Exploring Developmental Structural Connectivity Patterns by In Vivo Diffusion Tensor Imaging Tractography on Longitudinal Pediatric Data

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INTRODUCTION: The human brain is organized as a collection of interacting networks with specialized functions to support various cognitive functions. Recent research has reached a consensus that brain networks manifest small-world topology, which implicates both global and local efficiencies at minimal wiring costs, and also modular organization, which indicates functional segregation and specialization. However, the important questions of how and when the small-world topology and modular organization come into existence remain largely unanswered. Taking a graph theoretic approach, we attempt to shed some light on this matter by an in vivo study, using diffusion tensor imaging based fiber tractography, on 39 healthy pediatric subjects with longitudinal data collected at the average ages of 2 weeks, 1 year, and 2 years. Our results indicate that the small-world architecture exists at birth, with low global and local efficiencies, and is strengthened in later stages of development. In addition, we found that the node degree distributions of the networks have Gaussian tails, signifying their single-scale nature. We also observe, across development, that the brain network seems to evolve progressively from a local, predominantly proximity based, connectivity pattern to a more distributed, predominantly functional based, connectivity pattern. These observations suggest that the brain in the early years of life has relatively efficient systems that may solve similar information processing problems, but in divergent ways.

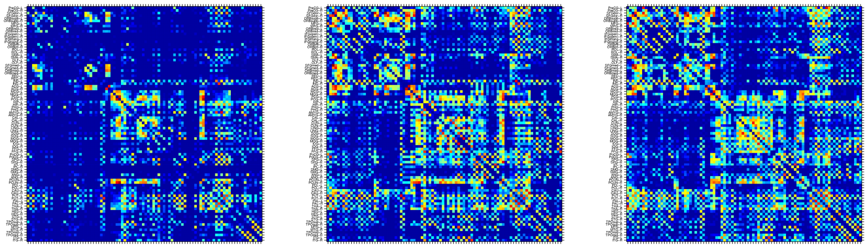

Fig. 1. Inter-region fiber count map, from left to right, of 2-week, 1-year, and 2-year olds. Red indicates a high value and blue otherwise. A general increase in the inter-region connection can be observed.

METHODS AND MATERIALS: The Automated Anatomical Labeling (AAL) template [1] was used to parcellate the brain into 90 regions (45 for each hemisphere) for the brain network analysis of 39 pediatric subjects (18 males, 21 females) in three age groups: 2-week-olds (mean: 1.62 weeks), 1-year-olds (mean: 54.15 weeks), and 2-year-olds (mean: 105.22 weeks). After aligning all images in all age groups onto a common template, we performed whole brain fiber tractography on each image and evaluated the inter-region connectivity. Two regions were considered as anatomically connected if fibers passing through their respective mask were present. For each subject, the number of fibers passing through every pair of regions was counted. These fiber counts were however taken as only an indication of the existence, and not weight, of an anatomical connection. For analyzing the brain network topology, we took a classical unweighted approach [2-4], since it was not obvious how the edge weights, i.e., the number of connection fibers, should be interpreted when computing the minimum path length [2]. Given the variability of brain anatomy, it is not surprising that anatomical connectivity between regions differs across subjects. In this study, we focused on the connections that were most consistent across subjects, i.e., the backbone network [5]. To identify highly consistent connections, a nonparametric one-tailed sign test was employed on a fiber count maps (see Fig. 1). For each pair of brain regions, the sign test was performed to evaluate the null hypothesis that no connection exists. Bonferroni correction was used to address the problem of multiple comparisons (i.e., 90x89/2=4005 pairs of regions). However, considering that different thresholds would affect the number of links in the resulting brain networks, we evaluated the brain network by applying multiple statistical thresholds (Bonferroni-corrected P values of 0.001, 0.005, 0.01, 0.05 and 0.10) to gauge the stability of our results. We considered 39 subjects from the neonatal project on early brain development led by Dr. Gilmore at the University of North Carolina at Chapel Hill [6]. For each subject, diffusion-weighted images were acquired at 2 weeks (mean: 1.62 weeks), 1 year (mean: 54.15 weeks) and 2 years (mean: 105.22 weeks). Diffusion gradients with a b-value of 1000s/mm^2 were applied in six non-collinear directions, (1,0,1), (-1,0,1), (0,1,1), (0,1,-1), (1,1,0), and (-1,1,0). A b=0 reference scan was also obtained for the diffusion tensor matrix calculations. Forty-six contiguous slices with a slice thickness of 2mm covered a field of view (FOV) of 256x256mm^2 with an isotropic voxel size of 2mm. Eighteen acquisitions were used to improve the signal-to-noise ratio (SNR) in the images.

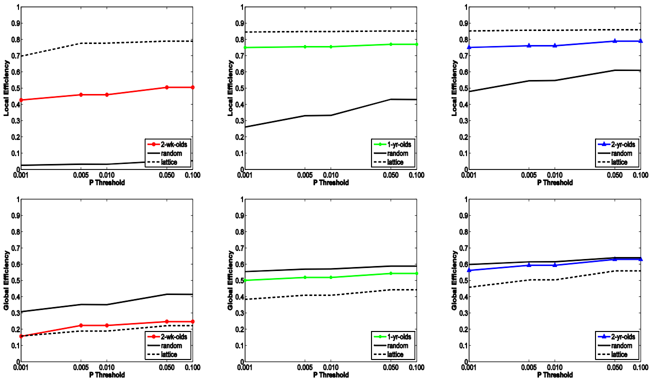

Fig. 2. Global and local efficiencies, from left to right, of 2-week, 1-year, and 2-year olds show an increasing trend. All networks are small-world in nature.

RESULTS: [Local and Global Efficiencies Increase With Growth] The neonatal brain has lower local and global efficiencies compared to that of 1-year-olds and 2-year-olds, as can be seen from Fig. 1. This observation parallels the fact that myelination happens rapidly in the first year of life and stabilizes at the age of two. Myelination has a direct impact on the impulse propagation speed along the fiber, and the state of progressive myelination in the first year of life implies that many connections are in progress, and hence resulting in overall lower efficiency. **[Pediatric Brain Networks Exhibit Single-Scale Characteristic]** The node degree distributions of the pediatric brain networks display Gaussian tails, indicating that they are single-scale in nature. Goodness-of-fit was tested using the coefficient of determination R^2 (better fit indicated by a value closer to 1), and the values given by the curves of the 2-week-olds, 1-year-olds, and 2-year-olds were 0.9938, 0.9934, 0.9972, respectively. **[In Early Development, the Brain Shows a Local-to-Distributed Organization]** We also observe a trend of fiber length increase and modularity [8] decrease with growth, which is indicative that brain growth begins with segregated small communities and then progresses to form more distributed global communities [7]. To further investigate this, we detected brain network communities using a fast algorithm which partitioned the network into subsets to achieve maximum network modularity [9]. The results show that for the neonatal brain, connections between regions of the frontal gyri are stronger within themselves than with other farther regions, while the 2-year-old brain has more distributed strong connections, such as those from the frontal gyri to the occipital gyri.

REFERENCES: [1] Tzourio-Mazoyer, NeuroImage, 2002. [2] Watts and Strogatz, Nature, 1998. [3] Achard et al. J. Neuroscience, 2006. [4] Latora and Marchiori, Phys. Rev. Lett., 2001. [5] Gong et al., Cere. Cortex, 2009. [6] Gilmore et al., J. Neuroscience, 2007. [7] Newmann and Girvan, Phys. Rev. E, 2004. [8] Fair et al., PLoS Comp. Bio. 2009. [9] Clauset et al, Phys. Rev. Letter, 2004.