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 medial temporal lobe systems, 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 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 the 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.

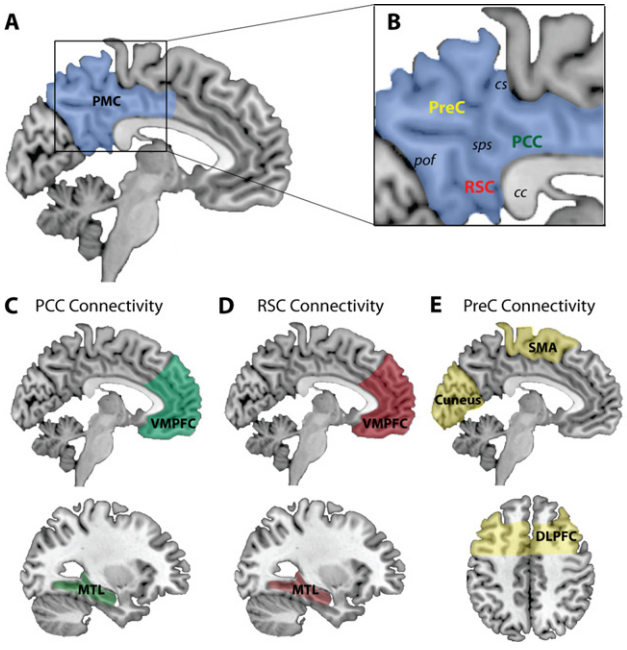


Figure 1. Summary of posteromedial cortex (PMC) anatomy and connectivity based on the work of Margulies and colleagues (25). **(A)** The PMC encompasses the posterior cingulate cortex (PCC), retrosplenial cortex (RSC), and precuneus (PreC) **(B)**. Ventral aspects of the PMC, including the PCC **(C)** 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

Table 1. Participant Demographics

	ASD Children ($n = 20$)	TD Children ($n = 19$)
Age	9.96 ± 1.59 (7–12 years)	9.88 ± 1.61 (7–12 years)
Gender	16 M, 4 F	15 M, 4 F
Full-Scale IQ	112.6 ± 17.8	112.2 ± 15.8
ADOS Social	8.2 ± 2.1	—
ADOS Communication	3.6 ± 1.5	—
ADI Social	20.4 ± 5.4	—
ADI Communication	15.9 ± 5.1	—
ADI Repetitive Behaviors	5.8 ± 2.5	—
Movement (RMS)	.33 ± .23 mm	.30 ± .24 mm

ADOS, Autism Diagnostic Observation Schedule; ADI, Autism Diagnostic Interview; ASD, autism spectrum disorder; F, female; M, male; RMS, root mean square; TD, typically developing.

skip) parallel to the anterior commissure–posterior commissure line and covering the whole brain were imaged using a T2*-weighted gradient echo spiral in-out pulse sequence (37) with the following parameters: repetition time = 2000 msec, echo time = 30 msec, flip angle = 80°, 1 interleave. The field of view was 20 cm, and the matrix size was 64 × 64, providing an in-plane spatial resolution of 3.125 mm. Reduction of blurring and signal loss arising from field inhomogeneities was accomplished by using an automated high-order shimming method before data acquisition.

fMRI Data Analysis

fMRI Preprocessing. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (37). Functional MRI data were then analyzed using SPM8 analysis software (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to correct for motion, corrected for errors in slice timing, spatially transformed to standard stereotaxic space (based on the Montreal Neurological Institute [MNI] coordinate system), resampled every 2 mm using sinc interpolation, and smoothed with a 6-mm full-width at half-maximum Gaussian kernel to decrease spatial noise before statistical analysis. Translational movement in millimeters (x, y, z) and rotational motion in degrees (pitch, roll, yaw) was calculated based on the SPM8 parameters for motion correction of the functional images in each subject.

ROI Selection. ROI coordinates were selected from a seminal study by Margulies and colleagues that identified heterogeneous patterns of intrinsic brain connectivity across the PMC in both neurotypical adults and nonhuman primates (25). We included coordinates corresponding to the PCC ROI (MNI coordinates x = −2, y = −36, z = 35), RSC (MNI coordinates x = −3, y = −45, z = 23) and precuneus (MNI coordinates x = −2, y = −51, z = 41). Each ROI consisted of a sphere with a 6mm radius. The precuneus seed used in our study overlaps closely with the ventral precuneus seed (MNI coordinates x = −5, y = −53, z = 41) used in previous reports investigating DMN connectivity in adults and adolescents with ASD (17,18,30).

Functional Connectivity Analysis. For each ROI, a resting-state time series was extracted by averaging the time series of all voxels within it. The resulting ROI time series was then used as a covariate of interest in a linear regression whole-brain analysis. A global time series, computed across all brain voxels, along with six motion parameters, were used as additional covariates to remove confounding effects of physiologic noise and participant movement (see Figure S3 in Supplement 1 for group differences after alternative cerebrospinal fluid and white matter regression analysis). Data was bandpass filtered (low pass .008 Hz, high pass .1 Hz). Group-level and between ROI connectivity maps were generated using *t* tests of individual functional connectivity contrast images. Between-group and between-ROI functional connectivity maps were thresholded at $p < .01$ for height and a family wise error corrected cluster extent $p < .05$ (corresponding to a minimum cluster size of 100 voxels). Combined group (ASD and TD) functional connectivity maps for each ROI were thresholded at family wise error $p < .0001$ height and a 100-voxel cluster extent. To demonstrate the robustness of our findings against potential movement confounds, we performed several analyses (see Tables S3 and S4 in Supplement 1), including the "scrubbing procedure" proposed by Power and colleagues (see Figure S2 in Supplement 1).

Multivariate Regression Analysis of Connectivity and Clinical Symptoms. To investigate whether connectivity between PMC ROIs and their associated group difference targets predicted social symptom severity in ASD, we used a sparse regression algorithm (38). The sparse regression algorithm identifies connections that predict symptom severity by modeling the relationship between the dependent variable (score on specified domain of ADOS/ADI-R) and the independent variables (strength of connectivity between seed ROI and peak coordinates generated from group differences). See Supplement 1 for a detailed description of the sparse regression analysis.

Results

Differential Connectivity of Dorsal and Ventral Posteromedial Cortex Subregions

We first examined the functional connectivity patterns of the PCC, RSC, and precuneus in the combined group ($n = 39$) of children. Figure 2 demonstrates findings of heterogeneity between dorsal (precuneus) and ventral (PCC/RSC) aspects of the PMC. Both the PCC and RSC demonstrated stronger connections with VMPFC and medial temporal lobe DMN nodes compared with the precuneus (Figure 2A–2D). In contrast, the precuneus was most strongly connected with the supplementary motor area (Figure 2E), dorsolateral prefrontal cortex (Figure 2F), anterior inferior parietal lobule (Figure 2G), and dorsal aspects of the medial prefrontal cortex (Figure 2H). See Figure S1 in Supplement 1 for within-group connectivity maps of the PCC, RSC, and precuneus. Information regarding degree of functional unity within the PMC in ASD and TD children is demonstrated in Figure S4 in Supplement 1.

Posterior Cingulate Cortex Is Hyperconnected in Children with ASD

Relative to the TD group, children with ASD showed greater functional connectivity of the PCC with several brain regions (Figure 3A). PCC hyperconnectivity in children with ASD was detected in the anterolateral temporal cortex (middle and inferior temporal gyrus), lingual gyrus, posterior parahippocampal gyrus, temporal pole, and both the entorhinal and perirhinal cortex within the anterior aspect of the medial temporal lobe (MNI coordinates of target regions for each ROI are in Table S2 in Supplement 1). There were no brain regions that showed decreased PCC connectivity in the ASD group compared to the TD group.

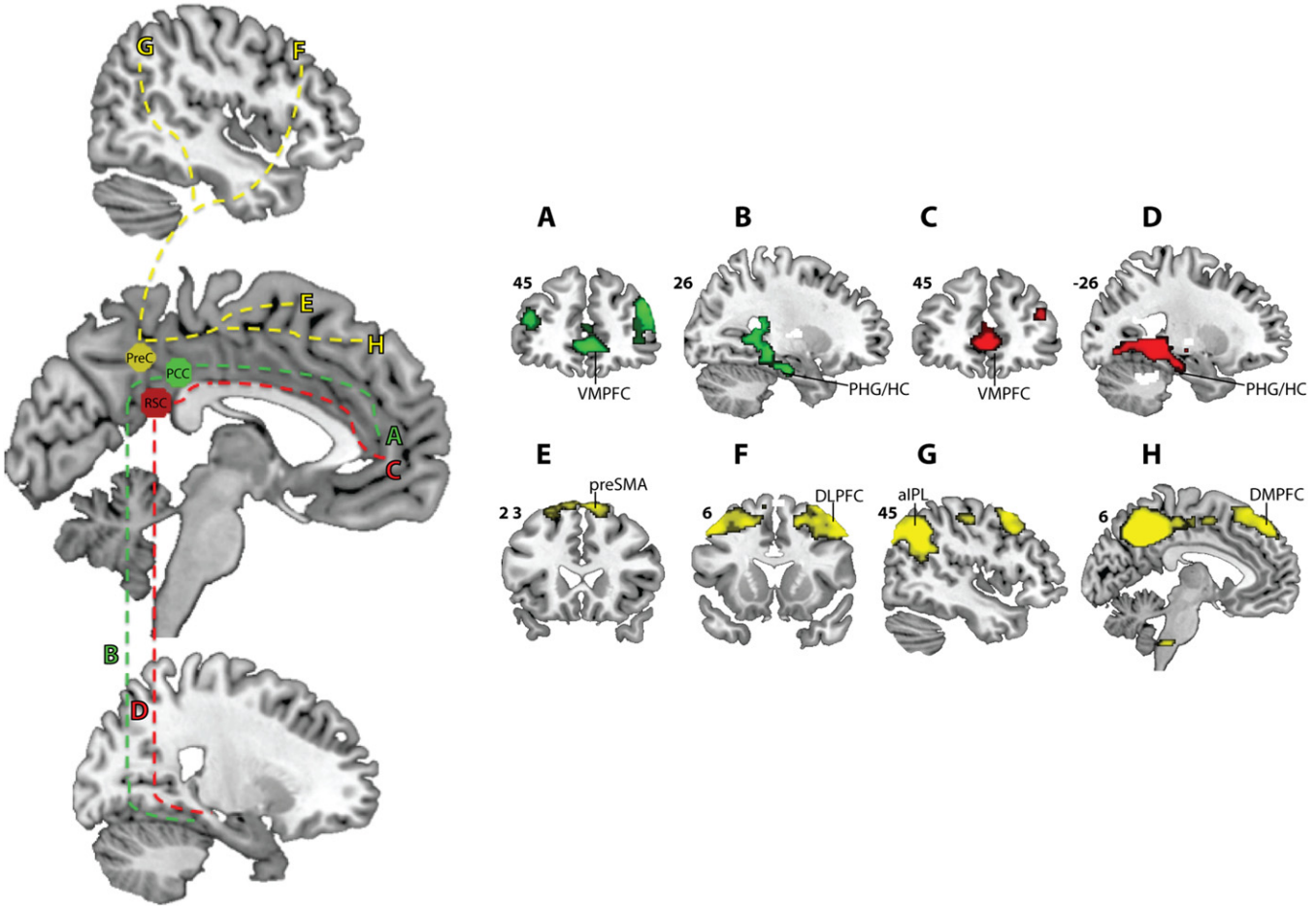


Figure 2. Posteromedial cortex ventral and dorsal subregions demonstrate differential profiles of connectivity. Posterior cingulate and retrosplenial cortices demonstrated stronger connections with ventromedial prefrontal cortex (VMPFC) and medial temporal lobe default mode network (DMN) nodes compared with the precuneus **(A–D)**. The precuneus was most strongly connected with the presupplementary motor area (preSMA) **(E)**, dorsolateral prefrontal cortex (DLPFC) **(F)**, anterior inferior parietal lobule (aIPL) **(G)**, and dorsomedial aspects of the medial prefrontal cortex (DMPFC) **(H)**. HC, hippocampus, PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; PreC, precuneus; RSC, retrosplenial cortex.

Retrosplenial Cortex Is Hyperconnected in Children with ASD

Similar to findings revealed by the PCC ROI, children with ASD also demonstrated increased RSC functional connectivity with several brain regions (Figure 3B). RSC hyperconnectivity in children with ASD was detected in the inferior frontal gyrus, middle frontal gyrus, dorsomedial prefrontal cortex, posterior insular cortex, lingual gyrus, posterior parahippocampal gyrus, temporal pole, posterior superior temporal sulcus, and anterior supramarginal gyrus. There were no brain regions that showed reduced RSC connectivity in the ASD group compared to the TD group.

Precuneus Is Hypoconnected in Children with ASD

Relative to the TD group, children with ASD showed reduced connectivity of the precuneus locally within the PMC (PCC, RSC, and precuneus), cuneus, as well as with caudate and dorsal medial thalamic nuclei (Figure 3C). There were no brain regions that showed greater precuneus connectivity in the ASD group compared with the TD group.

Relation Between Altered DMN Connectivity and Social Impairments in Children with ASD

To examine how aberrant DMN-related circuits are related to social deficits in children with ASD, we used a multivariate regression analysis (Figure 4). Functional connectivity between each PMC ROI and associated hyper- and hypoconnected target regions were regressed against scores from the social domain of the ADOS. Significant correlations were found between PCC seed targets in the right posterior parahippocampal gyrus, left temporal pole, and left lingual gyrus ($R^2 = .57$, $p < .009$). No significant relations were observed for target regions identified by the RSC ($R^2 = .17$) or the precuneus ($R^2 = .04$).

Discussion

The critical issue of how DMN connectivity manifests in young children with ASD and how aberrant connectivity of this network is linked with social behavioral deficits is an open question. Previous investigations of DMN connectivity in ASD have not explored the unique connectivity patterns across PMC modules (25). A novel finding from our study is that the ventral PMC, comprising the PCC and RSC, demonstrated hyperconnected effects, whereas the precuneus was hypoconnected in children with ASD. These findings highlight the importance of precise anatomic methods and the necessity for studying functional brain connectivity in ASD at earlier time points in development.

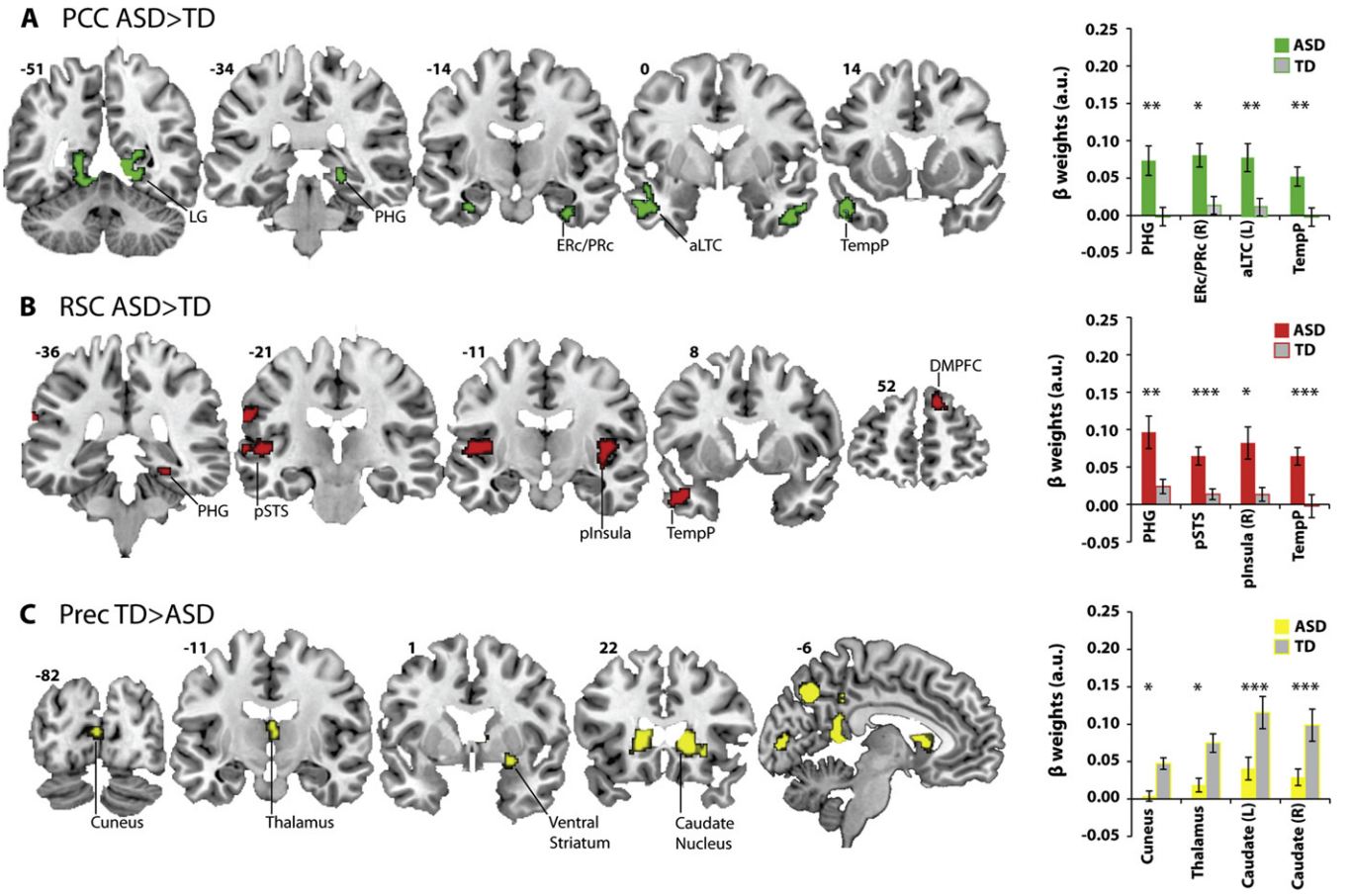


Figure 3. Children with autism spectrum disorder (ASD) demonstrated both hyperconnectivity (ASD > typically developing [TD] children) and hypoconnectivity (TD > ASD) of posteromedial cortex subregions. The posterior cingulate cortex (PCC) and retrosplenial cortex (RSC) revealed ASD hyperconnectivity, whereas the precuneus (PreC) demonstrated ASD hypoconnectivity. *$p < .01$, **$p < .005$, ***$p < .001$. aLTC, anterolateral temporal cortex; DMPFC, dorsomedial prefrontal cortex; ERc, entorhinal cortex; LG, lingual gyrus; PHG, parahippocampal gyrus; pInsula, posterior insular cortex; PRc, perirhinal cortex; pSTS, posterior superior temporal sulcus; TempP, temporal pole.

Studies of typical development suggest that functional brain maturation involves simultaneous pruning of local connectivity and strengthening of long-range connectivity with age (39). Although the underconnectivity theory of ASD posits that the disorder can be attributed to reduced synchrony between anterior and posterior brain regions (40), the mixed literature on brain connectivity in ASD has yet to converge on findings obtained from different methods and periods of development (41). Our findings, which oppose canonical brain connectivity theories in adults and adolescents with ASD, highlight the critical importance of studying ASD at earlier time points.

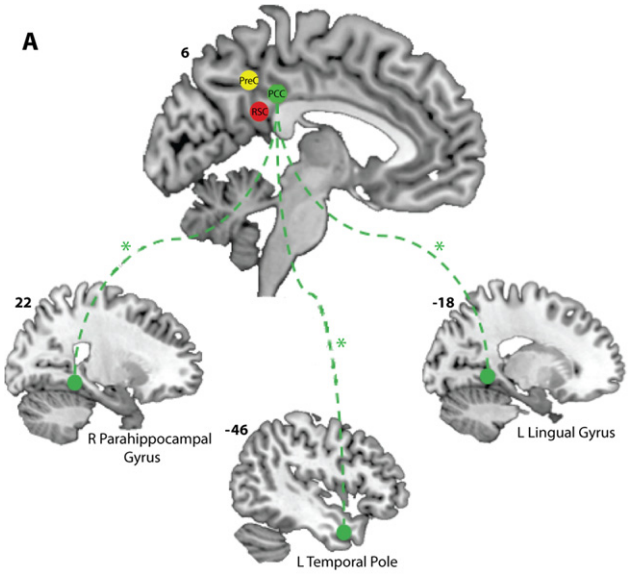
Posteromedial Cortex Is Functionally Heterogeneous Early in Development

Previous work in adults and convergent findings from the macaque tracing literature have identified a robust differentiation between the connectivity of ventral and dorsal aspects of the PMC (26,28). Consistent with this literature, we found that in both ASD and TD children, ventral aspects of the PMC were most tightly connected with key medial prefrontal and temporal DMN nodes. In contrast, the precuneus was more strongly connected with anterior inferior parietal, dorsolateral, and dorsomedial prefrontal regions relative to the PCC and RSC. These findings suggest that, as in adults, the PMC has a heterogeneous profile of connectivity in children and that anatomically distinct ROIs can be used to map DMN connectivity more precisely in both normative and atypical development.

DMN Is Hyperconnected in Children with ASD

We found that the PCC and RSC demonstrated stronger connectivity in children with ASD compared with TD children. Target brain regions where such differences were noted included several regions belonging to the DMN, including the entorhinal and perirhinal cortex in the anterior medial temporal lobe, the parahippocampal gyrus in the posterior aspect of the medial temporal lobe, anterolateral temporal cortex, and the temporal pole. Although these medial and anterolateral temporal lobe nodes are less often identified as belonging to this network, several studies have highlighted the role of these regions within the DMN (11,42).

Our findings support an emerging view that the "underconnectivity" theory of ASD may be too simplistic and that numerous variables including point of development, anatomic specificity, and choice of analytic technique (43) may preclude a single global theory of brain connectivity in ASD. This work raises additional questions to be addressed by future studies regarding the developmental trajectory of the DMN, along with other brain systems, in ASD. We are aware of no



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Seed ROI	Connections Predictive of ADOS Social Score	R2	*p*
Posterior Cingulate Cortex	PHG, TempP, LG	0.57	0.009
Retrosplenial Cortex	-	0.17	n.s.
Precuneus	-	0.04	n.s.

Figure 4. Posterior cingulate cortex hyperconnectivity predicts social deficits in autism spectrum disorder. Connections between the posterior cingulate cortex (PCC) seed region of interest (ROI) and associated autism spectrum disorder hyperconnected target regions were found to be predictive of social impairments as measured by the Autism Diagnostic Observation Schedule (ADOS) social subscale **(A)**. No such significant relationships were demonstrated by the retrosplenial cortex (RSC) and precuneus (PreC) **(B)**. *Significant. L, left; LG, lingual gyrus; n.s., not significant; PHG, parahippocampal gyrus; R, right; TempP, temporal pole.

existing studies, either cross-sectional or longitudinal, that examine the development of brain connectivity in ASD and suggest that this is an important direction for future work. We speculate that our findings of ASD hyperconnectivity in childhood may represent a stage before a critical point in development, perhaps puberty, in which unknown mechanisms may facilitate a transition from hyperconnectivity to the reduced connectivity commonly observed in adolescents and adults with the disorder. In other work, we have shown that the ASD brain in childhood may be characterized by greater instances of hyperconnectivity than hypoconnectivity (20).

However, considering the complex ASD behavioral phenotype, it is likely that the disorder is characterized by instances of both hyper- and hypoconnectivity, as demonstrated by this analysis. We speculate that this a complex network phenomena arising from the presence of aberrant local circuits in some brain regions but not others. Multivariate pattern analysis of structural MRI data has revealed that children and adolescents with ASD could be discriminated from typically developing individuals with 92% accuracy based on gray matter in the PCC (3). Furthermore, a recent postmortem study identified altered PCC cytoarchitecture as a characteristic of brains of individuals with autism (44). Taken together, these findings suggest that loci of structural disorganization may underlie specific altered functional circuits in ASD.

Precuneus Is Hypoconnected in Children with ASD

Children with ASD showed decreased functional connectivity of the precuneus locally within the PMC, cuneus, caudate nuclei, and the medial dorsal thalamic nucleus. Our findings of precuneus hypoconnectivity are consistent with previous literature reporting "underconnectivity" of this brain region in adults and adolescents with ASD (17,18,30). However, these previous studies identified the medial prefrontal cortex and temporal lobe regions as underconnected with the precuneus in adults with ASD, whereas in the present study underconnectivity of the precuneus in children was seen most robustly with the caudate nucleus. Although precuneus underconnectivity in the present study implicates different targets, the general finding of precuneus underconnectivity in children with ASD suggests a similar direction of effects.

DMN Hyperconnectivity and Social Deficits in Childhood ASD

Hyperconnectivity between the PCC and select targets, including the temporal pole, posterior parahippocampal gyrus, and lingual gyrus was associated with increased social behavioral impairments as measured by the ADOS diagnostic assessment ($R^2 = .57$, $p < .009$). Social behavioral deficits in the ASD group were specifically linked to aberrant connectivity of the PCC. No significant relationships were found for atypical connectivity patterns associated with the RSC or the precuneus. Because the core regions of the DMN participate in cognitive functions that are of a social nature (9), it is plausible that altered connectivity of this system may contribute to deficits in the social domain in ASD. We propose that this hyperconnectivity may prevent task-relevant communication between the nodes of the DMN.

The temporal pole has been linked with socioemotional processes including theory of mind and face recognition (6,45). Bilateral temporal pole lesions in primates have demonstrated symptoms similar to those seen in Klüver-Bucy syndrome, a disorder characterized by social withdrawal and blunted affect (45). Additional work observing strong connections between the temporal pole and the VMPFC, PCC/RSC, and parahippocampal gyrus has suggested that these regions collectively are involved with emotional or self-referential processes (46). The posterior parahippocampal gyrus also demonstrated hyperconnectivity related to social impairment severity. The parahippocampal gyrus has also been variably implicated as part of the "medial temporal lobe subsystem" of the DMN (4) and along with the temporal pole has been proposed to be functionally linked with autobiographical memory and semantic memory (47,48), as well as making decisions about one's own personal future (42). It has been proposed that these regions comprise a memory system fundamentally linked with social cognition (48). Taken together, our findings suggest that PCC hyperconnectivity with DMN-related circuits not only reflects atypical interactions within one or more networks important for inter- and intrapersonal social cognitive processes but is also associated with severity of social impairment in children with ASD.

Several limitations of our work must be taken into consideration and addressed by future studies. First, at present no comparable studies have investigated PMC heterogeneity in children of the age group we are studying, and therefore the ROI coordinates used here were defined in adults. However, because the majority of cerebral volume development seems to occur before age 6 and become relatively stable by age 10 (49), this issue of using ROI coordinates from an adult study is likely to be minimal. An alternative approach would be to use an age-specific template, but this practice is more common with participants below the age of four (50). Future work should also control for potential effects of medication, the presence of comorbid conditions (e.g., ADHD and anxiety), and different

genotypes that may contribute to the variable findings of brain connectivity in ASD (19).

Despite these limitations our findings of both hypo- and hyperconnectivity within PMC regions underscore the importance of "tedious anatomy" (51) and highlight the need for more anatomic precision in functional connectivity studies of the DMN in ASD. Here we show that subtle but salient differences in anatomy reveal different patterns of altered brain connectivity in ASD. Taken together, our findings of differential patterns of connectivity within the PMC in children with ASD highlight the importance of addressing heterogeneity within neighboring cortical regions and show for the first time that social impairments in childhood ASD are linked to hyperconnectivity of the DMN.

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Supplementary material cited in this article is available online.

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