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Age effects on the default mode and control networks in typically developing children

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ABSTRACT

Background: The investigation of neurodevelopment during late childhood and pre-adolescence has recently attracted a great deal of interest in the field of neuroimaging. One promising topic in this field is the formation of brain networks in healthy subjects. The integration between neural modules characterizes the ability of the network to process information globally. Although many fMRI-based neurodevelopment studies can be found in the literature, the analyses of very large samples (on the order of hundreds of subjects) that focus on the late childhood/pre-adolescence period and resting state fMRI are scarce, and most studies have focused solely on North American and European populations.
Aims: In this study, we present a descriptive investigation of the developmental formation of the Default Mode Network and the Control Network based on a Brazilian, cross-sectional community sample of 447 typically developing subjects aged 7–15 years old.
Methods: Resting state fMRI data were acquired using two MRI systems from the same manufacturer using the same acquisition parameters. We estimated the age effects on the strength of the links (between brain regions) and the network features (graph descriptors: degree and eigenvector centrality).
Results: Our findings showed an increase in the antero-posterior connectivity in both studied networks during brain development. The graph analyses showed an increase in centrality with age for most regions in the Default Mode Network and the dorsal anterior and posterior cingulate, the right anterior insula and the left posterior temporal cortex in the Control Network.
Conclusion: We conclude that the period of 7–15 years of age is crucial for the development of both the Default Mode and Control networks, with integration between the posterior and anterior neuronal modules and an increase in the centrality measures of the hub regions.

1. Introduction

At rest, the brain displays patterns of spontaneous activity that form multiple dissociable networks that are increasingly thought to be related to a specific set of brain operations (Crossley et al., 2012).

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Two networks have been more consistently studied in the literature: the Default Mode Network (DMN) (Gusnard et al., 2001; Raichle et al., 2001) and the Control Network (CN) (Dosenbach et al., 2007, 2006; Fair et al., 2007). The integrity of the brain operations that result from the activities of these networks is a direct consequence of their structural and functional development (Power et al., 2010). This relationship opens the possibility of predicting the level of brain maturity by examining the functional networks (Dosenbach et al., 2010) and will shed light on atypical development, which may be associated with mental health disorders (Insel, 2009).

The default mode network (DMN, see Supplementary Table 1 for a description of the regions) is a distributed network of brain regions that are more active during rest than during the performance of a task (Shulman et al., 1997a, 1997b; Gusnard et al., 2001; Raichle et al., 2001). Several studies in healthy adults have provided evidence of task-induced decreases in brain activity relative to rest in this network (Binder et al., 1999; Mazoyer et al., 2001; McKiernan et al., 2003), with some authors suggesting that the DMN supports "self-referential" or "introspective" mental activity (Gusnard et al., 2001). Our knowledge of the DMN in children remains very limited. Some studies have not identified the default-mode-like components (Fransson et al., 2011, 2007) in infants (40–44 weeks, acquisition in sleep) with very low gestational age (24–27 weeks) or full term (mean age at MRI acquisition was 39 weeks and 2 days). In addition, Smyser et al. (2010) completed a longitudinal study of preterm infants (initial scan at approximately 2 weeks old) and found a poorly assembled network. Others studies have provided some support for a rudimentary DMN assembly very early in life using different methods of analysis, including seed-based (Fair et al., 2008; Kelly et al., 2009), independent component analysis (Gao et al., 2009; Stevens et al., 2009; Supekar and Musen, 2009; Thomason et al., 2008) and graph theory approaches (Fair et al., 2008). In a cross-sectional groups comparison, Fair et al. (2008) described that the DMN is only sparsely connected in children (7–9 years), which is in contrast to adults (21–31 years), who present a highly integrated DMN (Fair et al., 2008). Current evidence supports an increase in the functional connectivity within the regions in the DMN with age (for a detailed review, see Power et al., 2010). However, the specific brain regions that are more sensitive to the age-related changes during childhood remain unclear. These previous studies point toward a crucial role of the anterior medial prefrontal cortex (aMPFC) and the posterior cingulate (and the precuneus) as network hubs. The literature also suggests the maturation of the prefrontal cortex during childhood and adolescence (Shaw et al., 2008). Thus, an increasing involvement of the aMPFC and the posterior cingulate through age is expected.

In contrast with the DMN, the control network (CN, see Supplementary Table 1 for regions description) is thought to be responsible for a task-dependent cognitive state mode, i.e., the general set that is maintained for the execution of goal-directed brain operations (Logan and Gordon, 2001). Dosenbach et al. showed that a network composed of the fronto-parietal and cingulo-opercular components presented activations across several tasks (Dosenbach et al., 2006, 2007). The authors suggested that these regions formed a "core" task set system that was anatomically separate from the domain-specific task-set functions (Dosenbach et al., 2006). Only a few studies have explored the developmental changes in the control networks during childhood. In a cross-sectional study, Fair et al. (2007) showed that the CN undergoes increased functional segregation (decreased short-range connections) and integration (increased long-range connections) during childhood (7–15 years). In their study, the authors found a segregation of the dACC/msFC region from the frontoparietal network and a disconnection between the anterior and dorsolateral parts of the prefrontal cortex. Also in their study, by using a larger sample (7–35 years old), connections between the dorsal part of the anterior cingulate and the cingulo-opercular network, the left dorsolateral prefrontal cortex to the left intraparietal sulcus (IPS) and the left frontal to the left IPS were positively correlated with age. These findings were reinforced by a group comparison between adults (21–31 years) and children (7–9 years). To summarize, most connections with strength that were negatively correlated with age were short-range connections, and the connections with positive correlations were long-range connections.

While motion can bias the estimate of the functional connectivity (Power et al., 2011; van Dijk et al., 2012; Yan et al., 2013; Power et al., 2014), these changes in long-range connections are consistently found in studies that adequately control for movement (Satterthwaite et al., 2013). Further studies are needed to understand how these networks are assembled in childhood and adolescence.

Nevertheless, most studies have focused on North American and European populations (Satterthwaite et al., 2014). Although some samples were heterogeneous (e.g., Caucasians and African Americans; Satterthwaite et al., 2014), they were restrictive not only in terms of the genetic diversity (miscegenation), but arguably also in the social and environmental conditions typical of the developed world. Second, the majority of the studies to date have included very specific sample ascertainment, i.e., voluntary research subjects or specific populations. Therefore, how these networks develop in non-referred children drawn from the community (i.e., the subjects were not referred from a hospital or clinic, but were recruited at school or home) remains to be further investigated. Moreover, past studies have relied on relatively small sample sizes and/or very broad age ranges, thereby limiting the ability to detect more subtle changes that occur in specific windows of development.

Finally, very few studies have used modern analytic approaches, such as graph descriptors, to investigate the developmental changes in the brain networks. Graph descriptors are suitable to explore the networks beyond the analysis of the strength in connectivity between pair nodes. The graph analysis of fMRI data usually considers the brain regions as nodes, and the edges that connect these nodes are the functional connectivity measures (e.g., the correlation between the BOLD signal at each region). One of the attractive features of this approach is the ability to quantify how central a node (centrality measures) is to the network from both the local and global perspectives (Rubinov and Sporns, 2010).

This study aimed to replicate previous findings of DMN and CN maturation in a cross-sectional sample of 447 healthy children (7–15 years) from a developing country with high genetic admixture. The subjects included in the study were carefully evaluated for the exclusion of mental disorders. The brain scans were performed at two research centers using the same acquisition parameters. The aim of this study was to investigate the functional connectivity and the graph centrality measures of the DMN and the CN in different aged youth. Although this was primarily a descriptive study, we hypothesized that the functional connectivity within the DMN and the CN, as well as the degree of centrality (integration from a more local perspective) and the EVC (global information processing), would present an increasing connectivity pattern across age, thereby indicating the formation of both networks during childhood.

2. Materials and methods

2.1. Participants

This study is based on a subsample of the '*High Risk Cohort Study for Psychiatric Disorders in Childhood*' (HRC), which included two