Emergence of the Brain's Default Network: Evidence From Two-week-old to Four-year-old Healthy Pediatric Subjects

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Introduction

Decades of functional brain imaging research unveils various mechanisms of brain function while a recently introduced default network [1] has shown great promise on further improving our understanding of the brain's cognitive functions. Although different imaging modalities/approaches have been employed to discern the default network, the main anatomical architecture has been remarkably consistent, which mainly contains ventral/dorsal medial prefrontal cortex (v/d MPFC), posterior cingulated cortex (PCC), inferior parietal lobule (IPL), lateral temporal cortex (LTC) and hippocampus regions (HF) [2]. This great convergence suggests that the default network is a distinct brain system much like the motor or visual system which has its own function and whose dysfunction may have great impact on various brain diseases.

While most of the studies on default network have focused on adult subjects, the delineation of its developmental process may shed light on its functional evolution with age. Recently, Fair et al [3] investigated default network in school-age children (i.e. 7-9 years old) and found that the network is only sparsely connected in children when compared with adults, suggesting a potential age-dependence of the default network. However, when the default network starts to emerge remains unknown. To this end, healthy pediatric subjects from 2wks to 4yrs of age were recruited in this study and resting functional MRI (rfcMRI) were employed to acquire resting MRI images so as to gain insights into the temporal evolution of the default network in the developing brain.

Methods

Subjects: 81 healthy subjects including 20 neonates (9 male, mean age 24 $\pm$ 12 days (SD)); 24 1-year-olds (16 male, mean age 13 $\pm$ 1 months); 27 2-year-olds (17 male, mean age 25 $\pm$ 1 months) and 10 4-year-olds (5 male, mean age 48 $\pm$ 1 months) were included in this study. With the exception of the 4-year-old group, all subjects slept during the imaging examination. None of the subjects was sedated for MR imaging. Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board.

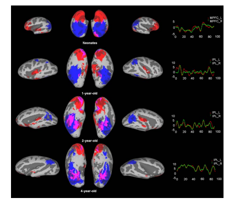

Fig.1. The brain's default networks.

MR acquisition: For the rfcMRI studies, a T2*-weighted EPI sequence was used and the imaging parameters were as follows: TR = 2sec, TE = 32 ms; 33 slices; and voxel size = 4x4x4 mm3. This sequence was repeated 150 times to provide time series images. A 3D MP-RAGE sequence with imaging parameters TR = 1820ms; TE = 4.38 ms; inversion time = 1100ms; 144 slices; and voxel size = 1x1x1mm3 was used to provide anatomical images and co-register among subjects.

Group Independent Component Analysis (ICA): Before group ICA, the BOLD time series images went through standard preprocessing including time shifts, rigid body correction for head movement within runs, and spatial smoothing (6-mm FWHM Gaussian kernel), followed by a data reduction step using PCA. The infomax algorithm was applied for ICA analysis (GIFT software proposed by Calhoun et al [4]) to obtain a set of aggregate independent components for each age group. The number of components for each age group was 28, 31, 27 and 29 for neonate, 1yr, 2yr and 4yr groups, respectively, determined using the minimum description length criteria.

Correlation/statistical Analysis: Based on the Z-transformed and thresholded (Z>1) group ICA spatial maps, a neuroradiologist (JKS) and a cognitive neuroscientist (KG) carefully went through all independent components. Anatomical locations (ROIs) specifically associated with the default network were identified. The mean time course of each ROI was extracted from each individual subject separately to construct a correlation matrix. Subsequently, Fisher's Z-transform was applied on each connection value for each subject and averaged across subjects to compute the mean correlation matrix of each group. One-sample t-test (two-tailed) on the Fisher's Z-transformed group mean value of each connection was performed. The false discovery rate approach was applied to correct for multiple comparisons at $\alpha<0.05$. A spring embedding algorithm was applied to calculate the position of each node (ROI) based on the group mean correlation matrices for visualization of the connection pattern.

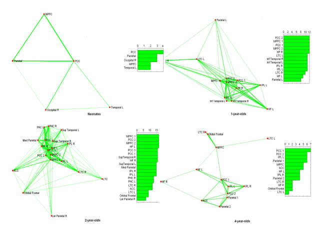

Fig.2. Connectivity graphs of all 4 groups

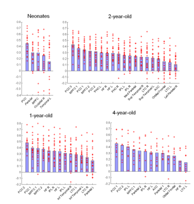

Fig.3. Mean connection strength of each node for all 4 groups.

Results

Two ICA components (red and blue in Fig.1 while pink indicating overlapped regions between the two components) comprising regions consistent with the default network were identified for all four age groups. In neonates, the regions encompass the entire medial prefrontal cortex (MPFC) and medial parietal, and occipital area (PCC). In contrast, the lateral and inferior temporal lobe (LTC), the hippocampus formation, and the inferior parietal lobe start to emerge in 1yr olds. In 2yr olds, the appearance of the parahippocampal cortex (PHC) makes the entire network more complete. Finally, in 4yr olds, with the exception of the absence of PHC area and a relatively smaller LTC, the default network appears almost identical to those reported in adults

The connection patterns of the network are shown in Fig. 2. The connection percentage is 70% (7 out of 10) in neonates, increases remarkably to 91.03% (71 out of 78) in 1yr group, decreases to 78.4% (134 out of 171) in 2yr group and continues to reduce to 34.62% (27 out of 78) in 4yr group. Closely examining the graphs of the four age groups, both the MPFC and PCC regions always locate close to the center of the corresponding graphs and exhibit the most connections with other regions (degree plot on the right of each graph), which suggest that the MPFC and PCC may serve as the "hub" of the default network. This could be further evident through the mean connection strength between each region and all other regions (Fig.3). With the exception of the neonates where the MPFC ranks as the third and 4 yr olds where the MPFC ranks as the fourth, the MPFC/PCC regions always rank at the top of each age group, suggesting that MPFC and PCC exhibit the strongest connections with the remain regions. Finally, regions that are not typically observed within the default network in adult studies show weak connection strength with other regions.

Discussion/conclusion

With rfcMRI, we report the temporal evaluation of the default network in healthy normal pediatric subjects between 2wks and 4-yrs of age. A primitive and incomplete default network is observed in 2wk olds, followed by a marked increase in the number of brain regions exhibiting functional connectivity, and the percent of functional connection at 1yr olds, becoming a similar network as that reported in adults at 2yr olds, and finally, reversing the trend of growth at 4yr-old. In addition, although the default network changes substantially among different age groups, both PCC and MPFC are consistently observed in all groups and are among the most and strongest connections of the default network, suggesting that both PCC and MPFC may serve as the two hubs of the default network. To the best of our knowledge, these are the first reported results on the temporal development of the default network in a critical time period of brain development.

References

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