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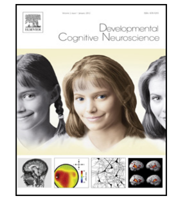

Intrinsic connectivity networks from childhood to late adolescence: Effects of age and sex

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ABSTRACT

There is limited evidence on the effects of age and sex on intrinsic connectivity of networks underlying cognition during childhood and adolescence. Independent component analysis was conducted in 113 subjects aged 7–18; the default mode, executive control, anterior salience, basal ganglia, language and visuospatial networks were identified. The effect of age was examined with multiple regression, while sex and 'age × sex' interactions were assessed by dividing the sample according to age (7–12 and 13–18 years). As age increased, connectivity in the dorsal and ventral default mode network became more anterior and posterior, respectively, while in the executive control network, connectivity increased within frontoparietal regions. The basal ganglia network showed increased engagement of striatum, thalami and precuneus. The anterior salience network showed greater connectivity in frontal areas and anterior cingulate, and less connectivity of orbitofrontal, middle cingulate and temporoparietal regions. The language network presented increased connectivity of inferior frontal and decreased connectivity within the right middle frontal and left inferior parietal cortices. The visuospatial network showed greater engagement of inferior parietal and frontal cortices. No effect of sex, nor age by sex interactions was observed. These findings provide evidence of strengthening of cortico-cortical and cortico-subcortical networks across childhood and adolescence.

1. Introduction

Brain functional activation during cognitive tasks requiring executive control, attention, timing and motivation increases over development (for review see Rubia, 2013). Less is known, however, regarding functional connectivity of resting-state networks (RSN) associated with these cognitive functions. Given that cognitive and motivational strategies undergo significant changes across childhood and adolescence (Berl et al., 2010; Blakemore and Choudhury, 2006; Steinberg, 2005) the study of RSN underlying memory, executive, language, emotional and higher order visuospatial processes during this age period is of particular interest. However, the assessment of cognitive RSN in children and/or adolescents has only been partially addressed so far, by studies that either focus on selected brain networks, namely frontoparietal networks such as the default mode and executive control networks (Sato et al., 2014; Supekar et al., 2010; Gao et al., 2009; Fair et al., 2008; Thomason et al., 2008) or on a limited age range (de Bie et al., 2012; Thomason et al., 2011; Jolles et al., 2011; Uddin et al., 2010; Stevens et al., 2009), with few exceptions. Two recent studies have assessed samples with a wider age range (van Duijvenvoorde et al., 2015; Fareri et al., 2015), although both have focused on subcortical connectivity. We are aware of no study so far assessing RSN such as the default mode, executive control, salience, cortico-subcortical, language and visuospatial networks, including subjects from childhood to late adolescence.

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The default mode network (DMN) is the most widely investigated RSN to date. It includes a set of brain regions involved in both cognitive (Buckner et al., 2008) and social cognition processes (Li et al., 2014), and in adult subjects it encompasses the posterior cingulate, precuneus, medial temporal lobe and medial prefrontal cortex. Two weeks after birth, a primitive DMN can be identified, while the posterior nodes of a more adult-like DMN can be distinguished by age two (Fransson et al., 2007; Gao et al., 2009). Several studies have suggested that the strength of connectivity between core regions of the DMN increases from childhood to late adolescence (Rubia, 2013; Fair et al., 2008; Power et al., 2010). The executive control network (ECN) includes the dorsolateral prefrontal cortex and the lateral posterior parietal cortex and is involved in cognitive flexibility and decision making (Seeley et al., 2007). In relation to the DMN, findings regarding age-related development of executive networks are less consistent, with some studies reporting different connectivity in children relative to adults (Barber et al., 2013; Jolles et al., 2011) and others finding little or no evidence of age effects (Vinette and Bray, 2015; Sato et al., 2014). De Bie and colleagues reported that in early childhood, components corresponding to the DMN and ECN appeared incomplete and fragmented (de Bie et al., 2012) in contrast to those related to basic motor function and sensory related processing, which had a functional organisation that was similar to mature adult patterns.

Another RSN identified in adults, which has been subject to more limited research in childhood and adolescence, is the anterior salience network, which encompasses the fronto-insular cortex and dorsal anterior cingulate, and has a role in emotional processing, homeostatic regulation and reward (Seeley et al., 2007). Fair and colleagues, employing graph-based measures, found that, in relation to adults, children showed incomplete connectivity between the dorsal anterior cingulate and medial superior frontal cortex, while connectivity was intermediate in adolescents (Fair et al., 2007). In addition, they demonstrated that during childhood, connectivity of the cingulo-opercular network was more closely connected to the frontoparietal network, and became segregated from this network with age. A later study by Uddin and colleagues also demonstrated differences in both structural and functional connectivity of the right fronto-insular cortex between children and adults (Uddin et al., 2011). A cortico-subcortical network involving the basal ganglia, engaging the inferior frontal gyri, striatum and thalami, has also been suggested to have a role in processing cognitive and motor information (Shirer et al., 2012; Tisch et al., 2004). van Duijvenvoorde and colleagues explored intrinsic connectivity in a sample of subjects from 8 to 25 years old in two main components: one frontoparietal and one subcortical component including the striatum, hipopocampus and the medial prefrontal cortex. In this latter component, the authors observed an age-related increase in connectivity in the anterior cingulate cortex but a decrease in the ventromedial prefrontal cortex (van Duijvenvoorde et al., 2015). Conversely, for the frontoparietal component they found an adolescent-specific increase in connectivity in the right anterior prefrontal cortex.

With regards language-related processing, two RSN have been previously identified in children aged 5–8: one including the auditory and opercular cortices, and the other encompassing fronto-temporal cortices and the posterior cingulate/precuneus (de Bie et al., 2012). The auditory network is considered to be involved in higher order functions related to language (Smith et al., 2009), and therefore has been studied as a component underlying language processing (Jolles et al., 2011). In a comparative study between children and young adults, Jolles and colleagues found greater functional connectivity of the left middle and inferior frontal cortices in younger subjects, denoting a more diffuse pattern of functional connectivity of this network in children (Jolles et al., 2011). To our knowledge, only one study so far, which was conducted in children, has identified a specific language network, separate from the auditory network and associated with a ventral attentional system (de Bie et al., 2012). However, this study did not examine age effects as it focused on a limited age range. Despite the fact that networks underlying the visual system have been characterised (de Bie et al., 2012; Jolles et al., 2011), to the best of our knowledge no study so far has explored the presence of a cognitive component underlying visuospatial processing, which has been suggested to rely on lateral frontal, inferior temporal and inferior parietal cortices (Shirer et al., 2012).

A source of discrepancy between studies is the distinct methods available to post-process resting-state functional magnetic resonance imaging (fMRI) (for review, see Margulies et al., 2010). For instance, both seed-based and graph-theoretical approaches require prior definition of regions of interest (ROI), and hence, decisions regarding specific ROI location, size and shape may influence results (Margulies et al., 2010). Conversely, ICA is an exploratory, data-driven approach that enables decomposition of the haemodynamic signal obtained with fMRI into brain regions showing synchronised patterns of signal fluctuation (Calhoun et al., 2008; Beckmann et al., 2005). This allows for the identification of spatial maps or components that are later studied independently. Furthermore, ICA is particularly good at removing motion artefacts, which can be particularly problematic in child fMRI studies (Uddin et al., 2010). It has been suggested that when motion is properly controlled, RSN of children and adolescents are robust and reliable, and may provide an accurate reflection of underlying neurobiology (Thomason et al., 2011).

Another issue that has received limited attention so far has been the investigation of sex effects on age-related changes in functional connectivity (Rubia, 2013). While sex-related differences have been observed in task-based fMRI studies undertaken in children and adolescents (for a review see Rubia, 2013), this evidence is more limited in studies assessing intrinsic connectivity. In a study using graph-based indices, boys showed greater global efficiency while girls presented a trend towards higher clustering in regions related to the default mode, language and vision systems (Wu et al., 2013). The authors concluded that boys may have a more optimal configuration for global processing, and girls for specialised processing; a distinction that could contribute to sex-related cognitive differences in children. However, we are unaware of any study so far examining the effect of sex on within-network connectivity during the resting state in youth.

Therefore, given the limited number of available studies examining a range of cognitive RSN in childhood and adolescence, we set out to assess six resting-state networks linked to cognitive and emotional processes: the default mode, executive control, anterior salience, cortico-subcortical or basal ganglia, language and visuospatial networks in a sample of healthy children and adolescents aged 7–18. In view of the abovementioned studies pointing to a progressive increase of within-network connectivity with age, and bearing in mind that performance in cognitive and emotional tasks underlying these networks shows age-related gains during childhood and adolescence, we expected to find age-related increases of intrinsic connectivity within the core regions of each network. A secondary objective was to study the effect of sex and the interaction between age and sex in intrinsic connectivity of these RSN. To this respect, and taking into account the following issues: first, cognitive performance differences have been observed between males and females (Blakemore, 2012), second, task-based fMRI studies have shown sex-related differences in tasks of executive function, language and visuospatial processing (Boghi et al., 2006; Bell et al., 2006; Halari et al., 2006) and third, previous literature also suggests sex-related differences in networks underlying default mode, language, and visual processes (Wu et al., 2013); we expected to observe different patterns of functional connectivity between