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Research Report

Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders☆

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ARTICLE INFO

Article history:
Accepted 21 November 2009
Available online 11 December 2009

Keywords:
Functional Magnetic Resonance Imaging, development
Symptom severity
Asperger's syndrome
Pervasive developmental disorder not otherwise specified

ABSTRACT

Autism spectrum disorders (ASD) are associated with disturbances of neural connectivity. Functional connectivity between neural structures is typically examined within the context of a cognitive task, but also exists in the absence of a task (i.e., "rest"). Connectivity during rest is particularly active in a set of structures called the default network, which includes the posterior cingulate cortex (PCC), retrosplenial cortex, lateral parietal cortex/angular gyrus, medial prefrontal cortex, superior frontal gyrus, temporal lobe, and parahippocampal gyrus. We previously reported that adults with ASD relative to controls show areas of stronger and weaker connectivity within the default network. The objective of the present study was to examine the default network in adolescents with ASD. Sixteen adolescents with ASD and 15 controls participated in a functional MRI study. Functional connectivity was examined between a PCC seed and other areas of the default network. Both groups showed connectivity in the default network. Relative to controls, adolescents with ASD showed widespread weaker connectivity in nine of the eleven areas of the default network. Moreover, an analysis of symptom severity indicated that poorer social skills and increases in restricted and repetitive behaviors and interests correlated with weaker connectivity, whereas poorer verbal and non-verbal communication correlated with stronger connectivity in multiple areas of the default network. These findings indicate that adolescents with ASD show weaker connectivity in the default network than previously reported in adults with ASD. The findings also show that weaker connectivity within the default network is associated with specific impairments in ASD.

☆ Data from this study were presented at the International Meeting for Autism Research, Chicago, IL, May 2009.
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doi:10.1016/j.brainres.2009.11.057

1. Introduction

Three core features define autism spectrum disorders (ASD): impairments in social functioning, difficulties in communication, and restricted and repetitive behaviors and/or interests (APA 1994). Converging lines of evidence indicate that ASD is a disorder of brain connectivity (Belmonte et al. 2004; Just et al. 2007). First, individuals with ASD show marked disturbances in cortical organization as evidenced by narrower and more densely packed columns of neuronal cells (Casanova et al. 2006). These morphological differences suggest an alteration in structural connectivity which could in turn have an impact on the functional connectivity between brain structures. Second, individuals with ASD have increases in white matter volume that are present in outer zones and not inner zones of white matter, such as the corpus callosum (Herbert et al. 2004). This suggests that individuals with ASD have a greater number of short to medium range intrahemispheric connections and fewer longer range interhemispheric connections (Herbert et al. 2003; Herbert et al. 2004). In addition, diffusion tensor imaging (DTI) techniques show that white matter integrity is compromised in ASD (Alexander et al. 2007; Barnea-Goraly et al. 2004). Third, individuals with ASD have abnormalities in functional connectivity within regions of the brain. Specifically, some studies found that individuals with ASD, relative to controls, show stronger connectivity (Mizuno et al. 2006; Noonan et al. 2009; Turner et al. 2006) and others report weaker connectivity (Just et al. 2007; Kana et al. 2006; Kleinhans et al. 2008; Koshino et al. 2008; Villalobos et al. 2005; Welchew et al. 2005; Wicker et al. 2008). Thus, both structural and functional evidence suggest that there is profound disruption in brain connectivity in ASD.

The functional connectivity studies reported above were carried out in the context of a cognitive task. However, the brain is highly active even when participants are not engaged in any task (i.e., at rest). The default network is a set of structures that is known to be particularly active when participants are at rest (Fox et al. 2005; Greicius et al. 2003; Shulman et al. 1997). The brain regions that form the default network are the posterior cingulate cortex (PCC), retrosplenial, lateral parietal/angular gyrus, medial prefrontal cortex, superior frontal gyrus, regions of the temporal lobe, and finally the parahippocampal gyrus (Fox et al. 2005; Greicius et al. 2003; Shulman et al. 1997). Because of the tremendous amount of energy that this activation consumes (Raichle and Mintun 2006), many have speculated that the default network's function may extend beyond thought processes and encompass the role of maintaining homeostasis between excitatory and inhibitory neuronal responses (Biswal et al. 1995; Laughlin and Sejnowski 2003). Others have argued that the default network is active when contemplating scenarios and events, mind wandering, or lower-level observations of the individual's external surroundings (Buckner et al. 2008; Christoff et al. 2009; Mason et al. 2007; Raichle and Snyder 2007). Thus, although the precise role of the default network remains unclear, investigators suggest that it may be involved in fundamental aspects of nervous system functioning (Raichle and Snyder 2007).

The majority of default network studies have focused on typical adults (Fox et al. 2005; Greicius et al. 2003; Greicius et al. 2009). Recently, investigations have examined functional connectivity within the default network in individuals with ASD (Cherkassky et al. 2006; Kennedy and Courchesne 2008; Monk et al. 2009). The results of these three studies are not entirely consistent. In the first study, Cherkassky et al. (2006) found broad-based weaker connectivity. For the second study, Kennedy and Courchesne (2008) identified selective areas of reduced connectivity. Finally, in the third study, we found weaker connectivity between the PCC and the superior frontal gyrus and stronger connectivity between the PCC and two other regions in the default network (Monk et al. 2009). The three studies employed different data collection and analytic procedures, which might explain the differential findings. In addition, the age ranges in each study was very broad and this might contribute to inconsistent findings. In the present study, we closely followed the procedures of our study of adults and we also selectively examined an adolescent age group. No known published study has focused solely on the default network in adolescents with ASD.

Dramatic anatomical changes occur within the brain during adolescence (Giedd 2008; Sowell et al. 2003). These

Table 1 – Subject characteristics.

	ASD	Control	*t* (*df*)	*p* value
Age, mean (SD)	15 (1.45)	16 (1.44)	1.21 (29)	0.24
Age range	13 - 17	13 - 18		
Male to female ratio	14:2	14:1		
Verbal cognitive functioning mean (SD)	114 (18.58)	113 (14.10)	0.21 (29)	0.83
Non-verbal cognitive functioning mean (SD)	117 (13.82)	106 (12.53)	2.38 (29)	0.024
Handedness left to right ratio	1:15	2:13		
Social responsiveness scale (SD)	75 (10.41)	45 (8.10)	8.81	<0.001
ADI-R social total (SD)	19 (6.22)			
ADI-R social current (SD)	8.62 (4.21)			
ADI-R verbal communication total (SD)	16 (3.66)			
ADI-R verbal communication current (SD)	9 (3.72)			
ADI-R non-verbal communication total (SD)	9 (2.67)			
ADI-R non-verbal communication current (SD)	4 (2.66)			
ADI-R restricted, repetitive behaviors total (SD)	6 (2.78)			
ADI-R restricted, repetitive behaviors current (SD)	5 (2.06)			