Structural network development of human brain during childhood

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Introduction

After birth, complicated molecular and biochemical processes take place in the human brain white matter, which is reshaped to better adapt sophisticated functional and cognitive requirements. The axonal connectivity undergoes dramatic structural changes, causing the significant variations of brain network properties. DTI based tractography allows us to noninvasively access the structural connectivity which underlies the formation and evolution of the network during human brain development. Previously, resting state fMRI (see Ref. 1 for review) has been applied to studying the network development. The structural network has been investigated during different time periods (2,3) with DTI tractography only recently. However, the comprehensive dynamics of structural network has not been characterized covering the landmark postnatal time points during early childhood, including birth time, 2 year old and around puberty. In this study, high resolution DTI data of 25 neonates, 13 infants and 15 young children were acquired. Brain cortex was parcellated into 80 regions or nodes with automated anatomical labeling (AAL) labeling (4) and structural connectivity between these nodes were quantified with probabilistic tracking (5). Significant changes among the network properties at these key developmental time points were found although the property of small-world organization is kept for structural networks at all time points.

Methods

DTI/MRI acquisition for neonates, toddlers and young children: 25 neonates (age: 0 month, 13M/12F), 13 toddlers (age: 2.4±0.6, 8M/5F) and 15 young children (age: 11.8±1.2, 8M/7F) were recruited. DTI/MRI of these subjects was acquired with Philips 3T scanners in two institutions with identical imaging protocol. DTI data were acquired using a single-shot EPI with SENSE. The image parameters were: resolution=2x2x2 mm^3, 30 directions; b=1000 sec/mm^2, repetition=2. T1 weighted images (MPRAGE) were scanned with 1x1x1mm^3 isotropic resolution. *Cortical parcellation for network node definition:* The AAL labeling was obtained by transforming the AAL template to native space using a transformation matrix that was obtained by registering T1 weighted images of toddler and young child groups and b0 images of neonate group to ICBM152 template using SPM8. Intra-subject registration was then conducted to make AAL labeling aligned with DTI images, resulting in 80 parcellated regions or nodes for each brain. *DTI tractography for network edge definition:* With each of 80 nodes as seed, probabilistic tracking (5) was performed by using FSL package. P_{ij} of each node was calculated following the literature (6). Due to very different brain sizes and connectivity efficacy (2), the effects of brain size and connectivity efficacy were scaled by using $w_{ij}=P_{ij}*BrainSize/ADC$ as the weight between node i and j. ADC is the apparent diffusion coefficient of the traced white matter. An 80x80 connectivity matrix was then established for each subject. *Network and statistical analysis:* With different thresholds, following global network measures were calculated: strength, global efficiency, local efficiency, normalized shortest path length (λ), normalized clustering coefficient (γ) and small-worldness. The statistical comparisons among the three groups were analyzed using one-way ANOVA with post-hoc pair-wise t-tests ($p<0.05$).

Results

Averaged connectivity matrix of each age group: The averaged connectivity matrix of neonate group was shown in Fig. 1. While the connectivity pattern looks quite similar, the general stronger connectivity in infant and young child group, compared to that in the neonate group, can be clearly appreciated from Fig. 1. *Dynamics of shortest path length, clustering coefficients and small-worldness:* From upper row of Fig. 2, all three groups show a small-world organization with a normalized C_p (γ) greater than 1 and normalized L_p (λ) close to 1. Normalized L_p values of neonate and infant group are close for most thresholds while normalized L_p of young children is much higher ($p<0.001$). The normalized Cp show age-dependent decrease ($p<0.001$), indicating network segregation is reduced during development. The small-worldness, an index of small world configuration, also decreases from neonate to young child group ($p<0.001$), showing alterations of segregation and integration of the network with brain maturation. *Network strength, global and local efficiency during development:* The lower row of Fig. 2 demonstrates that the strength, global and local efficiency of the brain network increase monotonically with all thresholds during brain development (all $p<0.001$). *Hub distributions and increased regional efficiency during development:* As shown in Fig. 3, bilateral PCG, bilateral PCUN and right CUN were identified hubs in all three groups. During development, regions with the most significantly increased efficiencies were located in bilateral PCG, left DCG, left OLF, right REC and right PHG (all $p<0.0001$).

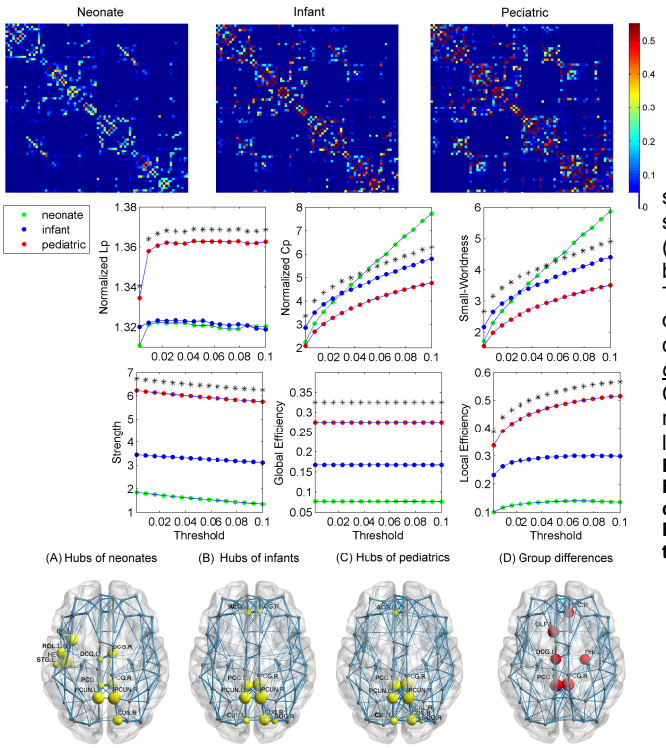

Fig. 1 (up): The averaged connectivity matrix of neonate, infant and young child group.
Fig. 2 (middle): Group differences in global network measures among three groups with different thresholds.
Fig. 3 (down): Distributions of hub regions in each group (A, B and C) and regions with the most significantly increased efficiency during development (D).

Conclusion and discussion

In this study, we aimed to comprehensively characterize how the structural network evolves during childhood by analyzing the structural network properties of three landmark time points of postnatal development. The network quantification shows a general stronger connectivity with development. The monotonic increase of network strength, global and local efficiency indicates the brain network is getting more efficient while monotonic decrease of clustering coefficients and small-worldness suggests that segregation decreases with brain maturation. The recent measurements of DTI-derived metrics of major white matter tracts revealed increased myelination (e.g. 7,8) as an important microstructural process during brain development. Combined with our network analysis results, it suggests the brain white matter development is characterized with parallel and heterogeneous processes to reshape of the structural connectivity. Specifically, these network property changes found in our study are underlined by growth of major white matter tracts including increased myelination concurrent with pruning of small white matter fibers during postnatal brain development. Acquisition and analysis of DTI data at other developmental time points are under way.

References: [1] Power et al (2010) Neuron 67: 735-748. [2] Hagmann et al (2010) PNAS 107: 19067. [3] Yap et al (2011) PloS ONE 6: e24678. [4] Tzourio-Mazoyer et al (2002) Neuroimage 15: 273. [5] Gong et al (2009) J Neurosci 29; 15684. [6] Behrens et al (2007) Neuroimage 34: 144. [7] Lebel C et al (2008) Neuroimage 40: 1044. [8] Gao W et al (2009) AJNR 30: 290-296. **Acknowledgement:** This study is sponsored by NIH MH092535 and NIH EB009545.