The Evolution of Brain Functional Architecture from the Age of 2 weeks to 2 years

W. Gao[1], H. Zhu[2], K. Giovanello[3], K. Smith[4], D. Shen[5], J. Gilmore[6], and W. Lin[5]

[1]Department of Biomedical Engineering, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, United States, [2]Department of Biostatistics and BRIC, University of North Carolina-Chapel Hill, [3]Department of Psychology and BRIC, University of North Carolina-Chapel Hill, [4]Department of Radiology, University of North Carolina-Chapel Hill, [5]Department of Radiology and BRIC, [6]Department of Psychiatry, University of North Carolina-Chapel Hill

Introduction Human brain is intrinsically organized as a functionally connected network, facilitating efficient information integration, processing and decision making [1]. In adults, a general functional connectivity pattern characterized by significant connections between inter-hemisphere homologous regions and among anatomically adjacent regions has been demonstrated. This connectivity pattern suggests a small-world property due to its dense local clustering or cliquishness of connections between neighboring nodes [2, 3]. However, when this efficient network starts to emerge and how it develops across age, especially during the first years of life, remain largely unknown. Answers to these questions may shed great light on delineating the functional developing trajectory of the brain network. To this end, healthy pediatric subjects from 2wks to 2yrs of age were recruited and functional connectivity based on partial correlation was computed using resting functional MRI (rfcMRI) to investigate the development of brain network in a critical time period of early brain development.

Methods 71 normal subjects including 20 neonates (9M, 24 $\pm$ 12 days (SD)), 24 1-year-olds (16M, 13 $\pm$ 1 months), and 27 2-year-olds (17M, 25 $\pm$ 1 months) were included in this study. All subjects were at sleep during the imaging examination. None of the subjects was sedated. Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board.

For the rfcMRI studies, a T2*-weighted EPI sequence was used with TR = 2sec, TE = 32 ms; 33 slices; and voxel size = 4x4x4 mm^3. 150 volume data were acquired to provide time series images. Anatomical images using a 3D MP-RAGE sequence were acquired with TR = 1820ms; TE = 4.38 ms; inversion time = 1100ms; 144 slices; and voxel size = 1x1x1mm^3. MP-RAGE images were used for co-registration across subjects in each age group.

The BOLD time series images were preprocessed, including time shifts, rigid body correction for head movement, and spatial smoothing (6-mm FWHM Gaussian kernel), followed by data reduction using PCA. Subsequently, the infomax algorithm was applied for ICA analysis to obtain a set of aggregate independent components for each age group. The number of components for each age group was 28, 31 and 27 for neonate, 1yr and 2yr groups, respectively, determined using the minimum description length criteria. GIFT software proposedd by Calhoun et al [4] was used for group ICA. Based on Z-transformed and thresholded (Z>1) group ICA spatial maps, a neuroradiologist (JKS) and cognitive neuroscientist (KG) carefully went through all independent components and identified components corresponding to motion artifacts, CSF and blood vessels which were removed from subsequent analysis. ROIs were defined on the remaining components based on the spatially un-connected regions (Z>1). The mean time course of each ROI was extracted from each individual subject separately to compute partial correlation as a scaled inverse covariance matrix [2]. Fisher's Z-transform was applied on each connection value for each subject and averaged across subjects to compute the mean partial correlation matrix for each age group. One-sample t-test (two-tailed) on the Fisher's Z-transformed group mean value for each connection was performed to determine significance. The false discovery rate (FDR) approach was applied to correct for multiple comparisons at $\alpha<0.05$. A spring

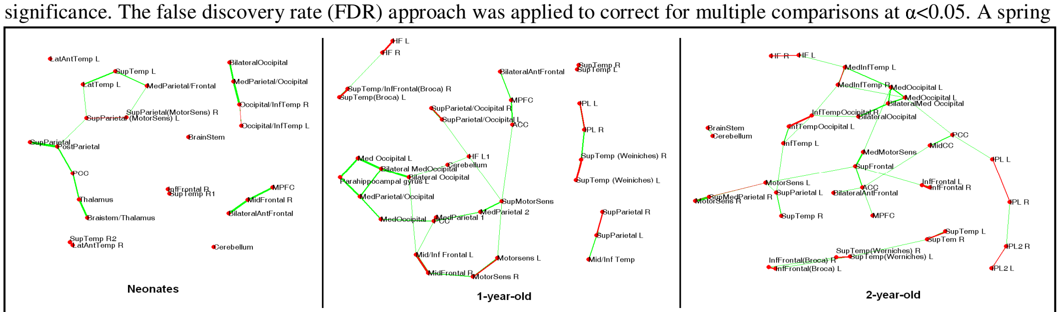

Fig.1 Connectivity pattern based on partial correlation.

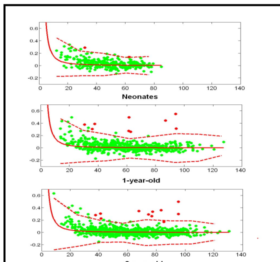

Fig.2. Dependence of connection on distances.

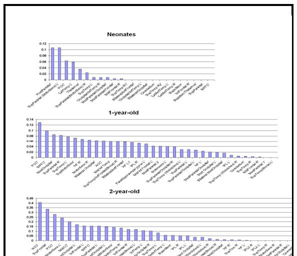

Fig.3. Betweenness centrality for each region.

embedding algorithm was applied to calculate the position of each node (ROI) based on the group mean correlation matrices for graph visualization of the connection pattern. Graph metrics including clustering coefficient C_p, characteristic path length L_p and betweenness centrality were computed. C_p and L_p were compared with those from random graphs (controlled with a same degree distribution, repeated100 times) to obtain the small world property measures.

Results Twenty-four, thirty-four and thirty-seven ROIs are defined for neonates, 1yr and 2yr olds, respectively, covering the whole brain. Connectivity patterns represented by significant pair-wise connections are shown in Fig.1. Generally, 3 regions are left out unconnected (cerebellum, brainstem and lateral anterior temporal lobe) in neonates but all regions are connected to at least one other region in 1yr and 2yr olds. Moreover, only 2 connections between symmetric homologous regions are significant in neonates (Motor-Sensory L/R; Occipital/InfTemporal L/R), while 9 (Motor-Sensory L/R; MidFrontal L/R; HF L/R; SupTemporal L/R; Brocas' L/R; IPL L/R; Werniches' L/R; SupParietal L/R; SupParietal/Occipital L/R) in 1yr olds and 10 (Motor-Sensory L/R; InfFrontal L/R; HF L/R; SupTemporal L/R; Brocas' L/R; IPL L/R; IPL2 L/R; Werniches' L/R; Occipital/InfTemporal L/R; MedInfTemporal L/R) in 2yr olds (Fig.1, red edges). In Fig.2, all connection values from the group mean correlation matrix are plotted against their corresponding anatomical distances (Euclidian distance between region centers). A general pattern can be discerned; the connection strengths (correlation coefficients) follow an inverse distance square law (red solid line) with the exception of the connections between homologous regions between two hemispheres (red points) which are generally located beyond the 3*σ (standard deviation) range (red dashed line). Small world property as calculated by $(C_p/C_p^{Random})/(L_p/L_p^{Random})$ are 0, 1.10 and 2.20 for neonates, 1yr and 2yr olds, respectively. Neonates has zero value as C_p=0 for the thresholded graph. Betweenness centrality values indicate that parietal regions (PostParietal, Motor-Sensory, PCC) in neonates, parietal (PCC), frontal (MPFC) and Occipital (MedOccipital) regions in 1yr olds, frontal (ACC, SupFrontal) and parietal regions (PCC) in 2yr olds perform as center nodes essential for efficient connection.

Discussion Three findings in this study provide information regarding the emergence and development of the brain network from 2wks olds to 2yr olds. First, significant connections between inter-hemisphere homologous regions start to appear in neonates but the number of connections increases dramatically from 2 to 9 and 11 in 1yr and 2yr olds, which may partially be explained by the fast myelination process during this period [5]. Second, the small world property measures increase almost linearly from 0 in neonates to and 1.10 and 2.20 in 1yr and 2yr olds suggesting a fast optimization of information processing for the whole brain network. Finally, betweenness centrality plots suggest that the posterior cingulate cortex (PCC) may serve as a functional "hub" in neonates while the frontal regions such as medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC) gradually emerge as new hubs as age increases. To the best of our knowledge, this is the first reported results on the temporal development of the whole brain network in the critical time period of early brain development.

References [1] Bassett and Bullmore, *Neuroscientist*, 12, 512-523, 2006. [2] Salvador, et al, *Cerebral Cortex*, 15, 1332-1342, 2005. [3] Stam, *Neurosci Lett*, 355,25-28, 2004. [4] Calhoun, et al, *HBM*, 14, 140-151, 2001. [5] Gao et al., AJNR, in press.