Default Mode Network in Childhood Autism: Posteromedial Cortex Heterogeneity and Relationship with Social Deficits

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Background: The default mode network (DMN), a brain system anchored in the posteromedial cortex, has been identified as underconnected in adults with autism spectrum disorder (ASD). However, to date there have been no attempts to characterize this network and its involvement in mediating social deficits in children with ASD. Furthermore, the functionally heterogeneous profile of the posteromedial cortex raises questions regarding how altered connectivity manifests in specific functional modules within this brain region in children with ASD.

Methods: Resting-state functional magnetic resonance imaging and an anatomically informed approach were used to investigate the functional connectivity of the DMN in 20 children with ASD and 19 age-, gender-, and IQ-matched typically developing (TD) children. Multivariate regression analyses were used to test whether altered patterns of connectivity are predictive of social impairment severity.

Results: Compared with TD children, children with ASD demonstrated hyperconnectivity of the posterior cingulate and retrosplenial cortices with predominately medial and anterolateral temporal cortex. In contrast, the precuneus in ASD children demonstrated hypoconnectivity with visual cortex, basal ganglia, and locally within the posteromedial cortex. Aberrant posterior cingulate cortex hyperconnectivity was linked with severity of social impairments in ASD, whereas precuneus hypoconnectivity was unrelated to social deficits. Consistent with previous work in healthy adults, a functionally heterogeneous profile of connectivity within the posteromedial cortex in both TD and ASD children was observed.

Conclusions: This work links hyperconnectivity of DMN-related circuits to the core social deficits in young children with ASD and highlights fundamental aspects of posteromedial cortex heterogeneity.

Key Words: Autism spectrum disorders, default mode network, functional connectivity, posterior cingulate cortex, posteromedial cortex, resting-state fMRI

Autism spectrum disorder (ASD) is characterized by profound deficits in social behaviors and affects 1 in 88 children (1). These impairments encompass multiple forms of social cognition, including both interpersonal social processes and self-referential thought (2,3). These social and self-referential cognitive processes have been linked with a pair of cortical midline brain regions, the ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC), which serve as hubs of the default mode network (DMN) (4,5). The VMPFC is involved in mentalizing or theory of mind, person perception, and representation of self-knowledge (6). The PCC, with its strong connections to the medial temporal lobe, has been linked with episodic and autobiographical memory retrieval (7), visuospatial mental imagery, prospection, and self-projection (8). Although the DMN is typically attenuated in the context of task performance (5), regions belonging to this network are often engaged during social tasks (9,10). This overlap between the DMN and nodes of the "social brain" has led to the proposal that the DMN is strongly associated with the social cognition (11–13).

Motivated by the potential link between DMN function and social deficits in ASD, several studies have investigated DMN activation and connectivity in adults and adolescents with the disorder (14–18). Task-induced "deactivations" of the anterior midline DMN node have been reported to be absent in adults with ASD relative to control subjects (16). Subsequent resting-state functional magnetic resonance imaging (fMRI) studies have identified altered DMN connectivity in adults and adolescents with ASD using both region of interest (ROI) and independent component analysis approaches (14–18). These studies collectively suggest that functional connectivity of the DMN is reduced in adults and adolescents with the disorder, with the exception of one investigation that identified a more complex pattern of both reduced and increased connectivity (17). At present, however, there are no published studies examining intrinsic functional connectivity of the DMN in childhood ASD. The only comparable study is a recently published article by Rudie and colleagues reporting reduced connectivity between the PCC and medial prefrontal cortex in a mixed group of children and adolescents with ASD (19). We recently found that, contrary to what has been reported in adults and adolescents, childhood ASD may be characterized by greater instances of hyperconnectivity than hypoconnectivity (20,21). This underscores the need for studying age groups that are tightly restricted, rather than those that may encompass several distinct developmental stages.

Several critical questions regarding the nature of DMN integrity in ASD remain unaddressed. First, because ASD is a disorder with early-life onset and variable developmental trajectory, it is important to understand how DMN connectivity manifests in

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young children with the disorder. Currently little is known regarding network development in ASD. However, recent work examining the structural and functional connectivity within the DMN in healthy children and adults (22–24) has highlighted significant changes in this network with development. Therefore, findings in adolescents and adults with ASD may not be directly relevant to understanding the DMN in childhood ASD. Second, considering recent findings of posteromedial cortex (PMC) heterogeneity (25), specifically between the precuneus and the more ventral posterior cingulate and retrosplenial cortices, it is possible that previous studies have missed critical nodes of the DMN, thereby potentially misrepresenting the network. Third, it is not known whether aberrant DMN-related circuits are associated with social behavioral deficits in children with ASD.

Inadequate attention to the neuroanatomy of the PMC is a potential limitation of previous clinical studies of the DMN. Anatomically, the DMN consists of prominent nodes in the PCC, retrosplenial cortex (RSC), angular gyrus, VMPFC, and both anterolateral and medial aspects of the temporal lobe (4,11). The PMC collectively encompasses the PCC, RSC, and precuneus (26) (Figure 1A). Converging evidence from tracing studies in nonhuman primates (27,28) and resting-state fMRI connectivity studies in both adult humans and primates (25) have revealed that the PCC, RSC, and precuneus, although interconnected, each demonstrate unique patterns of anatomic and functional connectivity, suggesting the presence of distinct functional modules within the PMC (26). Importantly, these studies suggest that both the PCC and RSC have robust anatomic and functional connections with other key nodes of the DMN, particularly with VMPFC and the medial temporal lobe areas (25,28,29) (Figure 1C,D). In contrast, the precuneus has stronger connectivity with dorsolateral prefrontal, supplementary motor, and occipital regions (25) (Figure 1E). On the basis of these differences in connectivity and neuroanatomy of PMC subregions, it has been proposed that the ventral PMC (consisting of the PCC and RSC), rather than the neighboring precuneus (11,25), is the core posterior midline node of the DMN.

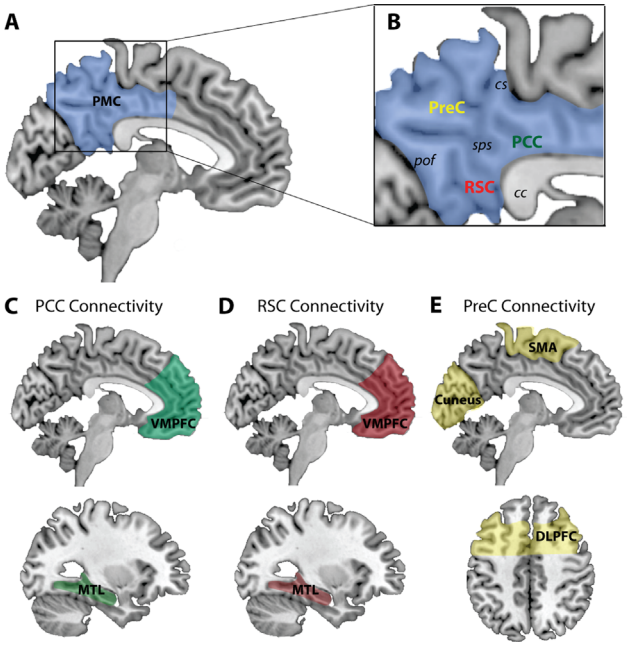

Figure 1. Summary of posteromedial cortex (PMC) anatomy and connectivity based on the work of Margulies and colleagues (25). **(A)** The PMC encompasses the posterior cingulate cortex (PCC), retrosplenial cortex (RSC), and precuneus (PreC) **(B)**. Ventral aspects of the PMC, including the PCC **(C)** and RSC **(D)**, have strong connections with medial temporal lobe (MTL) and ventromedial prefrontal cortex (VMPFC). The PreC **(E)** has stronger connections with dorsolateral prefrontal cortex (DLPFC), supplementary motor (SMA), and occipital regions. cc, corpus callosum; cs, cingulate sulcus; pof, parieto-occipital sulcus; sps, subparietal sulcus.

Despite anatomic and functional evidence suggesting that the ventral PMC is the most representative posteromedial cortical node of the DMN, studies of putative DMN connectivity have not clearly delineated these nodes from dorsal regions within the PMC. DMN studies have reported atypical functional connectivity in both adolescents (18) and adults (17,30) with ASD using identical ROI coordinates as starting points for functional connectivity analyses. Curiously, in both cases, the seed coordinates used in these connectivity analyses were reported as selected from a previous meta-analysis of task-deactivated regions (31,32) and correspond more closely to the ventral precuneus, rather than the PCC proper. In light of this recent literature demonstrating functional heterogeneity within the PMC in normal healthy adults (33,34) and evidence for robust PCC functional and anatomic connectivity with core DMN components (25,28,29), DMN connectivity in ASD should be reassessed.

The current study addresses these open questions regarding the nature of DMN connectivity in childhood ASD and provides insights into the aberrant functional organization of brain systems mediating social cognitive deficits in ASD. We use precisely defined ROIs in the PCC, RSC, and precuneus, encompassing the dorsal and ventral aspects of the PMC, to assess DMN connectivity in children with ASD. Additionally, we examine the relationship between aberrant DMN connectivity and social behavioral deficits in childhood ASD.

Methods and Materials

Participants

The Stanford University Institutional Review Board approved all study protocols. Children were recruited from schools and clinics near Stanford University. All children were required to have a full-scale IQ greater than 70, as measured by the Wechsler Abbreviated Scale of Intelligence. A group of 20 children aged 7 to 12 years who met criteria for ASD on the Autism Diagnostic Observation Schedule (ADOS) (35) or criteria for autism on the Autism Diagnostic Interview-Revised (ADI-R) (36) were included in the study. Participants were matched on full-scale IQ, age, and gender with a group of 20 typically developing (TD) children aged 7 to 12 years (Table 1). Table S1 in Supplement 1 contains additional clinically relevant information on the ASD sample. One TD participant was excluded from the analysis because of issues related to data quality. The final group consisted of 20 children with ASD and 19 TD children.

Data Acquisition

Functional images were acquired on a 3T GE Signa scanner (General Electric, Milwaukee, Wisconsin) using a custom-built head coil. For the resting state fMRI scan, subjects were instructed to keep their eyes closed and try not to move for the duration of the 6-min scan. Head movement was further minimized by memory foam pillows placed around the participant's head. Twenty-nine axial slices (4.0 mm thickness, .5-mm