

Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects

Wei Gao^a, Hongtu Zhu^{b,c}, Kelly S. Giovanello^{c,d}, J. Keith Smith^e, Dinggang Shen^{c,e}, John H. Gilmore^f, and Weili Lin^{c,e,1}

Departments of ^aBiomedical Engineering, ^bBiostatistics, ^cPsychology, ^eRadiology, and ^fPsychiatry, and ^dBiomedical Research Imaging Center, University of North Carolina, Chapel Hill, NC 27599

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Several lines of evidence have implicated the existence of the brain's default network during passive or undirected mental states. Nevertheless, results on the emergence of the default network in very young pediatric subjects are lacking. Using resting functional magnetic resonance imaging in healthy pediatric subjects between 2 weeks and 2 years of age, we describe the temporal evolution of the default network in a critical, previously unstudied, period of early human brain development. Our results demonstrate that a primitive and incomplete default network is present in 2-week-olds, followed by a marked increase in the number of brain regions exhibiting connectivity, and the percent of connection at 1 year of age. By 2 years of age, the default network becomes similar to that observed in adults, including medial prefrontal cortex (MPFC), posterior cingulate cortex/retrosplenial (PCC/Rsp), inferior parietal lobule, lateral temporal cortex, and hippocampus regions. While the anatomical representations of the default network highly depend on age, the PCC/Rsp is consistently observed at in both age groups and is central to the most and strongest connections of the default network, suggesting that PCC/Rsp may serve as the main "hub" of the default network as this region does in adults. In addition, although not as remarkable as the PCC/Rsp, the MPFC also emerges as a potential secondary hub starting from 1 year of age. These findings reveal the temporal development of the default network in the critical period of early brain development and offer new insights into the emergence of brain default network.

brain development | resting functional magnetic resonance imaging

A growing body of evidence suggests that a distinct brain network—referred to as the default network—is engaged during passive or undirected mental states (1). Broad awareness of the default network emerged when Shulman et al. (2) conducted a meta-analysis, pooling resting PET images from 132 normal subjects who underwent a variety of goal-directed cognitive tasks (e.g., word reading). Remarkably, despite the differences in activation paradigms among the subjects, several brain regions consistently exhibited a higher cerebral blood flow (CBF) during undirected (passive) states than during task conditions. It was suggested that the increased brain activity (CBF) during the passive condition reflected ongoing thoughts and monitoring of the external environment. Subsequently, a series of seminal studies were conducted and reported by Gusnard, Raichle and colleagues (1, 3) which focused on the functional significance of such increased brain activity during resting/passive conditions. The term "default mode of brain function" was thus coined by Raichle et al. (1) to describe the baseline state in the human brain. Since then, substantial efforts have been devoted to further determining the anatomical and functional implications of the brain's default network using both PET and MRI techniques (2, 4–6).

Remarkably, despite the utilization of different neuroimaging methods including PET (2, 4) and resting functional magnetic resonance imaging (rfcMRI) (5, 6), a consistent pattern of the main architecture of the default network has been reported across different studies. Specifically, these reports suggest that the default

network consists mainly of the ventral/dorsal medial prefrontal cortex (v/d MPFC), posterior cingulate cortex/retrosplenial (PCC/Rsp), inferior parietal lobule (IPL), lateral temporal cortex (LTC), and hippocampus regions (HF) (7). This convergence in anatomical representations of the brain among different imaging approaches suggests that the default network is likely to be a distinct brain system with its own function and for which dysfunction may have great impact on various brain diseases (8).

While the anatomical representations of the default network are highly consistent in the literature, the specific functions of the default network remain controversial (1, 9–11). In adult studies, the default network is typically reported as an intact network indicating a temporally synchronized functional composition (12). However, evidence also suggests that the default network has specialized subsystems that converge on 2 main "hubs"—PCC/Rsp and MPFC (13). Udden et al. (13) investigated the 2 hubs of the default network and found that the interaction patterns with other networks are significantly different for these 2 hubs, suggesting functional differentiation within the default network. Nevertheless, to date most of the existing literature on the default network focuses largely on adult subjects. As a result, it is difficult to determine how and when it is formed. The delineation of the default network's developmental process not only offers profound scientific implications on its functional evolution during a critical time period when the brain undergoes tremendous development (14) but also potentially provides great insights into the etiology and pathophysiology of neurodevelopmental disorders. Fair et al. (15) investigated default network in school age children (7–9-years-old) and found that the network is only sparsely connected. Fransson et al. scanned preterm infants at a gestational age of 41 weeks and failed to discern the default network (16). Together, one would hypothesize that the default network cannot be completely discerned until children are 7- to 9-years-old. However, subjects in studies by Fransson et al. were born prematurely, and whether the development of this particular network follows a monotonic pattern remains elusive. To this end, our studies aimed to reveal the temporal development of the default network by partially filling the age gap between studies by Fair et al. (15) and Fransson et al. (16), to determine the emergence of the default network, and to discern the presence or absence of the specialized subsystems (hubs) within the default network in a critical time period of brain development.

Results

Using a group independent component analysis (ICA) approach (17) excluding components related to artifacts (Fig. S1), an auto-

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¹To whom correspondence should be addressed. E-mail: weili.lin@med.unc.edu.

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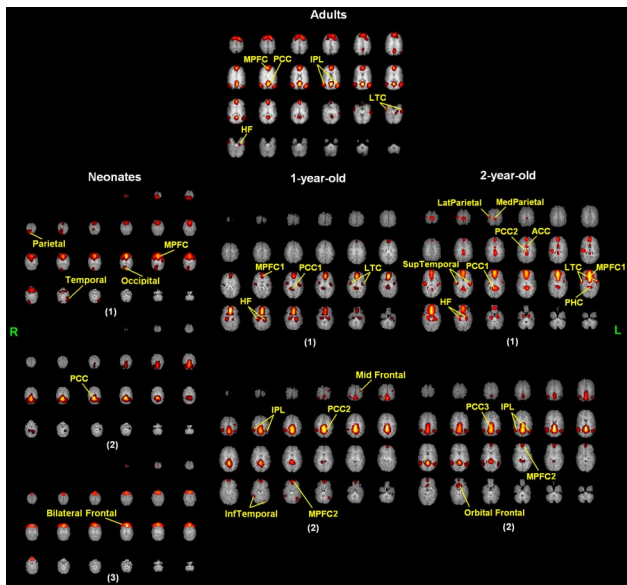


Fig. 1. Spatial ICA identified default network components in each age group are shown. The anatomical locations of each group are labeled in the figure. Abbreviations: MPFC: ventral/dorsal medial prefrontal cortex; PCC: posterior cingulate cortex/retrosplenial; LTC: the lateral temporal lobe; HF: the hippocampus formation; IPL: inferior parietal lobe; PHC: parahippocampal cortex; ACC: anterior cingulate cortex; InfTemporal: inferior temporal cortex; SupTemporal: superior temporal cortex; MedParietal: medial parietal cortex; LatParietal: lateral parietal cortex; MidFrontal: middle frontal cortex.

mated procedure (Fig. S2) (18) was used to select the component(s) comprising brain regions that best matched with the commonly observed brain regions in the default network (7). The anatomical representations of the default networks are shown in Fig. 1; the volume ratios and mean Z scores of these anatomical regions are

offered in Table 1. The corresponding surface rendering is provided in Fig. 2. (The definitions of all abbreviations are listed in Table S1.) It is evident that the anatomical representations of the adult's default network are highly consistent with that reported in the literature (7). In contrast, the temporal and spatial evolution of the default network in pediatric subjects is summarized below.

A rather primitive, incomplete default network consisting of 6 brain regions is observed in neonates. At 1 year of age, a total of 13 regions are observed and 10 of them are consistent with that observed in adults, including v/d MPFC, PCC/Rsp, bilateral LTC, bilateral IPL, and HF (7). However, the remaining 3 regions have not been reported in adult studies, including the parietal and bilateral inferior temporal regions. Similar to that observed in 1-year-olds, the default network of the 2-year-olds consists of 13 regions covering anatomical locations consistent with adults plus 6 additional regions, including the orbital frontal, anterior cingulate cortex (ACC), right and medial parietal, and bilateral superior temporal regions. Despite the observed temporal and spatial evolution of the default network from neonates to 2-year-olds, both the v/d MPFC and PCC/Rsp are consistently observed across the 3 pediatric groups. In addition, the volume ratios (volume in a specific region/total intracranial volume) of the MPFC and PCC/Rsp are the highest in each age group but are inversely proportional with age (Fig. 2 and Table 1); it starts from 12.9%/11.8% (MPFC/PCC/Rsp) in neonates, reduces to 4.3%/5.9% in 1-year-olds, 5.6%/5.6% in 2-year-olds, and 4.02%/1.8% in adults; the latter finding is of interest. Although not specifically focused on the default network, Johnson suggested that the infant brain often employs a larger area of cortex than those used in adults (19), consistent with our findings.

The averaged group correlation matrices were used for graph analysis (20). The spring embedding method (21) was used to depict the connection pattern of each group (Fig. 3). In addition, the width of the connecting lines indicated the connection strengths. A summary of the mean connection strengths for all regions is provided in Fig. 4.

Several main features regarding the temporal evolution of the default networks can be derived from Figs. 3 and 4. First, the

Table 1. Anatomical regions of the default network in neonates, 1-year-olds, 2-year-olds, and adults

	Region	Volume fraction	Mean Z score		Region	Volume fraction	Mean Z score
	Adults				Neonates		
IC 1	MPFC	0.0402	2.32	IC 1	MPFC	0.1287	3.65
	PCC	0.0183	3.21		Occipital R	0.0167	1.50
	HF L	0.0015	1.36		Parietal	0.0248	2.37
	LTC R	0.0016	1.43		Temporal L	0.0066	1.45
	LTC L	0.0021	1.58	IC 2	PCC	0.1183	4.39
	IPL R	0.0067	2.07	IC 3	Bilateral frontal	0.1271	3.57
	IPL L	0.0097	2.38				
	1-year-old				2-year-old		
IC 1	MPFC 1	0.0428	2.87	IC 1	MPFC 1	0.0562	2.58
	HF R	0.0059	1.91		HF R	0.0041	1.56
	HF L	0.0076	1.85		HF L	0.0043	1.39
	LTC R	0.0032	1.52		LTC R	0.0012	1.23
	LTC L	0.0034	1.42		LTC L	0.0023	1.25
	PCC 1	0.0048	1.57		PHC R	0.0007	1.48
IC 2	MPFC 2	0.0063	1.61		PHC L	0.0011	1.24
	Inf temporal R	0.0013	1.46		PCC 1	0.0084	1.68
	Inf temporal L	0.0022	1.38		Sup temporal R	0.0045	1.63
	PCC 2	0.0588	3.03		Sup temporal L	0.0027	1.44
	IPL R	0.0057	1.27		ACC	0.0016	1.48
	IPL L	0.0009	1.08		PCC 2	0.0056	1.59
	Mid front L	0.0013	1.18		Med parietal	0.0037	1.43
					Lat parietal R	0.0012	1.25
				IC 2	PCC 3	0.0550	3.07
					IPL R	0.0105	1.48
					IPL L	0.0096	1.36
					MPFC 2	0.0050	1.49
					Orbital frontal	0.0037	1.40

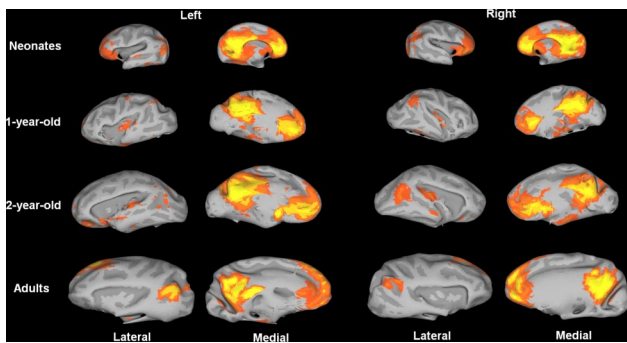


Fig. 2. The brain's default networks in all 4 age groups. Z score maps ($Z > 1$) are mapped on to the template brain surface for each individual group. For the pediatric groups, although multiple components were chosen, they were pooled together to show on the same brain surface (Z scores showed here is taken as the maximum from different components).

connection percentage starts from 66.7% (10 significant connections out of 15 possible ones) in neonates, increases to 91.03% in 1-year-olds, levels off to 78.4% in 2-year-olds and increases to 100% in adults, suggesting a non-linear evolution pattern of the connectivity of the default network. Second, as mentioned previously, the pediatric default networks include regions that are consistent with the adult group as well as additional regions not observed in adults. Interestingly, with the exception of LTC, the former regions are typically located near the center of the graph while the latter regions are located a distance away from the center in all pediatric groups. This finding implies that the regions consistent with those observed in adults are more strongly connected when compared with those not observed in adults. The only exception for the observed weak connection at LTC appears consistent with that reported by Buckner et al. (7). Third, both PCC/Rsp and MPFC are consistently located at the center of each graph with the exception of the neonate group (only PCC/Rsp), implying that these 2 regions are most strongly connected with other regions. This finding is also consistent with the degree of connection plots (Fig. 3*B*)—the ratio of the number of regions connected to a specific region to the total possible connections. Fourth, regarding the mean connection strength—a measure previously suggested to be positively correlated with functional performance (22)—the PCC/Rsp and MPFC reliably exhibit the highest mean connection strengths across all ages while the brain regions located at a distance away from the center regions (Fig. 3) are unexceptionally ranked with low mean connection strengths (Fig. 4). Consistent findings are observed in the validation studies (Figs. S3 and S4) where PCC/Rsp and MPFC exhibit the statistically strongest connection strengths while those distant regions show statistically weaker connection strengths. Finally, a regression analysis reveals that the connection strength between these 2 regions linearly ($P = 0.0059$) increased with age (Fig. 4*B*), although one must be cautious that there is a large age gap between 2-year-olds and adults.

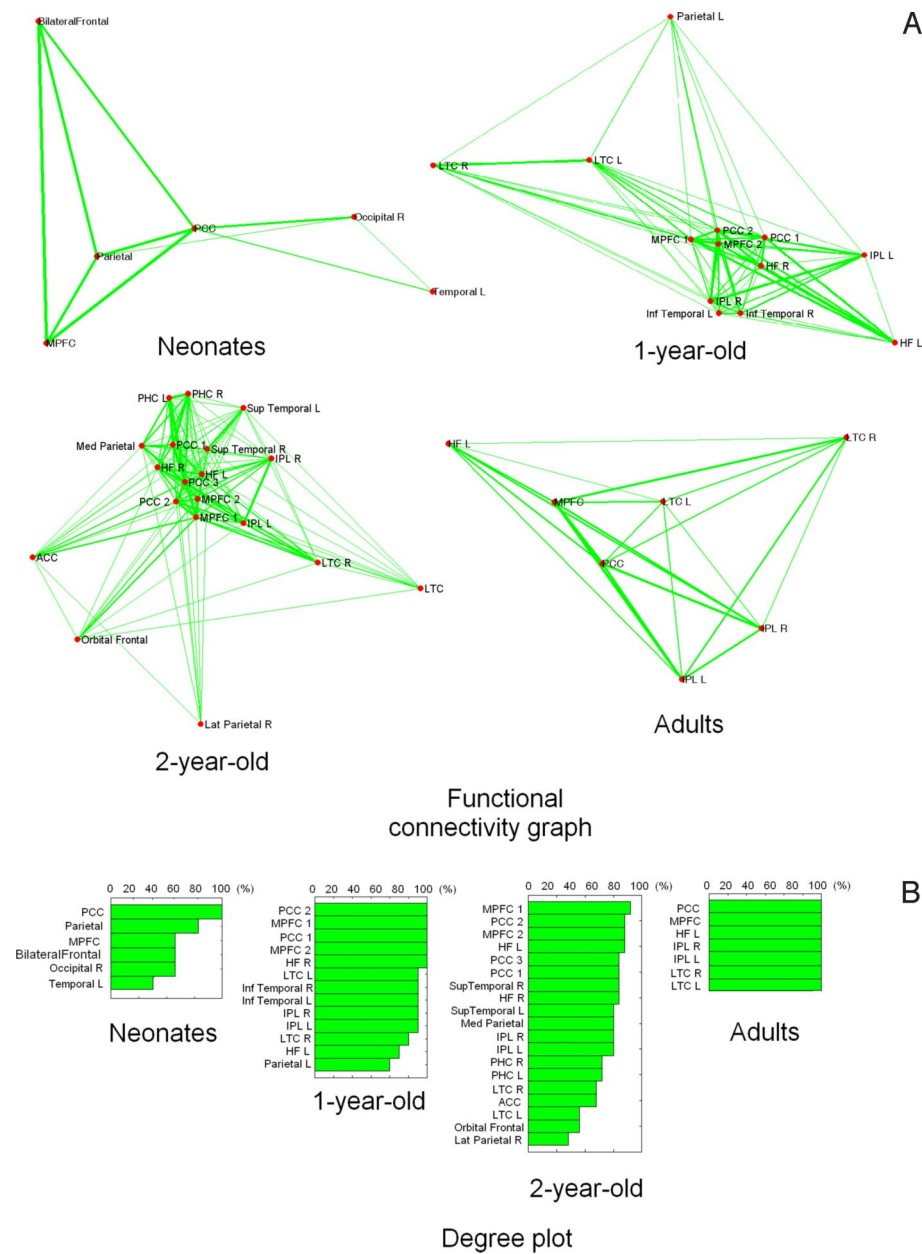
Thus far, our findings consistently indicate that the PCC/Rsp and MPFC may play a critical role in the default network. The notion of the presence of hub regions in the brain has been proposed (23). Therefore, to further determine if the PCC/Rsp and MPFC are the 2 potential hubs in the pediatric default networks, the “betweenness” centrality (BC) (24)—a measure of node importance in graph theory—was calculated for each region based on the individual network within each age group (Fig. 5). The most elevated centrality measure for all age groups is the PCC/Rsp. In addition, although lower than the PCC/Rsp, the MPFC in 1- and 2-year-olds also exhibit elevated centrality measures when compared with the remaining regions. These results suggest that the PCC/Rsp may be the major hub of the default network whereas the MPFC subsequently emerges, potentially, as the secondary hub starting at 1 year of age.

Discussion

The temporal evolution of the default network during a critical time period when the brain undergoes highly dynamic axonal pruning and establishes axonal connections to form different networks was investigated in this study. With the rfcMRI approach (25) and full-term healthy normal pediatric subjects ranging from 2 weeks to 2 years of age, group ICA revealed the anatomical representations of the default network. Specifically, a primitive and incomplete default network was observed in neonates (Table 1). This observation is consistent with that reported by Fransson et al. (16) where they also failed to detect a direct equivalent of a default-mode network in infant brain. The default network at 1 year old became more complex and was intensively connected among different brain regions (91.03%), indicating the formation of a well synchronized default network. In contrast, the changes of the default network from 1- to 2-year-olds were more subtle, particularly considering those regions that are commonly observed in the adult's default network. All of the regions presented in 1-year-olds persist in 2-year-olds with the addition of parahippocampal cortex (PHC), making the architecture of the whole network more complete (1, 7).

One of the major findings of our study is the notion that both PCC/Rsp and MPFC may play a critical role in the default network. Both PCC/Rsp and MPFC are consistently observed (Figs. 1 and 2), exhibit the largest volume ratios (Table 1), are located at the center of each network (Fig. 3), and have the largest mean connection strengths in all ages (Fig. 4). Indeed, the centrality measures revealed that the PCC/Rsp may serve as the main hub while the MPFC is the secondary hub starting to emerge at 1 year of age (Fig. 5). This finding is intriguing and appears consistent with that reported in the adult studies; it has been suggested that the MPFC and PCC/Rsp are the 2 hubs involved in different aspects of cognitive function in adults (13). Specifically, MPFC has been implicated to be more involved in self-referential activity, mentalizing process, and theory of mind (3, 26–28) whereas the PCC/Rsp is more associated with episodic memory retrieval (29). However, translating these functions of MPFC and PCC/Rsp in adults to pediatric subjects is elusive. In addition, since independent behavioral measures were not available in our study, the observed temporal and spatial development of the default network cannot directly translate to functional development. Nevertheless, some similarities are observed between our findings and the reported functional development in the literature. Amsterdam (30) found that infants from 6 through 12 months of age demonstrate prolonged and repeated reaction to their mirror images as a sociable playmate. Wariness, withdrawal, self-admiring, and embarrassed behaviors start at 14 months and have been observed in 75% of the children after 20 months of age. From 20 to 24 months of age, the majority of subjects demonstrate recognition of their mirror images. These temporal behaviors demonstrate an evolving trajectory of self-consciousness before the age of 2, which is essential for self-projection/self-referential activity. Studies on toddlers also revealed that 18- to 24-month-olds are able to use speaker's gaze direction (31) and affective expression (32) as cues leading to speaker's communicative purposes. Akhtar and Tomasello (33) further proposed that children are able to infer the meaning of words through an understanding of people's minds (34). These primitive mental functions may actually act as a promising source where more sophisticated functions such as mentalizing about others and theory of mind can be originated and developed. Together, these findings suggest that the functions associated with MPFC regions undergo gradual development during the first years of life, which is in line with our findings: MPFC emerges as one of the hubs of the default network from 1-year-olds.

In contrast to MPFC, the PCC/Rsp is associated with episodic memory retrieval in adult studies. The appearance of the right occipital region and the bilateral posterior parietal/occipital area encompassing the PCC (termed simply as PCC here) in neonates



A

B

Fig. 3. (A) Functional connectivity graphs for all 4 age groups. The most strongly connected regions are clustered near each other while weakly correlated regions are placed further away from each other. The width of the line between 2 nodes is proportional to the corresponding connection strength. Only significant correlations ($P < 0.05$) were plotted. (B) Bar plots of the degree of connection for each node in a descending order (the ratio of the number of regions connected to a specific region to the total possible connections).

may suggest the formation of some forms of memory (i.e., implicit memory). Consistent with these findings, Davidson (35) suggested that implicit memory is robustly presented in neonates and toddlers. Additional studies further demonstrated that the sensorimotor experiences of the fetus (36) and the voice of mother (37) can be memorized. In contrast, the emergence of bilateral HF, bilateral IPL and PCC/Rsp starting from 1 year to 2-years of age forms a hippocampal-parietal memory network much like that defined by Vincent et al. (38) in adults. In line with our findings, Fivush and Hamond (39) showed that 2-year-olds can already retrieve much detail about a trip to the zoo. Together, our findings of the PCC/Rsp appear to be consistent with that reported in the literature and demonstrate a memory-related architecture in 1- and 2-year-olds.

Despite the possible default-network related functions discussed above and the observed adult-like architecture of the default network in 1- and 2-year-old groups, one must be cautious in further interpreting our results since it is highly unlikely that such young pediatric subjects may have the brain circuitry capable of adult-like default network functions. It has been suggested that the “theory of

mind” emerges after the age of 3 and episodic memory is not formed until the age of 4 (28, 40). Therefore, although we observed a complete architecture of the default network in 1-year-olds, its related function remains largely unknown. These apparent discrepancies led us to hypothesize that the formation of the default network may predate its functional specialization. Although not specifically focusing on the default network, Johnson (19) also claimed that the cognitive functions of infants often employ both a larger area of cortex and also a wider range of interactions of brain regions that include and extend beyond those used in adults. While to directly prove or disprove that the default network’s formation may predate its functional specialization is beyond the scope of our study, our results may offer preliminary evidence to support this hypothesis. First, the decreasing volume ratios of PCC/Rsp and MPFC with age indicate the ongoing localization of these major regions. Second, in addition to those brain regions that are consistently observed in adults, extra brain regions in the 1- and 2-year-olds’ default networks are also observed. Finally, the connection percentage increases from 67% in neonates to more than 90% in

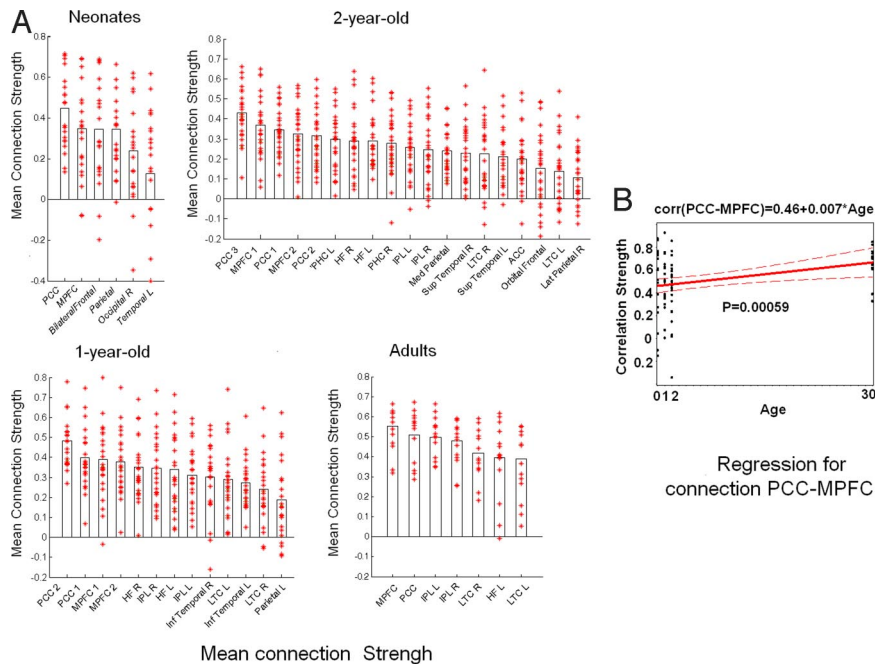


Fig. 4. (A) Mean connection strength of each node for all age groups. The bars indicate the mean connection strength averaged over the corresponding group and red asterisks represent the values of individual subjects. (B) Regression results for the connection between MPFC and PCC.

1-year-olds and then decreases to 78% in 2-year-olds. The latter 2 findings suggest a potential specialization process of removing redundant connections. Fair et al. (15) recently investigated the development of default network on school age children based on a region of interest (ROI) seeding approach. They found an incomplete default network in children when compared with adults. Considering our findings of the disappearance of extra regions and reduction of percent connections from 1- to 2-year-olds, it is plausible that this reduction trend continues until the age span in their study. Nevertheless, one should note that this trend of reduction at some point will be reversed to be consistent with the adults' results (7), suggesting a potential biphasic instead of mono-

tonic behavior of the development of the default network. Systematic studies covering the whole age span from neonates to adults are necessary to further investigate the temporal evolution of the default network.

The ROI and ICA approaches are commonly used to discern brain functional connectivity (15, 41). The ROI approach requires a priori information to place the ROIs, typically employing activated regions in task related studies. It allows direct comparisons between groups if the ROIs are identical among groups. It also offers a higher sensitivity if an ROI instead of a seed voxel was chosen for temporal correlation analysis. However, this approach may be biased and unable to identify new connections. Therefore, the ICA approach was used in our study. However, one of the difficulties associated with ICA is how to objectively determine which component(s) links to the default network. To partially circumvent this difficulty, an automated template matching approach (18) was used here to identify components comprising the default network. Although not completely eliminating the subjective nature of selecting components as the default network, this approach allows more consistently determining ICA components and offers the ability to explore temporal and spatial evolution of the default networks in the developing brain. With the template matching procedure (18), we have identified 3, 2, and 2 “best fitted” components for neonates, 1-year-olds and 2-year-olds, respectively (Fig. S2). Since the mean inner-component and inter-network connections reveal no significant difference ($P > 0.05$) (Fig. S5), it partially justifies our approach of combining the identified components for data analysis in each age group.

Finally, 2 additional technical issues warrant further discussion. First, since all of the subjects were sleeping during imaging acquisition, it is plausible that different depths of sleep among subjects may result in experimental variability. Nevertheless, it has been reported that resting functional connectivity appears to be independent of whether or not the subjects were at sleep, awake, or even under anesthesia (42). Therefore, we do not foresee that different depths of sleep would affect the outcomes of our studies. Second, the rather low spatial resolution has limited our ability to discern small cortical structures for the default network.

Conclusions

With rfcMRI, we report the temporal and spatial evaluation of the default network in healthy normal pediatric subjects between 2

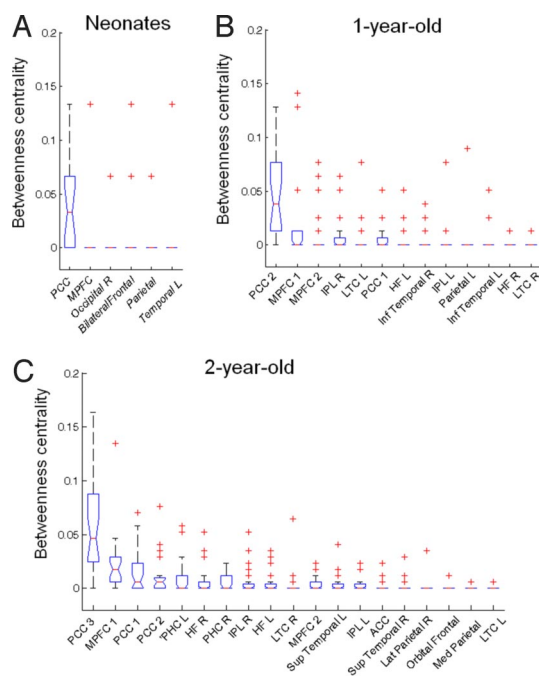


Fig. 5. Betweenness centrality measures for individual ROIs of the 3 pediatric groups, (A) neonates; (B) 1-year-old; and (C) 2-year-old.

weeks and 2 years of age. A primitive and incomplete default network is observed in 2 week olds, followed by a marked increase in the number of brain regions exhibiting functional connectivity and the percent of functional connection in 1 year olds, and finally a network similar to that reported in adults develops in 2 year olds. In addition, although the default network changes substantially among different age groups, PCC/Rsp is consistently observed in all age groups, among the most common and strongest connections and the highest centrality measure of the pediatric default networks, suggesting that PCC/Rsp is the main hub of the default network. Furthermore, although not as remarkable as the PCC/Rsp, the MPFC emerges as a potential secondary hub of the pediatric default networks starting from 1 year of age. 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.

Methods

Subjects. Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board. None of the subjects was sedated for MRI. Before the subjects were imaged, they were fed, swaddled, and fitted with ear protection. All subjects slept during the imaging examination. We retrospectively identified 71 normal subjects including 20 neonates [9 males, 24 ± 12 days (SD)]; 24 1-year-olds (16 males, 13 ± 1 month), and 27 2-year-olds (17 males, 25 ± 1 month) who met the inclusion and exclusion criteria (*SI Methods*). In addition, 15 (11 males, 30 ± 1.7 years) healthy adult subjects were recruited for comparisons with pediatric subjects. A board-certified neuroradiologist (J.K.S.) reviewed all images to verify that there were no apparent abnormalities in the acquired magnetic resonance (MR) images.

MR Acquisition. A 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence was used to provide anatomical images to coregister among subjects. For the rfMRI studies, a T2*-weighted echo planar imaging (EPI) sequence was

used to acquire images. This sequence was repeated 150 times so as to provide time series images.

Postprocessing. More detailed descriptions of the procedures used for image analysis are provided in *SI Methods*. In short, after removing voxels outside of the brain, time shift, and motion correction, rfMRI data were normalized to the template space using the transformation field acquired from T1 HAMMER non-linear registration (43), allowing group analysis.

Principal component analysis (PCA) was used for data dimension reduction followed by ICA to obtain a set of aggregate independent components for each age group. The number of components was determined using the minimum description length criteria (44). This group ICA was carried out using GIFT software (17).

Group Default Network Definition. For each of the aggregate components, the spatial maps were transformed to Z-score and a threshold of $Z > 1$ was chosen to define voxels exhibiting resting functional connectivity. An automated template matching approach as described in Greicius et al. (18) was applied to select the default-network related components for all 4 age groups (details in *SI Methods*).

Correlation/Statistical Analysis. Although PCA/ICA was done with all subjects in each age group, the mean time course of each ROI was separately extracted from each subject to construct a correlation matrix. Before computing correlations, the mean time course was low pass filtered at 0.08 Hz. To combine correlation coefficients across subjects in each age group, Fisher's Z-transform was applied for each subject and averaged across subjects so as to compute the mean correlation matrix for each group (transformed back to correlation values for analysis). One-sample t test on the Fisher's Z-transformed group mean value for each connection was performed to determine whether it was significantly different from zero. The false discovery rate (FDR) approach (20) was applied to correct for multiple comparisons ($\alpha < 0.05$). The mean connection strength (average of the connection values of each region with all other regions) was also calculated using Fisher's Z-transformed value and transformed back to correlation values for presentation.

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