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## Longer Gestation Is Associated with More Efficient Brain Networks in Preadolescent Children

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### Abstract

Neurodevelopmental benefits of increased gestation have not been fully characterized in terms of network organization. Since brain function can be understood as an integrated network of neural information from distributed brain regions, investigation of the effects of gestational length on network properties is a critical goal of human developmental neuroscience. Using diffusion tensor imaging and fiber tractography, we investigated the effects of gestational length on the small-world attributes and rich club organization of 147 preadolescent children, whose gestational length ranged from 29 to 42 weeks. Higher network efficiency was positively associated with longer gestation. The longer gestation was correlated with increased local efficiency in the posterior medial cortex, including the precuneus, cuneus, and superior parietal regions. Rich club organization was also observed indicating the existence of highly interconnected structural hubs formed in preadolescent children. Connectivity *among* rich club members and *from* rich club regions was positively associated with the length of gestation, indicating the higher level of topological benefits of structural connectivity from longer gestation in the predominant regions of brain networks. The findings provide evidence that longer gestation is associated with improved topological organization of the preadolescent brain, characterized by the increased communication capacity of the brain network and enhanced directional strength of brain connectivity with central hub regions.

### Keywords

connectome; diffusion tensor imaging; gestation; preadolescent; rich club

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## Introduction

There is a growing appreciation that longer gestation, even in children born full term, is associated with better developmental outcomes. Recent findings have led to a reconsideration of the implications of variations in gestational length for birth and infant outcomes (Spong, 2013b). This recognition has challenged the conventional 37 weeks cut-off for preterm and term deliveries. Shortened gestation is evidence that the fetus has been exposed to unfavorable intrauterine conditions. The human fetus adjusts its developmental trajectory in response to these conditions and modifies its nervous system to ensure survival (Sandman and Davis, 2012; Sandman et al., 2012). Because of this, abbreviated gestation, often a surrogate measure for prenatal exposure to adversity, has been associated with poor neurodevelopmental outcomes, including thalamocortical abnormalities (Ball et al., 2013; Ball et al., 2012), cerebellar volume deficits (Parker et al., 2008), alteration of hemispheric connections (Peterson et al., 2000), loss of gray/white matter (Groeschel et al., 2013; Nosarti et al., 2008) and abnormal cortical folding (Melbourne et al., 2013). Further, shortened gestation is associated with brain development even among children born full term (Davis et al., 2011). These structural abnormalities are accompanied by functional impairments in infancy and childhood, including working memory deficits (Beauchamp et al., 2008; Bhutta et al., 2002), resting state networks developed at different rates (Doria et al., 2010), reduced cortical plasticity for learning and memory (Pitcher et al., 2012), and absence of default mode network (Smyser et al., 2010). Several recent studies suggest that impairment of the brain's capacity to integrate information between different regions may be a primary consequence of preterm birth (Ment et al., 2009; Scheinost et al., 2012; Woodward et al., 2005). However, effects of the gestational length on the integrative interactions across distributed and specialized brain regions have not been fully evaluated.

The integrative organization of the brain has been conceptualized as a network comprised of anatomically distinct brain regions connected by axonal white matter tracts, sometimes termed the *connectome* (Sporns and Zwi, 2004). To investigate the characteristics of these networks, graph theoretical analysis has been recently applied where the local gray matter regions are represented as *nodes* and their axonal connections as *edges*. This network analysis has indicated that human brain is organized in a highly efficient way for integrated neural communication in a so called *small-world* topology – *i.e.*, an optimal integration of segregated brain regions; for a review, see Bullmore and Sporns (2009). Moreover, recent studies have found that, because a few cortical regions including precuneus, posterior cingulate, and medial prefrontal cortex have more connections to different brain areas, they play a pivotal role as structural *hubs* (or *cores*) within a network (Hagmann et al., 2008; Sporns et al., 2007; van den Heuvel and Sporns, 2013). Moreover, a specific set of these hub regions is to be preferentially connected to each other than expected by chance, *i.e.*, forming a *rich-club* (Sporns, 2012; van den Heuvel and Sporns, 2011). To date, while the small-world attributes (Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2010) and network hub architecture (Hwang et al., 2013) have been characterized in the context of normative brain development, it is unknown whether the length of gestation affects the development of structural brain networks and whether the network organization is preserved in a narrow age range of preadolescent human brain development.

Because recent evidence suggests that longer gestation benefits cognitive performance (Yang et al., 2010) and brain development even among term births (Davis et al., 2011), the present study investigated the effects of gestational length, including preterm delivery, on the structural network organization. Diffusion tensor imaging (DTI) was used to construct structural brain networks on the basis of white matter fiber tractography. These networks were examined with quantitative measures that determine the extent of global and local communication capacity in preadolescents.

## Materials and Methods

### Participants

One hundred and forty seven typically developing right-handed children (male:female = 81:66) underwent magnetic resonance imaging (MRI) scanning (Table 1). All children were born at one of two hospitals in the greater Los Angeles area (UC Irvine Medical Center or Long Beach Memorial Medical Center), and were recruited from ongoing protocols of developmental research. These children were between 6 and 11 years old (mean age =  $8.12 \pm 1.35$  years), and their handedness was defined by the modified version of the Edinburgh Handedness Inventory (Oldfield, 1971). The low risk samples of children were singletons, born between 29 and 42 (mean $\pm$ SD:  $37.37 \pm 3.31$ ) gestational weeks determined based on current ACOG guidelines. Preterm birth for a child was defined as delivery prior to 37 weeks 0 day (World Health Organization, International Classification of Diseases and Related Health Problems, 10th revision), resulting in 48 preterm ( $33.27 \pm 2.26$  weeks) and 99 term ( $39.25 \pm 1.29$  weeks) children. Our low risk sample had a stable neonatal course (median Apgar score = 9, range 7–10) and without known congenital, chromosomal, or genetic anomalies (e.g., trisomy 21), neonatal illness (e.g., respiratory distress, mechanical ventilation over 48 hours or sepsis). At the study entry, all children had normal neurological findings based on review by a neuroradiologist and no evidence of intraventricular hemorrhage (determined by ultrasound), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period. All children were typically developing and in the appropriate grade for their age. Further, no emotional and physical problems were reported in terms of a structural interview using the MacArthur Health and Behavior Questionnaire (HBQ; Armstrong and Goldstein, 2003). After providing a complete description of the study to all participants, written and verbal informed consents were obtained from parents and children. The research protocol was approved by the Institutional Review Board for protection of human subjects.

### MRI acquisition

Whole brain anatomical and diffusion tensor MRI scans were acquired on a 3T MRI system (Philips Achieva, Philips Medical System, Best, The Netherlands). Diffusion tensor images (DTI) were acquired using 8-channel phased array head RF coil and a spin-echo echo-planar imaging (SE-EPI) sequence. For each subject, DTI data consist of 32-directional diffusion weighted images including one non-diffusion weighted image with:  $b$ -value of  $800 \text{ s/mm}^2$ ,  $128 \times 128$  imaging matrix with 60 transverse slices, field-of-view  $224 \times 224 \times 120 \text{ mm}$ ,  $2 \times 2 \times 2 \text{ mm}^3$  voxels, echo time (TE) 55-ms, and repetition time (TR) 11,604-ms. The DTI acquisition time was 8 min 5 sec. In addition, anatomical scans consisting of high-resolution

T1-weighted MRI were also acquired using a T1 turbo field echo (TFE) sequence with the following parameters: 240×240 image matrix with 150 slices on the sagittal plane, 1×1×1 mm<sup>3</sup> voxels, echo time 3.35-ms, repetition time 11-ms and flip angle 18°. The duration of this imaging sequence was 7 min 1 sec. During MR scans, the head motion of children was minimized with restraining foam pads around the head, and the ear protection was also given to all children.

### Image preprocessing

Overall processing steps are illustrated in Fig. 1. Preprocessing of MR scans was performed using the FSL toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>, Version 5.0). First, non-brain regions were excluded for each DTI and T1-MRI using BET (brain extraction tool). In the DTI dataset, the image distortion from eddy-current and subject head motion was corrected by the affine realignment of each diffusion-weighted image to the first non-diffusion weighted image ( $b_0$ ) using FDT (FMRIB's diffusion toolbox). Then, a diffusion tensor was estimated to fit the measured diffusion profile at each voxel (Basser et al., 1994). Based on the fitted tensor, the fractional anisotropy (FA - a measure of the directional coherence for the fiber tracts) and the principal eigenvector as the preferred diffusion direction were computed. Using the diffusion direction estimated within each voxel, the fiber tractography was performed by FACT (Fiber Assignment by Continuous Tracking; Mori et al., 1999) algorithm in the native DTI volume using the Diffusion Toolkit (<http://trackvis.org>). To generate a sufficient number of fiber tracts, twenty seeds that are uniformly distributed within each voxel were used to reconstruct the whole-brain fibers (Cheng et al., 2012). All streamline tracts were computed for voxels with FA>.2 and a smooth turn of <30°. Using FNIRT (FMRIB's nonlinear image registration tool), brain parcellation was performed with the spatial normalization of individual T1-weighted anatomical images to AAL (automated anatomical labeling) atlas located in the MNI (Montreal Neurological Institute) space (Tzourio-Mazoyer et al., 2002). Ninety cortical and subcortical regions, excluding cerebellum, were transformed to each subject's diffusion space using affine registration of FLIRT (FMRIB's linear image registration tool).

### Construction of structural network

A brain network is defined by a set of nodes and edges (Bullmore and Sporns, 2009). Using 90 cortical and subcortical regions as network nodes for the whole brain, edges were defined by interregional structural connections generated from the fiber tractography. We assumed the presence of an edge connecting two brain regions if there were at least three fiber tracts connecting them (Lo et al., 2010), which minimized the effect of false-positive connections (Mori, 2006). Next, when an edge existed between *two* brain regions, the connection strength ( $w_{ij}$ ) was measured as the integrity of the interregional white matter connections, estimated by averaged FA values of interconnecting fiber tracts (van den Heuvel and Sporns, 2011; Wen et al., 2011). Since the tracking algorithm cannot discriminate between efferent and afferent connections (Mori, 2006), it was assumed that the computed strength is undirected. This resulted in a 90×90 weighted symmetric connectivity matrix, where the maximum number of all possible connections was 4,005 from  $(n^2-n)/2$  with  $n=90$ .

## Network analysis

The topological characteristics of structural brain networks were investigated using graph theory (Brain Connectivity Toolbox, <https://sites.google.com/site/bctnet>; Rubinov and Sporns, 2010). Since real-world networks, including the human brain, are known to have *small-world* properties (*i.e.* the network is both locally segregated and globally integrated compared to the random and regular networks), we first examined whether preadolescents show the conserved network organization as in adults with respect to the network segregation (clustering coefficient and modularity), integration (path length and efficiency), and their optimal balance (small-worldness) – see Sporns (2011). Then, we tested whether network characteristics of preadolescent children was associated with the gestational length.

**Clustering coefficients**—Densely coupled regions within a structural network are often likely to share the information processing resulting in the functionally coherent unit. The extent to which the network is organized into the densely segregated nodes can be defined by the clustering coefficient (Watts and Strogatz, 1998). The clustering coefficient at the  $i$ -th node ( $C_i$ ) represents the likelihood that the neighbors of a node are interconnected to each other as  $C_i = (k_i(k_i - 1))^{-1} \sum_{j,h \in N} (w_{ij}w_{ih}w_{jh})^{1/3}$ , where  $k_i$  is the degree representing the number of links connected to the  $i$ -th node (Onnela et al., 2005). Thus, the clustering coefficient of a given network ( $C$ ) can be defined by the average of clustering coefficients for *all* the nodes as  $C = \sum_{i \in N} C_i / n$ , where  $n$  is the number of nodes in the network. Given a real system, since the network measures from graph theory should be independent of the number of nodes and edges for the network (Sporns, 2011), some measures are typically compared with the value from a constrained null distribution that typically preserves the local node structure but randomized global topology. In this study, we generated 1,000 comparable random networks retaining the connection weights as well as the number of nodes, edges, and degree sequences of individual networks (Maslov and Sneppen, 2002). Then, the computed clustering coefficient  $C$  was normalized by the average of clustering coefficients ( $C_r$ ) from the population of 1,000 randomized graphs (*i.e.*  $\gamma = C/C_r$ ). The clustering coefficient provides information about the prevalence of clustered connectivity around a given node (Rubinov and Sporns, 2010) meaning a degree to which nodes tend to cluster around individual nodes.

**Characteristic path length**—It is assumed that locally segregated subsystems should communicate with each other in the most optimally integrated way, and a shorter path length between brain regions can represent stronger potential for structural integration (Rubinov and Sporns, 2010). In a given network, the characteristic path length ( $L$ ) was defined by the average of the shortest path length between a given node and the remaining nodes as  $L = \sum_{i \in N} \sum_{j \neq i} d_{ij} / (n(n - 1))$ , where  $d_{ij}$  is the weighted shortest path length between nodes  $i$  and  $j$ . As is the case for the clustering coefficient, the characteristic path length ( $L$ ) also depends on the size and density of the connectivity matrix, and it was normalized by the average of characteristic path length ( $L_r$ ) from the population of 1,000 randomized graphs (*i.e.*  $\lambda = L/L_r$ ).

**Small-worldness**—A small-world network has been defined by the network having short node-to-node distance with highly clustered nodes (Watts and Strogatz, 1998). The network

small-worldness in this study was defined by the ratio of clustering coefficient and characteristic path length – i.e.,  $\sigma = (C/C_r)/(L/L_r) = \gamma/\lambda$  (Humphries and Gurney, 2008). While the random network tends to be less clustered around a node with globally short paths, a non-random network such as the human brain is likely to be highly clustered ( $C > C_r$ ) with short paths ( $L \approx L_r$ ). It should be noted that the small-worldness of non-random and non-regular networks would be larger than one ( $\sigma > 1$ ).

**Global and local efficiency**—Since the path length highly depends on the possible disconnected nodes of a network (Bullmore and Bassett, 2011; Rubinov and Sporns, 2010), an alternative measure for network integration has been defined by the network efficiency representing the capacity to exchange information (Latora and Marchiori, 2001). The global efficiency ( $E_g$ ) of a whole network was defined by the average shortest path length,

$$E_g = (n(n-1))^{-1} \sum_{i \in N} \sum_{j \neq i} (d_{ij}^w)^{-1}, \text{ and local efficiency } (E_l) \text{ by}$$

$$E_l = \frac{1}{2} \sum_{i \in N} (k_i(k_i-1))^{-1} \sum_{j, h \in N, j \neq i} (w_{ij} w_{ih} (1/d_{jh}^w(N_i)))^{1/3}$$

meaning the averaged local efficiency for each node, where  $d_{jh}^w(N_i)$  is the shortest path length between node  $j$  and  $h$  containing neighbors of node  $i$ . In contrast to global efficiency, local efficiency represents the capacity to transfer information only within the neighbors of a given node, and reflects the degree of fault tolerance of the brain region within the network (Lo et al., 2010).

**Modularity**—A module in the network can be defined as a subdivision that has more connections within the module than outside the module (Radicchi et al., 2004). It quantifies the degree to which the network can be optimally partitioned into distinct subcommunities (Rubinov and Sporns, 2010). While there are a number of approaches to constitute the modular decomposition in a network (Blondel et al., 2008; Newman, 2006; Sun et al., 2009), we adopted Newman's method, a spectral optimization technique to compute a measure of

modularity ( $Q$ ), as  $Q = w^{-1} \sum_{j, h \in N, m_i = m_j} (w_{ij} - (d_i^w d_j^w / w))$ , where  $w$  is the sum of all connection weights in the network  $N$ ,  $m_i$  is the module containing the region  $i$ , and  $d_i^w$  is the degree defined by the sum of weights connected to the region  $i$ .

### Rich club analysis

In the human brain, highly connected nodes play a crucial role as the hub (Sporns et al., 2007) or core (Hagmann et al., 2008) within the structural network. Recently, it has been found that such highly connected nodes—the so-called *rich club*—are more likely to be connected to each other compared to lesser connected nodes (van den Heuvel and Sporns, 2011). The rich club phenomenon has been found in *C. elegans* (Towlson et al., 2013), the cat (de Reus and van den Heuvel, 2013), the macaque cerebral cortex (Harriger et al., 2012) and in healthy and psychiatric individuals (van den Heuvel et al., 2013). Here, we investigated the rich club behavior for children as follows: (1) All non-zero connections in a connectivity matrix were ranked with respect to their weights, giving a vector of  $w_l^{\text{ranked}}$  where  $w_l^{\text{ranked}} > w_{l+1}^{\text{ranked}}$ . (2) For the given nodal degree  $k$  (the number of links connected to the node), the subnetwork of nodes with a degree larger than  $k$  was selected. (3) The number of connections ( $E_{>k}$ ) and the sum of weights ( $W_{>k}$ ) were computed for the subnetwork. (4)



For the  $E_{>k}$  strongest connections within the whole network, the sum of their weights was computed. (5) The weighted rich club coefficient  $\Phi^w(k)$  was computed as

$\Phi^w(k) = W_{>k} / \sum_{l=1}^{E_{>k}} w_l^{ranked}$ . (6) Then,  $\Phi^w(k)$  was normalized relative to 1,000 random networks preserving the network size, weights, and degree distribution, giving the normalized rich club coefficient  $\Phi_n^w(k) = \Phi^w(k) / \Phi_{random}^w(k)$ . (Opsahl et al., 2008) Notably, if  $\Phi_n$  is larger than 1 over a range of  $k$ , it is considered that the rich club potentially exists in the network. Rich club regime was defined if  $\Phi_n$  is significant in >75% individuals for children (van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). Within the rich club organization, all connections of the network were classified into 3 categories (van den Heuvel and Sporns, 2011); rich club connections (only linking nodes of the rich club members), feeder connections (linking rich club and non-rich club nodes), and local connections (linking between peripheral nodes of non-rich club nodes). We also examined the association between gestational length and the structural connectivity with respect to rich club nodes.

### Statistical analysis

Continuous relations between network measures and the length of gestation for all children were computed by using partial correlation coefficients ( $r$ ) controlling for age and sex as possible confounding variables. A significance level of  $p < 0.05$  was used to investigate the relationships between global network measures and gestational length with a correction for false discovery rate (FDR; Benjamini and Hochberg, 1995). For local efficiency measures computed at each node, significant correlations were defined by a very strict Bonferroni correction to avoid Type I statistical errors.

## Results

### Network topology of preadolescent children

Small-world network organization was found in the structural network of preadolescent children (Supplementary Fig. 1); *i.e.*, the network nodes were highly clustered ( $\gamma > 1$ ) with relatively short paths ( $\lambda \approx 1$ ) compared to the random network, confirming the small-world organization ( $\sigma > 1$ ). These findings are consistent with the previous network studies using white matter tractography in preadolescents, adolescents and adults (Cao et al., 2013; Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2010) and indicate that the overall topological properties were largely conserved in this narrow age range of preadolescent brain development.

### Gestational length vs. network characteristics

Network efficiency was highly correlated with the length of gestation (Fig. 2). Both higher global and local network efficiency had a positive association with a longer gestation period (global:  $r = 0.27$ ,  $p = 0.0009$ ; and local:  $r = 0.28$ ,  $p = 0.0008$ ). No significant associations were found for the network clustering, path length, small-worldness, or modularity (all  $p > 0.05$ ; see Supplementary Fig. 2).



### Regional changes of network efficiency

Positive linear relations between network efficiency and gestational age at birth were found in local brain regions (Fig. 3). Longer gestation was associated with the higher local network efficiency in bilateral precuneus (left:  $r=0.36$ ,  $p=0.12 \times 10^{-4}$  and right:  $r=0.33$ ,  $p=0.55 \times 10^{-4}$ ), superior parietal (left:  $r=0.29$ ,  $p=0.38 \times 10^{-3}$  and right:  $r=0.30$ ,  $p=0.32 \times 10^{-3}$ ), postcentral cortex (left:  $r=0.29$ ,  $p=0.52 \times 10^{-3}$  and right:  $r=0.29$ ,  $p=0.40 \times 10^{-3}$ ), left cuneus ( $r=0.29$ ,  $p=0.40 \times 10^{-3}$ ), calcarine cortex ( $r=0.29$ ,  $p=0.36 \times 10^{-3}$ ), right superior occipital cortex ( $r=0.40$ ,  $p=0.10 \times 10^{-5}$ ), superior frontal cortex ( $r=0.30$ ,  $p=0.22 \times 10^{-3}$ ), and supramarginal cortex ( $r=0.36$ ,  $p=0.11 \times 10^{-4}$ ).

### Rich club organization

Fig. 4A shows the curves of normalized weighted rich club coefficient for the children in this study. Over a range of nodal degree ( $25 \leq k \leq 49$ ), the network structure of these children showed the rich club organization with rich club coefficient  $\Phi_n > 1$  ( $p < 0.05$  in  $>75\%$  subjects after 10,000-times permutation test), suggesting existence of rich club organizations in the preadolescent children. The highly interconnected rich club members (Fig. 4B) were found to be the bilateral precuneus, putamen, hippocampus, insula, lingual cortex, middle occipital cortex, and superior frontal (orbital) cortex, left inferior temporal cortex, and right superior occipital regions of children, which is largely consistent with previous rich club findings in adults (van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). The structural connectivity as measured by the mean FA across individuals was positively and significantly associated with longer length of gestation in the rich club ( $r=0.18$ ,  $p=0.03$ ) and feeder connections ( $r=0.17$ ,  $p=0.04$ ) with a marginal effect for local connections ( $r=0.16$ ,  $p=0.06$ ) - see Fig. 4C. This is evidence that connectivity *between* and *from* hub regions is preferentially enhanced with longer gestational weeks.

### Discussion

The debate about what constitutes a “*term*” pregnancy has been leading to reconsideration of the conventional 37-week cut-off for preterm and term deliveries (Nicholson et al., 2013; Spong, 2013b). Most important, this debate is pointing to the importance of thinking about gestation as a continuous variable, thus moving away from a categorical approach (preterm/term). Moreover, this way of thinking raised important questions about the long-term effects of variations in gestational duration, even within a normal range, on health outcomes such as brain development. At the same time, a critical area of study in contemporary neuroscience has been brain network science, where the brain is understood as an integrated information processing system with anatomically differentiated and distinct subregions communicating in a highly efficient manner. With recent evidence suggesting that longer gestation benefits cognitive performance and brain development, the present study investigated the effects of gestational length on the structural network organization. This is the first study to investigate gestational influences on network efficiency in children using state-of-the-art network analysis. We also report that the *rich club* organization was found in the structural network of a narrowly defined age group of preadolescent children, suggesting the existence in childhood of highly interconnected structural hubs as found in the mature human brain. Furthermore, the rich club connectivity of children was positively correlated with longer

gestation. This is strong evidence that increased gestational length, even past the conventional cut-off for preterm birth, is associated with more differentiated organization of structural characteristics among the brain regions with pivotal connections. Also, the important finding of this study is the evidence for a strong association between gestational length and neural network characteristics measured in the preadolescent children. A longer gestational period in these typically developing children enhanced the efficiency of structural brain networks both globally and locally. We believe these findings provide strong support for the previous study (Spong, 2013a) in that the brain efficiency in children is associated with exposures during fetal life and that longer gestation favors more efficient neural networks, as Spong might predict.

### **Global network efficiency with gestational length**

Our results showed that the efficiency of structural networks is significantly associated with the gestational period in preadolescent children, which is directly comparable to a recent finding that global efficiency is reduced in school-age preterm infants (mean age = 6.7 years, and mean gestation = 29.8 weeks) with intrauterine growth restriction (Fischi-Gomez et al., 2014). Specifically, longer gestational length is associated with more globally efficient network structure. Since network efficiency has been defined as how rapidly and accurately information is transferred within the corresponding network (Latora and Marchiori, 2001), a network with global short-distance connections, reciprocal to higher connectivity, tends to directly interact for better neural communication (Sporns, 2011). Therefore, our global efficiency findings suggest that longer gestational period affects the direct coupling strength between brain regions resulting in the enhancement of network information transfer as a whole. Based on previous studies reporting that infants born preterm are at risk for disruptions in brain development (Delobel-Ayoub et al., 2009; Nosarti et al., 2002; Nosarti et al., 2008), increased network efficiency among infants born at longer gestation could be attributable to differences in the maturation of fiber bundles which impact optimal information transfer for neural communication. Our results also extend previous reports that there are benefits for both growth (Vinall et al., 2013) and brain development (Davis et al., 2011) from longer gestation, even after 37 weeks and that this benefit is observed in the neural efficiency in normal and healthy children.

### **Regional characteristics of network efficiency**

By definition (Latora and Marchiori, 2001), when the structural connectivity of a certain brain region is disrupted, the information transfer related to the region tends to be less efficient because of its lesser contribution to the total communication capacity, which can be more distinct on a local scale. Accordingly, the observed higher local efficiency would suggest the more tolerant local structure to internal connectivity disturbances in performing brain function. In this study, local network efficiency increased with longer gestation in the bilateral precuneus, superior parietal, and postcentral regions including cuneus, supramarginal, calcarine, superior frontal and occipital regions (Fig. 3). Notably, the association of network efficiency and longer gestational period was mostly prominent in the bilateral precuneus and superior parietal cortex, known as a putative structural hub across primate species (Li et al., 2013) performing multimodal neural processing with high levels of metabolic energy usage (Collin et al., 2013). Furthermore, the associations were also

found in the cuneus, calcarine cortex, and superior frontal cortex, also playing a central role in global communication and integration (Hagmann et al., 2008; Sporns et al., 2007; van den Heuvel et al., 2010). Therefore, findings in this study imply that positive associations of local efficiency and longer gestation mainly in the structural hub regions of preadolescent children might affect the characteristics of *hub complexes* (a group of hub nodes) in terms of the level of interconnectivity among those regions – so called *rich club* (Sporns et al., 2007; van den Heuvel and Sporns, 2011). Interestingly, we found associations between efficiency and the gestation length even in the non-core regions as well, *i.e.*, postcentral, supramarginal, and superior occipital cortex. These findings with non-core regions suggest that gestational length might also affect regions with a relatively small impact on the global communication of neural information transfer.

### Rich club organization and its connectivity property

We identified “rich club” organization in preadolescent children; that is, the existence of prominent brain hub regions which are densely interconnected to each other. The rich club organization was observed in the bilateral precuneus and superior frontal cortex as well as the subcortical regions including hippocampus and putamen, which are highly connected to each other. This set of rich club members was highly consistent with previous studies in healthy adults (mean age = 30.0; van den Heuvel and Sporns, 2011) including a neuropsychiatric disease (mean age = 29.4; van den Heuvel et al., 2013), and suggests that the rich club is formed at least by preadolescence and is resilient to perinatal and possibly later developmental insults. Although the precise relationship between the formation of rich club organization and the trajectory of brain development remain unclear, one of the main findings of this study is an increase in structural connectivity among the rich club and feeder connections as gestational length increases while connection densities were grossly preserved (Supplementary Fig. 3). While the connectivity strength among rich club members was found to be significantly increased with longer gestation, the connections from rich club nodes to the non-rich club nodes (*i.e.* feeder connections) were also increased with the length of gestation. This is directly consistent with a recent finding that the rich-club is evident by 30 weeks gestation and connections between core hubs and the rest of the brain increase through to birth; moreover, preterm birth is associated with disruptions in cortical–subcortical connectivity and short-distance corticocortical connections (Ball et al., 2014). In the present study, observed connectivity increases *among* rich club members and *from* rich club members provide empirical evidence supporting the central role of rich club nodes within a network in making global communication efficient over long distances in the brain (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2013). The findings of increased rich club connectivity are in agreement with our findings of increased global/local efficiency with longer gestation in preadolescents, and suggest slower postnatal growth of pivotal connectivity due to a reduction in gestational period. Indeed, it is also suggestive that the development of global information transfer with the gestational period might be affected by the characteristics of these prominent hub regions as in the course of normal development and aging (Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2010) and the network immaturity due to the short gestation (Ball et al., 2014) may persist into early childhood.

### Implication of network alteration on the shorter gestation

The network density [29.92±2.9(%), 23.42~42.22] and average connectivity strength [0.408±0.015, 0.373~0.448] across all children were positively correlated with gestational length (Supplementary Fig. 4). Accordingly, it is possible that the shorter gestation is associated with a *less connected and/or weaker connected* brain network rather than a sub-optimal network. However, because correlation findings on the network characteristics could be strongly influenced by network density and average strength (Ginestet et al., 2011; van Wijk et al., 2010), some cost-correction approaches might be more useful to interpret the topological changes of brain networks. Because an unbiased method that is able to simultaneously account for network density and strength does not exist, we computed the correlations with gestational length using four comparative approaches: (1) binarized network; (2) weighted network normalized by average strength; (3) partial correlation by density and strength; and (4) thresholded network by density. We found consistent positive associations between network efficiency and gestational length (see Table 2 and Results in Supplementary Materials). Furthermore, because these associations persisted even when the density and strength were accounted for, it is possible that the *sub-optimality* as well as *less and weaker connectivity* of the network may be associated with gestational length.

### Methodological issues

The network edges in this study were defined by a computational method based on fiber tractography. Typically, tracking algorithms cannot resolve the detailed fiber orientation for the crossing tracts, in particular when using deterministic approaches. To mitigate this potential problem, we applied the criterion that any tract must have at least three fiber tracts (Lo et al., 2010). More advanced acquisition techniques such as diffusion spectrum imaging (Wedeen et al., 2005) with probabilistic tractography (Behrens et al., 2003) may better resolve diffusion directions for fiber crossings. Second, even though the mean FA of the fiber tracts is accepted as an appropriate indicator to quantify the directional strength through the fiber coherence, defining edge weights using mean FA is but one possible approach. Alternatives for defining network edges include the number of fiber tracts, the distance between regions through fiber pathway, and combinations of these (Hagmann et al., 2008; Lo et al., 2010; van den Heuvel and Sporns, 2011). Still, evidence exists that structural network metrics and rich club organization is largely consistent regardless of how edge weights are defined (Lo et al., 2010; van den Heuvel and Sporns, 2011) and the consistent finding on network efficiency using binarized connections (Supplementary Fig. 5). In this study, we adopted the mean FA because we found no differences for the number and length of fiber tracts across the individuals (see Results in Supplementary Materials). Third, the constructed network in this study had a relatively low spatial resolution (*i.e.*, number of nodes = 90 from AAL atlas) with varying sizes, which might lead to a different network topology by different parcellation schemes (e.g, from FreeSurfer parcellation; Fischl et al., 2004) as has been reported for functional networks (Wang et al., 2009). While some studies used regions with higher resolution to avoid the spatial averaging effects of weak connectivity (Hagmann et al., 2008; Hagmann et al., 2010), the optimal formulation of the number of cortical regions as network nodes still remains unknown. Fourth, while the alterations of structural brain networks of infants with fetal growth restriction have been

reported (Batalle et al., 2012), we didn't exclude children with the birth weight percentile < 10%, defined by local reference standards (Oken et al., 2003), because only 11 of 147 ( $\approx 7.5\%$ ) children met the criteria for SGA (small for gestational age) in our population. We note, however, that the major findings in the present study was not changed even after such participants were excluded: positive associations between a longer gestation period and global ( $r=0.27$ ,  $p=0.002$ ) and local ( $r=0.26$ ,  $p=0.002$ ) efficiency were observed. No significant associations were found for the network clustering ( $r=-0.16$ ,  $p=0.075$ ), path length ( $r=-0.13$ ,  $p=0.123$ ), small-worldness ( $r=-0.14$ ,  $p=0.100$ ), or modularity ( $r=-0.14$ ,  $p=0.097$ ). It might be the case that the results are not changed due to the small proportion of infants below 10% percentile, and further studies will be required to investigate the long-term neurodevelopmental effects on the structural brain network with restricted fetal growth.

## Conclusion

Examination of structural networks of typically developing preadolescent children showed that higher network efficiency was associated with increased gestational length. This suggests that there are topological organizational benefits from longer gestation and that this benefit continues even among infants born after the conventional cut-off for term delivery (37 weeks). Specifically, increased network efficiency was positively associated with gestational length, especially in medial posterior regions known to be central hub regions in structural and functional networks. Our findings point to the importance of gestational age at birth on the subsequent structural network topology of preadolescent brains.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgement

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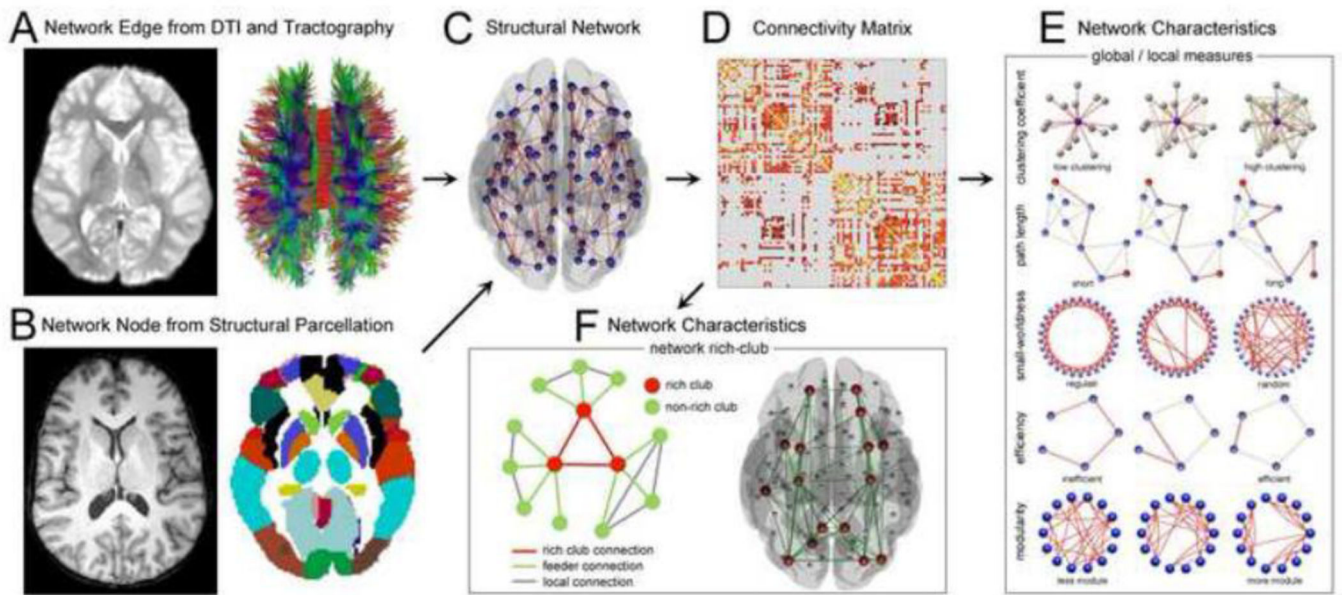


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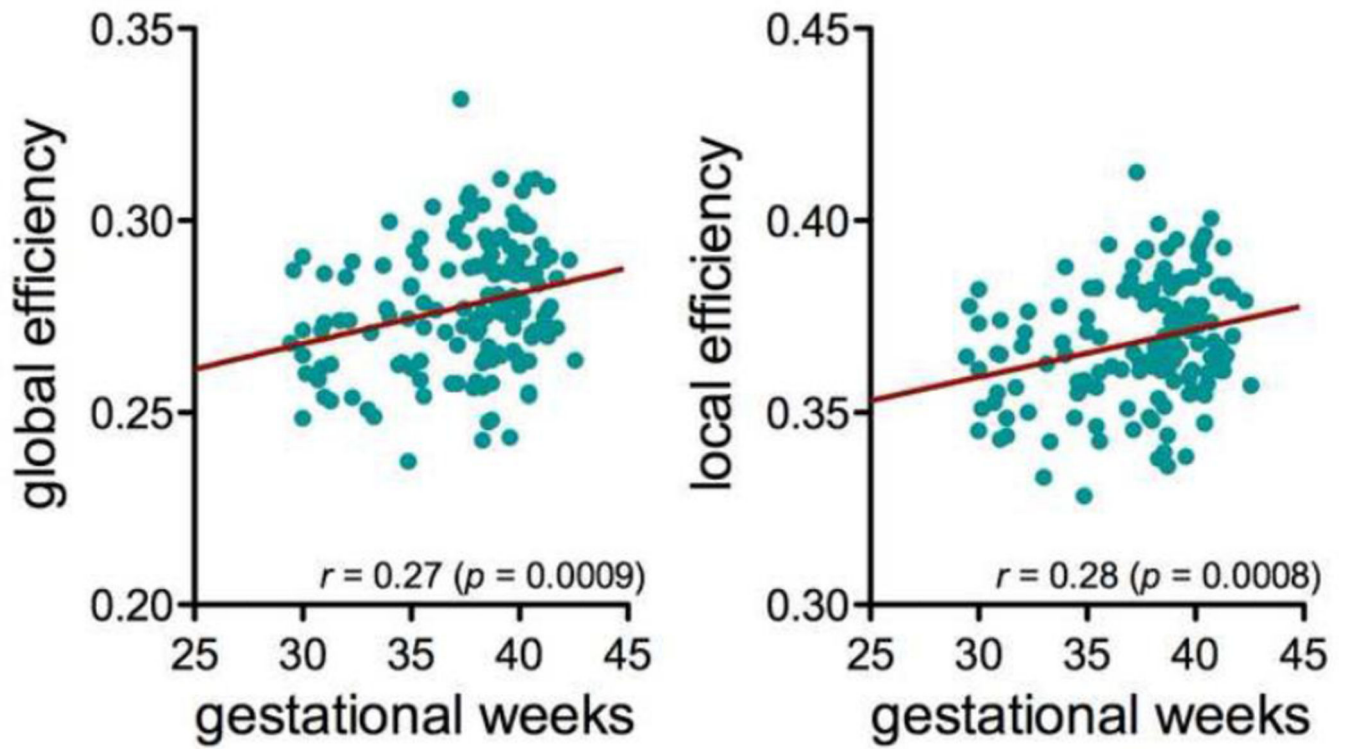
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### Highlights

- Structural network of 147 preadolescents (29–42 gestational age: GA) was examined.
- Longer GA was associated with higher global and local network efficiency.
- Presence of “rich-club” organization for preadolescents (6–11 ages) was confirmed.
- Connectivity was preferentially enhanced in rich-club regions with longer GA.
- The findings extend the topological organizational benefits from longer gestation

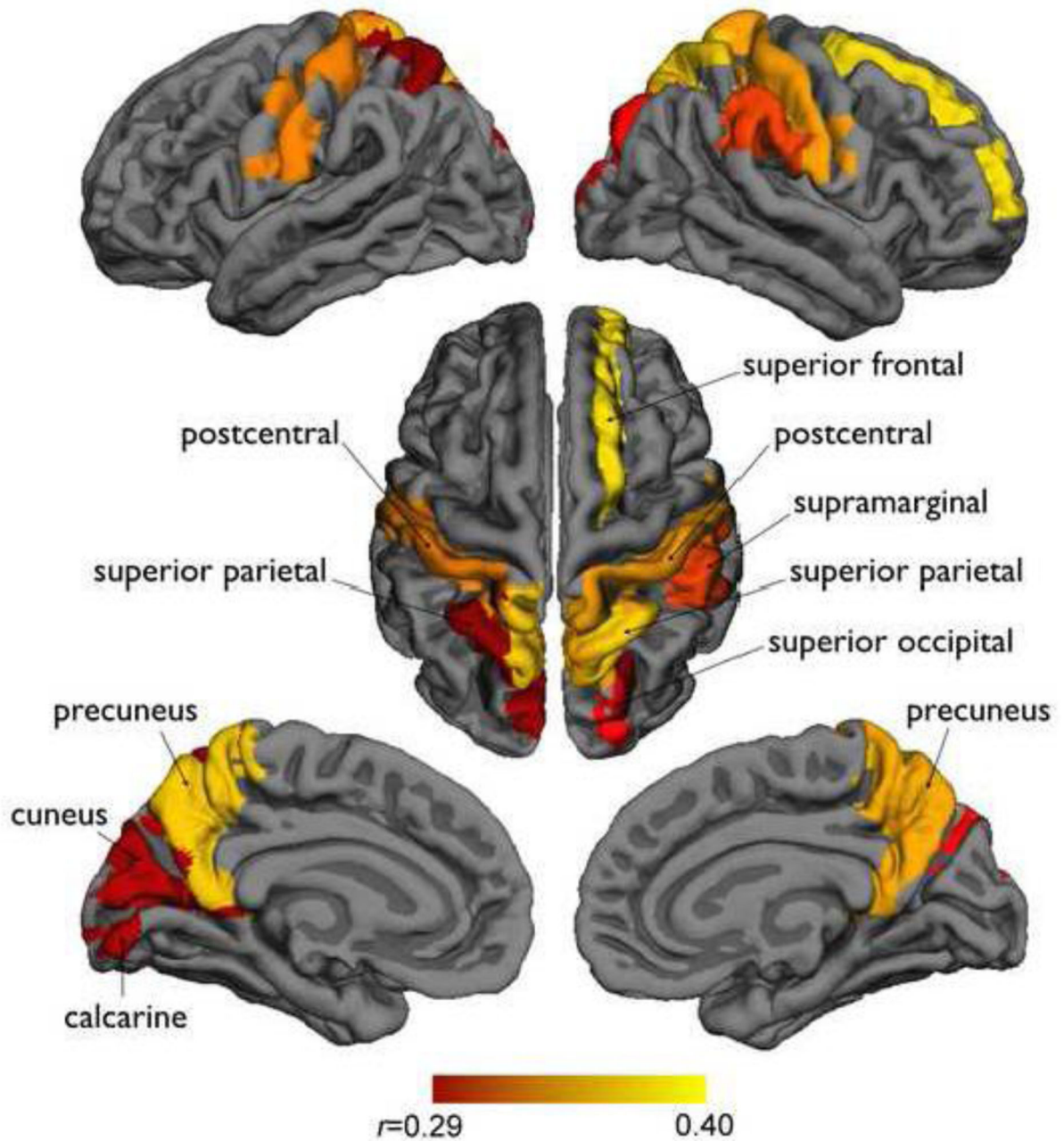


**Fig. 1.** Graph theoretic analysis of structural brain networks. A, The white matter pathways of brain were extracted using the fiber tractography with diffusion tensor imaging (DTI). B, Anatomical T1-MRI was used for the automatic regional parcellation to 90 distinct brain areas with automated anatomical labeling (AAL) atlas. C, Structural connectivity was defined by the mean fractional anisotropy (FA) of fiber tracts connecting two regions. D, The result was a 90×90 weighted symmetric connectivity matrix for each individual. E, The topological properties of the structural brain network were computed in terms of network segregation (clustering coefficient and modularity), integration (characteristic path length and global/local efficiency), and their optimal balance (small-worldness). The relationships between the computed network metric and the length of gestation were investigated in preadolescent children. F, The rich club organization was examined for the rich club, feeder, and local connections.

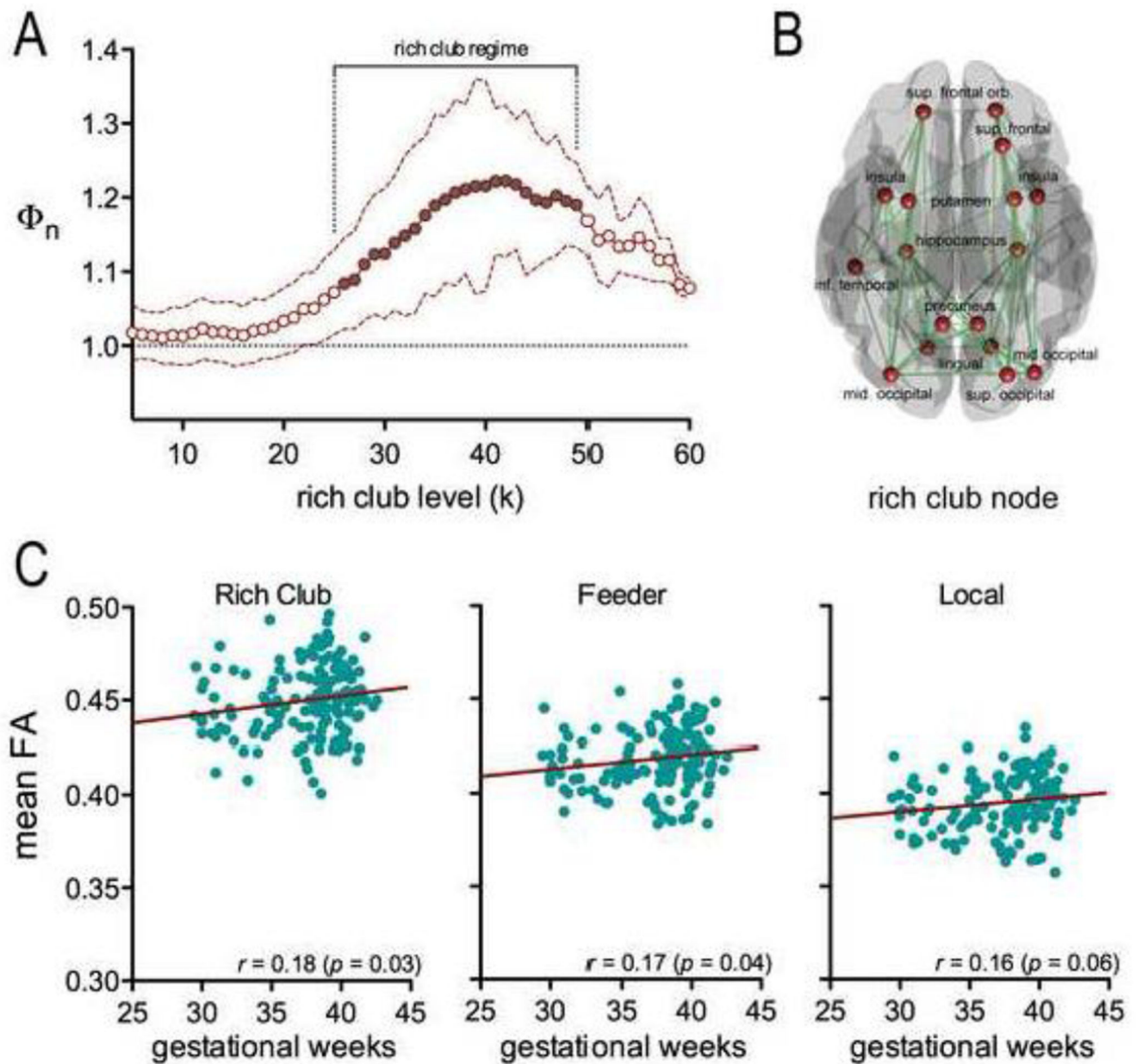


**Fig. 2.** Network efficiency and the length of gestation. Both global and local efficiency were positively correlated with the length of gestation, after controlling age and sex of children as possible covariates ( $p < 0.05$ ).





**Fig. 3.** Network efficiency and the length of gestation at local regions. Strong positive associations were found in the bilateral precuneus, superior parietal, and postcentral regions including cuneus, supramarginal, calcarine, superior frontal and occipital regions ( $p < 10^{-4}$  with Bonferroni correction; age and sex covariates).



**Fig. 4.** Rich club organization. A, Significant rich club nodes exist in the wide range of degree  $k$  ( $25 < k < 49$ ) suggesting a higher level of connectivity among brain hubs ( $p < 0.05$ ; 10,000-times permutation test). B, Rich club connections (green) linking rich club members (red). Rich club members include precuneus, putamen, hippocampus, insula, superior/middle occipital and inferior temporal cortex, compatible with previous rich club findings in adults. C, Structural connectivity as measured by the mean FA across the individuals within and from rich club members (*i.e.*, rich club and feeder connections) were significantly increased with longer length of gestation ( $p < 0.05$ ).



**Table 1**

## Demographic data of the study sample

Number of	Subjects	147
	Preterm	48 (32.7%)
	Term	99 (67.3%)
Gender	Male	81 (55%)
	Female	66 (45%)
Handedness	Right	147 (100%)
	Left	0 (0%)
	<i>Mean±SD</i>	<i>Min~Max</i>
Gestational Age at Birth (weeks)	37.37±3.31	29.42~42.57
Age at Assessment (years)	8.12±1.35	6.10~10.78
Birth Weight (gram)	2983.73±781.48	1042~4561
Birth Weight Percentile	47.00±25.71	1~100
Maternal Age (years)	29.57±6.69	16.16~44.59

*Note.* Birth weight percentile was defined by standard percentile charts by Oken et al. (2003).

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