRI data obtained between 2005 and 2009.

2.2. MRI procedures and analysis

2.2.1. Image acquisition and pre-processing

Imaging was acquired on a 1.5 T General Electric System (Ge-Medical Systems, Milwaukee, WI) using a pediatric head coil. Diffusion tensor images were acquired using the following parameters: echo-planar imaging (EPI) sequence, TE/TR $= 80/10{,}000$ ms, field of view $= 22$ cm, matrix $= 128 \times 128$, in-plane resolution of 2.5 mm, 25 directions and b-value of 1000 s/mm^2.

Standard pre-processing steps were performed using routines in FSL. Subject DTI images were motion and eddy current corrected using a rigid body registration, followed by brain extraction using Brain Extraction Tool (BET). DTI metrics, including fractional anisotropy (FA), signal intensity without diffusion weighting (S0), value of the principal eigenvalue (L1), and direction of the principal eigenvector were computed for each voxel.