Evolving Modular Structures during Early Functional Brain Development

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Introduction

The integrated action between functionally connected yet spatially distributed regions to form different "modules" is central to normal brain function. Numerous studies have been performed to detect possible brain modules supporting specific functions including sensory processing and the higher level cognition in adults [1]. However, the formation of modular structures is likely to be substantially influenced by both structural maturation and learning, particularly during the early stage of brain development. In this study, healthy pediatric subjects 2 wks to 2 yrs of age were recruited and modularity analysis was performed to discern whole brain functional networks so as to delineate the emerging and developing trajectory of brain modular structures in a critical time period of early brain development.

Methods

123 normal subjects, including 42 neonates (20M, 21 ± 11 days (SD)), 40 1yr olds (21M, 13 ± 1 mon), and 41 2yr olds (24M, 24 ± 1 mon) were included in this study. In addition, 16 normal adult subjects (11M, 25~35yrs) were also recruited for comparisons with the pediatric subjects. All pediatric subjects were at sleep without sedation during the imaging session. Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board.

For the resting functional connectivity MRI (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.

Preprocessing of rfcMRI data included time shifts, rigid body correction for head movement, spatial smoothing (6-mm FWHM Gaussian kernel) and low pass filtering (<0.08Hz). A longitudinal data set with images acquired from a subject (not included in the current study) at 2wk, 1yr- and 2yrs-old is available at our institution. This longitudinal data set was normalized to the MNI template to acquire 90 ROIs covering both cortical and subcortical regions of the whole brain. Subsequently, images of the study cohorts were normalized to this longitudinal data set at the corresponding time point so as to extract the BOLD signal of each ROI from each subject. The mean time series of each ROI was then used to construct a 90*90 correlation matrix describing the whole brain connectivity pattern. The individual matrix was Fisher-Z transformed and averaged to obtain a group-mean matrix for each age group providing basis for the following modularity analysis. The spectral optimization method proposed by Newman [2] was applied to detect optimal modular structures. Based on the notion that the brain is sparsely connected and results from one of our unpublished studies suggesting that the connection percentage (cost) of the three pediatric age groups ranges from 16% to 20%, a intermediate cost of 18% was used as a threshold for the correlation matrix for all 4 age groups so that the possible modularity differences would only arise from different connectivity structures, i.e., different arrangement of connections. The subsequent discussion will primarily focus on the results obtained using this threshold. Nevertheless, we also varied the threshold from 10% to 20% to explore possible threshold bias.

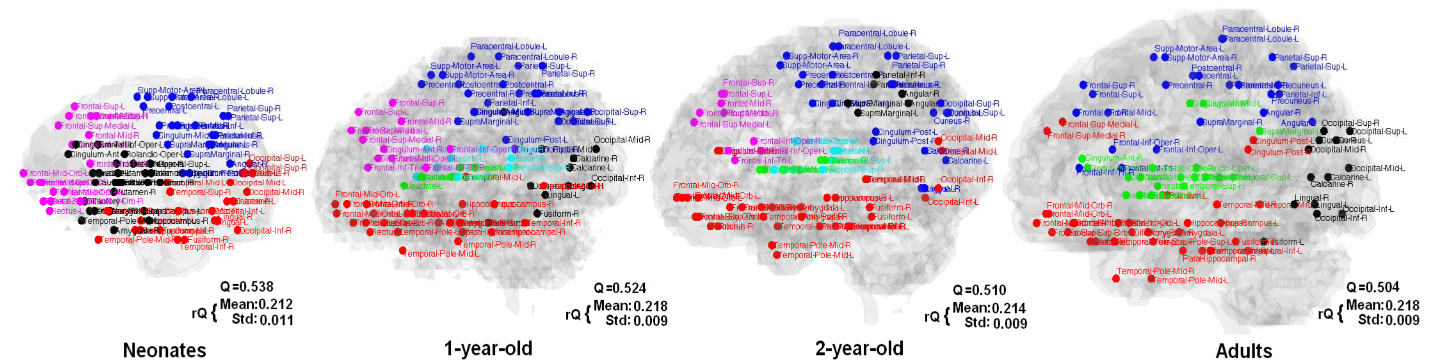

Figure.1 Modularity structures across 4 age groups. Q/rQ: modularity from observed/randomized brain networks.

Results

Fig.1 shows the modular structures of all 4 age groups (different colors correspond to different modules) together with the modularity scores (Q). Notice the Q is consistently above 0.5 for all four groups and is significantly higher than modularity score (rQ) derived from random networks (edges rewired but degree preserved; rQs tightly clustered around 0.2 with a standard deviation ~0.01). In addition, Fig.2 presents the spring embedding plots of all four whole brain networks with nodes colored the same way as in Fig.1, where the highly clustered pattern of same-colored-nodes nicely cross-validates the results of modular division presented in Fig.1.

As shown in Fig.1 and 2, there are a total of 4, 6, 6, and 4 modules for neonates, 1yr olds, 2yr olds and adults, respectively, demonstrating interesting functional segregation and integration patterns. The four modules in neonates cover mainly the frontal, parietal, temporal/subcortical and temporal/occipital, respectively (Fig.2). Dramatic topological changes occur at 1yr-old. Comparing with neonates, the dorsal part of the frontal module, the occipital regions, the subcortical regions, and the insula/heschl regions are segregated from their original corresponding modules and form separate modules at 1yr-old, demonstrating functional segregation/specialization during the first year of life. On the other hand, the combination of orbital frontal regions and temporal regions suggests important ongoing functional integration. The most noticeable changes occurring during the second year of life is the segregation of the occipital regions into a more dorsal and ventral areas, which subsequently merge with the parietal and orbital frontal/temporal regions, respectively. In addition, six regions including bilateral angular, inferior parietal and superior marginal also segregate and form their own modules. Finally, the adult's modular structure becomes noticeably more distributed and functionally relevant, especially the emergence of a compound cluster encompassing the superior medial frontal, posterior cingulum, hippocampus and mid-temporal regions which is highly consistent with the anatomical organization of the "default-mode" network reported in numerous recent studies [3].

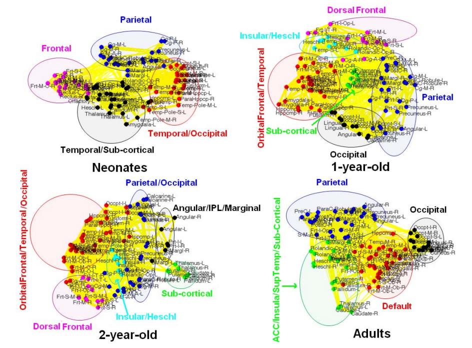

Figure.2 Spring-embedding plots of all brain networks.

Discussion

Interesting functional segregation/integration patterns during the first 2 years of early brain development are revealed in this study. Through a controlled modularity analysis, different modular structures are detected and their evolution pattern is elucidated. In summary, the first year of life witnesses drastic segregation although significant integration also occurs. In contrast, the second year demonstrates equally important segregation and integration process, which is especially evident concerning the visual functional development. Finally, the adult's modular structure appears to be more spatially distributed as well as functionally relevant.

References

[1] He et al., *PLoS ONE,* 4(4) e5226, 2009. [2] Newman, *PNAS*, 103 (23), 8577-82, 2006. [3] Raichle, *PNAS*, 98 (2), 676-82, 2001.