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Connectome hubs at resting state in children and adolescents: Reproducibility and psychopathological correlation

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ABSTRACT

Functional brain hubs are key integrative regions in brain networks. Recently, brain hubs identified through resting-state fMRI have emerged as interesting targets to increase understanding of the relationships between large-scale functional networks and psychopathology. However, few studies have directly addressed the replicability and consistency of the hub regions identified and their association with symptoms. Here, we used the eigenvector centrality (EVC) measure obtained from graph analysis of two large, independent population-based samples of children and adolescents (7–15 years old; total N = 652; 341 subjects for site 1 and 311 for site 2) to evaluate the replicability of hub identification. Subsequently, we tested the association between replicable hub regions and psychiatric symptoms. We identified a set of hubs consisting of the anterior medial prefrontal cortex and inferior parietal lobule/intraparietal sulcus (IPL/IPS). Moreover, lower EVC values in the right IPS were associated with psychiatric symptoms in both samples. Thus, low centrality of the IPS was a replicable sign of potential vulnerability to mental disorders in children. The identification of critical and replicable hubs in functional cortical networks in children and adolescents can foster understanding of the mechanisms underlying mental disorders.

1. Introduction

Graph theory has been increasingly applied in the analysis of connectivity in neuroimaging data. Graph-theory-derived centrality measures, especially eigenvector centrality (EVC), can rank the relevance of a node in a complex network (Zuo et al., 2012) in terms of strategic location. This feature is particularly useful for exploring the etiology of mental disorders that are associated with functional alterations at a network rather than a focal level (Fornito et al., 2015; Sporns, 2014; He et al., 2016). However, there is currently a lack of consistent findings from independent large samples in the literature (Horga et al., 2014). In particular, few studies have investigated if central functional brain regions in children and adolescents are replicable across different sites of acquisition (Zuo et al., 2012). In addition, even fewer studies have explored the

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replicability of associations between network-level disruptions and dimensional psychopathology in childhood.

Previous studies of human structural and functional brain networks have identified a set of highly connected brain regions (i.e., hubs) (Power et al., 2013). These hubs are believed to play a central role in the flow of information throughout the brain, integrating parallel and distributed networks (Gong et al., 2009; Hagmann et al., 2008; Hwang et al., 2013). Structural connectivity studies have shown that hubs are mainly located at integrative cortical areas in adults (Power et al., 2013; Sporns et al., 2007). In the adult brain, functional cortical hubs include the medial prefrontal cortex, posterior cingulate cortex (PCC), precuneus, inferior parietal lobule (IPL; particularly the angular gyrus) and medial temporal cortex (Buckner et al., 2009). Moreover, Betzel et al. (2014) have noted that functional hub regions are affected by changes in white matter connections and that the relationship between functional and structural connectivity changes with age.

Two major gaps can be drawn from the current neuroimaging literature of children and adolescents: (i) the replicability across different samples; and (ii) the differential effects of hubs over neurodevelopment. Several resting-state fMRI studies of large samples of children and adolescents have been carried out, but in healthy developing children as opposed to clinical samples (Grayson et al., 2014; Sato et al., 2015a,b; Supekar et al., 2009; Uddin et al., 2011; Hwang et al., 2013). Evidence for a typical developmental trajectory emerged from these studies: large-scale networks apparently shift from a locally segregated to a more distributed and integrated organizational pattern (Fair et al., 2008, 2009, 2007; Fransson et al., 2011; Gao et al., 2009; Supekar et al., 2009). Interestingly, in infants, hubs have been identified in primary sensorimotor regions as opposed to the association cortex, where hubs have been identified in adults (Fransson et al., 2011). Hwang et al. (2013) showed that the connectivity between frontal hubs and other brain regions increases from childhood to adolescence. However, Khundrakpam et al. (2013) described developmental changes in the topological properties of the networks that suggested an organizational shift towards a more random configuration. Moreover, Zuo et al. (2012) demonstrated the test-retest reliability of EVC in functional connectivity networks over a subject age range of 7–85 years old. Therefore, despite the emergence of several brain regions as potential hubs of intrinsic brain connectivity in children, few studies have investigated which regions are most replicable across different samples (Horga et al., 2014). This is a crucial point for progress in biological psychiatry. In addition, many findings from early resting-state fMRI studies were limited by the issue of head micro-motion artifacts (Power et al., 2012). These movement artifacts are also related to age and influence functional connectivity estimates, complicating the interpretation of results.

The fact that hub regions constitute potential points of vulnerability for network disintegration is a key issue (Albert et al., 2000). Indeed, the abnormalities associated with several brain disorders have been shown to concentrate in hubs; such disorders include ADHD (dos Santos Siqueira et al., 2014), autism (Ray et al., 2014) and schizophrenia (Tomasi and Volkow, 2014). As such, hub disruption has been proposed as a general pathological mechanism in brain disorders (Crossley et al., 2014; van den Heuvel and Sporns, 2013). Therefore, description of atypical neurodevelopmental trajectories of the brain connectome appears crucial to unveil the neural substrates of mental symptoms and disorders (Di Martino et al., 2014). However, full characterization of these functional networks and possible differences in their architecture in childhood has not yet been achieved.

Here, we first sought to explore the replicability of mapping regions with high EVC values in children and adolescents. Then, we investigated the hypothesis that diminished or "impaired" centrality of these hubs would reliably correlate with psychopathological symptoms in two independent, population-based cohorts of children and adolescents. For these purposes, we analyzed resting-state fMRI data acquired using identical acquisition protocols from two large samples of children and adolescents who were recruited at two different centers in Brazil.

2. Materials and methods

2.1. Subjects

The children and adolescents who participated in this study were part of the '*High Risk Cohort Study for Psychiatric Disorders in Childhood*' (HRC, N = 2512 children; for a detailed description see Salum et al., 2013, 2014). This is a population-based sample of children from among the 9937 students of 57 public schools in two Brazilian cities: São Paulo (site 1) and Porto Alegre (site 2). The members of the HRC cohort were screened using a modified version of the Family History Screen (Weissman et al., 2000). Nine hundred fifty-eight subjects were randomly selected, and 1554 were selected based on their risk of developing psychiatric disorders (using the same criteria at the two sites; Salum et al., 2013, 2014); these individuals comprised the 2512 subjects of the HRC.

Among the total of 2512 volunteers, 741 subjects (and their parent/guardian) accepted the invitation for MRI scanning session. Functional MRI data were acquired from these subjects using the same acquisition protocol at the two sites. Eighty-nine participants were discarded due to an incomplete session, missing data, observable excessive motion (as identified by the system operator) or preprocessing errors (failure in registration to the template/atlas).

Thus, 652 remaining subjects were considered in the analyses of the current study. Because this was a community sample, participants were not discarded depending on IQ. The mean age (years) ± standard deviation (sd) of the participants was 10.81 ± 2.00 at site 1 and 10.58 ± 1.75 at site 2, with ages ranging from 7 to 15 years at both sites. Three hundred forty-one subjects were scanned at site 1 (165 males, 159 randomly selected) and 311 at site 2 (179 males, 139 randomly selected).

The local ethics committee approved this study. Written consent was obtained from all of the parents (or legal guardians), and verbal assent was obtained from all of the participants.

2.2. Assessment

IQ was estimated using the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children (in a household interview) and the approach of Tellegen and Briggs (1967). The socioeconomic status of the families was classified according to the Brazilian rating scale (ABIPEME, 2010; low = E and D classes; medium = C and B classes; high = A class):

The parents/caregivers filled out a Portuguese-translated version of the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) on the day of scanning. This assessment tool provided scores for psychopathological manifestations. The total CBCL score is a measure of overall psychopathology. It represents the sum of points for 112 CBCL items (0, 1 and 2 points per item), including the 8 syndromes described by the questionnaire (anxiety/depression, withdrawal/depression, somatic, rule breaking, aggression, social problems, thought problems and attention problems) as well as other symptoms not classified with any syndrome. The total CBCL score is a common measure of overall psychopathology. The analyses were carried out only for the total CBCL scores and not for scores on all the subscales to reduce the number of multiple comparisons and because the subscale scores are highly correlated with low specificity.