Long range white matter connectivity deficit in pediatric cerebral palsy

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Target Audience: Researchers and clinicians interested in diffusion tensor based connectivity imaging, specifically in its application in brain injuries and development disorders.

Purpose: Cerebral palsy (CP) is a heterogeneous group of non-progressive motor and developmental disorders caused by brain injury during *in utero* or early development. Although the predominant feature of CP is motor disability, it has been consistently demonstrated that white matter injury in CP has both focal and global components, and is not restricted to motor regions [1]. Structural connectome analysis aims to classify the connectivity patterns of cortical fibers obtained from diffusion tensor imaging (DTI) between anatomically defined brain regions [2]. We performed a whole brain connectome analysis in a cohort of 18 pediatric patients with bilateral CP to assess global changes in white matter connectivity in relation to clinical assessment of disease severity. We hypothesized that white matter connectivity, measured as regional and inter-regional fiber volume, would show deficits proportional to disease severity throughout the brain, which can subsequently help investigate the impaired brain circuits related to motor impairment and developmental delays in CP.

Methods: Diffusion weighted images were acquired on a 3 GE HD scanner (TE=70.5 ms, TR = 12000 ms, 3×b0 + 25 directions, resolution =2 mm^3, acquisition matrix = 96×96, FOV = 192×192 mm^2). T1-weighted images used for white matter volume quantification were obtained (FSPGR, TE=2.5 ms, TI = 450 ms, TR = 6.5 ms, flip angle = 12^o, resolution = $1mm^3$). The JHU-DTI-MNI "Eve" atlas template was warped into each patient's DTI image space via the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm [3]. The whole brain connectome analysis was performed via a modified version of the Connectome Mapper Toolkit (http://www.cmtk.org) [4]. The relationship between mutual connectivity between pairs of brain regions and impairment was assessed by performing a correlation of number of streamlines, normalized by white matter volume, between each pair of ROIs with CP severity score using the Kendall-tau-b rank correlation test. The number of short range (<40 mm) and long range (≥ 40 mm) fibers in the whole brain were counted for each individual, normalized by the total white matter volume, and averaged for each category of individuals classified by the CP severity score.

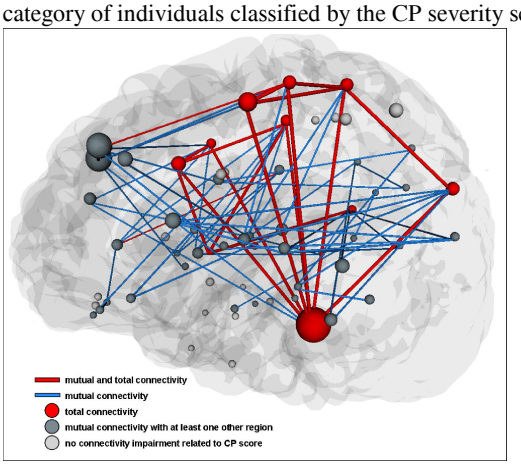

Fig 1. Whole brain connectome. Red nodes are regions that show a significant deficit (p<0.023, corrected) in total connectivity to all other brain regions, correlated with CP severity score. Red edges depict mutual connectivity deficits that are correlated with CP score, and connect two red nodes. Blue edges depict mutual connectivity deficits that are significantly correlated (p<0.026, corrected) with CP severity score. Node size is proportional to the total number of connections associated with each region.

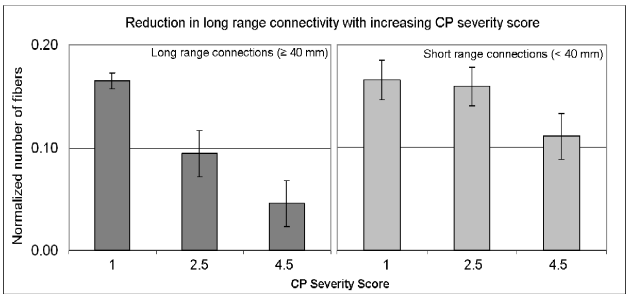

Fig 2. Selective reduction of long range fibers in CP with increasing CP severity score.

Results: Fig. 1 depicts mutual and total connectivities that are significantly related to CP severity score. Mutual connectivity impairment correlated with disease severity score is observed throughout the brain. More specifically, long range mutual connectivity decreased more sharply with increasing disease severity than did short range connectivity (shown in Fig. 2). Of individuals who qualified for cognitive assessment, those with lower cognitive scores showed more severe decreases in long range mutual connectivity than did individuals with higher cognitive scores.

Discussion: Our results, which showed diffuse and significant reduction in mutual connectivity throughout the brain, are consistent with previous reports in other brain injury-related disorders [5]. It is worth noting, however, that this reduced connectivity, as shown in our results, is primarily due to long range connectivity impairment. This finding, to our knowledge, has not been previously reported in the CP literature, but would play a significant role explaining the delayed pediatric brain development. Also, as expected, there is a reduction in overall and mutual connectivities throughout the motor regions including primary and supplemental motor areas, basal ganglia, and brainstem (shown in red in Fig. 1), contributing to motor deficits which are the most significant and apparent clinical observations in CP.

Conclusion: Through whole-brain connectome analysis with correlation to the CP disease severity, we demonstrate here that in addition to the significant impairments in motor circuitry, there is a diffuse white matter connectivity impairment in CP, specifically in long range mutual connectivity. Of individuals who qualified for cognitive assessment, those with lower cognitive scores showed more severe decreases in long range connectivity than did individuals with higher cognitive scores, suggesting a possible mechanism for the developmental delay and cognitive deficits that accompany sensorimotor dysfunctions in CP.

References: 1. Volpe, JJ (2008) Neurology of the newborn, Ed 5. Philadelphia: W.B. Sanders. **2.** Sporns et al. PLOS Comput Biol 2005; 1:4. **3.** Faria AV, et al. Neuroimage 2011; 54: 1854-61. **4.** Gerhard S et al. Front Neuroinform 2011; 5:3. **5.** Morey RA et al. Hum Brain Mapp. 2012.