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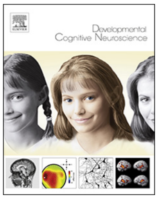

The development of functional network organization in early childhood and early adolescence: A resting-state fNIRS study

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ABSTRACT

Early childhood (7–8 years old) and early adolescence (11–12 years old) constitute two landmark developmental stages that comprise considerable changes in neural cognition. However, very limited information from functional neuroimaging studies exists on the functional topological configuration of the human brain during specific developmental periods. In the present study, we utilized continuous resting-state functional near-infrared spectroscopy (rs-fNIRS) imaging data to examine topological changes in network organization during development from early childhood and early adolescence to adulthood. Our results showed that the properties of small-worldness and modularity were not significantly different across development, demonstrating the developmental maturity of important functional brain organization in early childhood. Intriguingly, young children had a significantly lower global efficiency than early adolescents and adults, which revealed that the integration of the distributed networks strengthens across the developmental stages underlying cognitive development. Moreover, local efficiency of young children and adolescents was significantly lower than that of adults, while there was no difference between these two younger groups. This finding demonstrated that functional segregation remained relatively steady from early childhood to early adolescence, and the brain in these developmental periods possesses no optimal network configuration. Furthermore, we found heterogeneous developmental patterns in the regional nodal properties in various brain regions, such as linear increased nodal properties in the frontal cortex, indicating increasing cognitive capacity over development. Collectively, our results demonstrated that significant topological changes in functional network organization occurred during these two critical developmental stages, and provided a novel insight into elucidating subtle changes in brain functional networks across development.

1. Introduction

Recent findings from behavioral and brain imaging studies have demonstrated that the enhancement of cognitive processes during normal brain development involves a fine-tuning of structural and functional organization of the brain from birth to adulthood (Collin and van den Heuvel, 2013; Giedd et al., 1999; Hagmann et al., 2012; Sowell et al., 2003; Vertes and Bullmore, 2015). According to Piaget's theory of cognitive development (Piaget, 1999), early childhood (7–8 years old) is a critical period during which young children undergo the transition from the preoperational stage to the concrete operational stage. Specifically, they start thinking logically about concrete events and solving problems in a more logical manner, but their thinking remains very concrete. Additionally, although numerous important cognitive functions, such as attention, memory and inhibitory control, develop quickly, they are nonetheless less developed (Brocki and Bohlin, 2004; Davidson et al., 2006; Schneider and Ornstein, 2015). Early adolescence (11–12 years old) constitutes the starting point of the formal operational stage. In this stage, adolescents can use symbols related to abstract concepts to accomplish hypothetical and deductive reasoning, which benefits from improved working memory and executive inhibitions at this critical developmental stage (Bedard et al., 2002; Ernst and Mueller, 2008; Gathercole et al., 2004; Williams et al., 1999). These dramatic improvements of cognitive performance from early childhood to early adolescence may imply significant increases in the brain's efficiency with development. However, few studies have investigated the developmental topological characteristics of brain functional networks during these two critical periods.

The human brain constitutes an integrative, complex network system with numerous non-trivial local and global topological

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characteristics, which can be examined by graph theory (Bullmore and Sporns, 2009). A network's topological patterns are evaluated using the key properties of graph theory, such as clustering coefficient, characteristic path length, node degree, efficiency, and modularity (Sporns and Zwi, 2004) (see Section 2.6 for details). The clustering coefficient of a graph provides information about the level of local clustering within a graph, expressing how well the neighbors of a node are connected amongst themselves. This offers a measure of how much spatially-closer brain regions are connected with each other, or the local connectedness of the network. The level of global connectivity of the network can be assessed with the characteristic path length of a graph, which describes how close, on average, a node of the network is connected to every other node in the network. This provides information on how efficiently information can be integrated between different subgraphs. The degree of a node describes the number of connections of a node and offers information about the existence of highly connected hub nodes in the brain network. Nodes with a high nodal efficiency indicate that the network has a high tolerance for the elimination of a given node, which is associated with a high clustering of the neighborhood of this node (Achard and Bullmore, 2007). The level of modularity of a network describes the extent that groups of nodes in the graph are connected to other members of their own group, establishing sub-networks within the greater network. Taken together, these metrics of graph theory provide critical information about the structure of a network and characterize a specific organization style (e.g., small-world, modular) of that network.

Fair et al. (2009) applied resting-state functional connectivity and graph theory to investigate the topological organization of the developing brain in three age groups (aged 7–9, aged 10–15, aged 19–31). Their study revealed that children and adults have similar clustering coefficients and characteristic path lengths, but different spatial distributions of modularity organization throughout development (Fair et al., 2009). Furthermore, by comparing the organization of brain networks between 7–9 year old children and adults, Supekar et al. (2009) determined that children's and young adults' brains have a similar small-world regime, and demonstrated simultaneous reduction of short-range functional connectivity and strengthening of long-range functional connectivity from childhood to adulthood. A recent study over the age range of 6–18 years reported increases in the normalized clustering coefficient, local efficiency and small-worldness, but global efficiency was not significantly changed with development (Wu et al., 2013). The findings were further supported by a lifespan study (Cao et al., 2014) that demonstrated that local efficiency increased slightly from early childhood to early adulthood (7–30 years). To date, almost all extant literature focusing on topological developmental changes in functional networks has been performed over a relatively broad age range (Cao et al., 2014; Fair et al., 2009; Supekar et al., 2009; Wu et al., 2013). These combined results suggest that graph theoretical analysis constitutes a powerful tool to characterize the topological development of functional brain networks.

Since almost all relevant previous studies have considered a relatively wide age range, a refined examination of two relatively narrow and critical developmental periods is worthy of investigation. We predicted that the functional difference between two noncontiguous age groups will offer non-trivial insight for normal child development and a valuable reference for the clinical diagnosis of psychopathology across development. More importantly, in the current study, we adopted resting-state functional near-infrared spectroscopy (rs-fNIRS) to address the developmental changes of brain networks. Compared with functional magnetic resonance imaging (fMRI), fNIRS is silent and more tolerant to subtle movement artifacts, and can measure both oxy- and deoxy-hemoglobin chromophores, providing a more comprehensive measure of cortical hemodynamic response. Furthermore, it is generally acceptable for children to participate in fNIRS studies because data acquisition is performed in a natural environment. (Bunge and Wright, 2007; Davidson et al., 2006). In addition, compared to fMRI imaging, fNIRS has much better temporal resolution, up to hundreds of hertz, thus providing a more complete temporal picture for the characterization of brain activity (Lloyd-Fox et al., 2010).

In the present study, we utilized rs-fNIRS to examine developmental changes in both global and regional nodal topological properties from early childhood and early adolescence to adulthood. We hypothesized that from early childhood to early adolescence, there would be a significant linear improvement in certain topological characteristics of brain networks, such as local and global efficiency, revealing functional segregation and integration. Additionally, we predicted that diverse developmental trajectories in different functional cortices would be found throughout development.

2. Materials and methods

2.1. Participants

This study enrolled 90 healthy participants, including 30 young children (age range of 7.0–8.9 years old with mean and standard deviation of 8.1 ± 0.6 years; 14 M/16 F), 30 early adolescents (age range of 11.0–12.9 years old with mean and standard deviation of 11.9 ± 0.6 years; 19 M/11 F), and 30 adults (age range of 19–27 years old with mean and standard deviation of 23.2 ± 1.9 years; 16 M/14 F). All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The participants or their parents signed a written informed consent form prior to the initiation of the experiments. Approval for this study was obtained from the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University.

2.2. Data acquisition

Each participant's hemodynamic response was recorded using a continuous wave near-infrared optical imaging system (CW6, TechEn Inc., MA, U.S.A.) equipped with 12 light sources and 24 detectors at 690 nm and 830 nm wavelengths. The light sources and detectors were placed on a stretchable cap, forming 46 measurement channels (source–detector separation: 3.2 cm) and covering almost the whole head (Fig. 1A, B). The positioning of the probe array was determined according to the international 10–20 coordinate system, and referred to the external auditory canals and vertex of each participant as landmarks. Specifically, six detectors below channels 17–24 in both hemispheres were set along a coronal line from the vertex to the external auditory pores, and thus their midline was localized in Cz and the leftmost and rightmost detectors were fitted around T3 and T4, respectively. Data were recorded at a sampling rate of 50 Hz. For each participant, the rs-fNIRS data were collected for approximately 11 min, and the participants were instructed to relax, keep their eyes closed, and remain awake.

2.3. MRI coregistration

To validate the positioning method of the probes, a structural MR image was acquired from one arbitrarily selected adult subject (SJ). During MRI data acquisition, the participant lay supine while wearing the probe array. The probe array was pasted with vitamin E capsules placed precisely at each of the optode locations. All scans were performed using a 3T Siemens Tim Trio MRI scanner at the Imaging Center for Brain Research, Beijing Normal University. The vitamin E locations from these scans were used as landmarks for coregistration (Fig. 1C). A T1-weighted structural image was acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence: 176 slices, TR = 2600 ms, TE = 3.02 ms, FOV = $256 \times 224\ \text{mm}^2$, voxel size = 1 mm × 1 mm × 1 mm, flip angle = 8°, and slice orientation = sagittal. The MR image was normalized into MNI space using the NIRS_SPM software (http://bispl.weebly.com/nirs-spm.html#/), and

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