

# Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents

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**Background:** Very few studies have been performed to understand the underlying neural substrates of adolescent major depressive disorder (MDD). Studies in depressed adults have demonstrated that the subgenual anterior cingulate cortex (sgACC) plays a pivotal role in depression and have revealed aberrant patterns of resting-state functional connectivity (RSFC). Here, we examine the RSFC of the sgACC in medication-naïve first-episode adolescents with MDD.

**Methods:** Twenty-three adolescents with MDD and 36 well-matched control subjects underwent functional magnetic resonance imaging to assess the RSFC of the sgACC.

**Results:** We observed elevated connectivity between the sgACC and the insula and between the sgACC and the amygdala in the MDD group compared with the control subjects. Decreased connectivity between the sgACC and the precuneus was also found in the MDD group relative to the control subjects. Within the MDD group, higher levels of depression significantly correlated with decreased connectivity between the sgACC and left precuneus. Increased rumination was significantly associated with reduced connectivity between sgACC and the middle and inferior frontal gyri in the MDD group.

**Conclusions:** Our study is the first to examine sgACC connectivity in medication-naïve first-episode adolescents with MDD compared with well-matched control participants. Our results suggest aberrant functional connectivity among the brain networks responsible for salience attribution, executive control, and the resting-state in the MDD group compared with the control participants. Our findings raise the possibility that therapeutic interventions that can restore the functional connectivity among these networks to that typical of healthy adolescents might be a fruitful avenue for future research.

**Key Words:** Adolescent major depression, amygdala, default mode network, insula, resting-state, subgenual anterior cingulate

Adolescence is a crucial developmental period when the incidence of psychiatric illnesses, such as depression and other mood disorders, significantly increases (1). Epidemiological studies indicate that up to 8.3% of adolescents in the United States suffer from depression (2). Moreover, adolescent-onset depression is often recurrent and persists into adulthood, leading to elevated rates of divorce, loss of work, illness, and death (2). Vulnerability to the development of depression might be related to atypical maturational changes in the adolescent brain (3). Thus, understanding how departure from typical brain development patterns might influence the incidence of depression is particularly important, because it might ultimately improve our ability to prevent its emergence or lead to more effective treatments for those affected.

Despite the significance of this crucial developmental period, few studies have been performed to understand the underlying

neurobiological substrates of adolescent depression. In contrast, much more work has been done in depressed adults. This work has led to the development of several models of adult depression. One such model hypothesizes that a network of cortical regions and associated limbic structures is differentially affected by the disorder (4,5). Within this network the subgenual region of the anterior cingulate cortex (sgACC) is thought to be pivotal to affective regulation and depression (6–14).

Another model, the triple network model (TNM), suggests that major neuropsychiatric disorders including depression might be explained in part by the relationship between three core intrinsic connectivity networks (ICN) of the brain that can be identified in resting-state functional magnetic resonance imaging scans (15). The ICNs are interdependent distributed networks of brain regions observed in the human brain at rest that show strong correspondence with task-related connectivity patterns (16). The three core ICNs are the default mode network (DMN), the salience network (SN), and the central executive network (CEN). The DMN is anchored in the posterior cingulate cortex and ventromedial prefrontal cortex (PFC) (17,18) and extends into the sgACC (15,16,19,20). In this network, the ventromedial PFC node is involved in self-referential processing, social cognitive processes, value-based decision making, and emotion regulation (21–24). The SN involves the cingulate-frontal operculum system and often the amygdala (25). It is implicated in detecting, integrating, and filtering relevant interoceptive, autonomic, and emotional information (25). Finally, the CEN encompasses dorsolateral prefrontal and lateral posterior parietal cortical regions and is thought to be critical to higher-level cognitive effort (26). A core hypothesis of the TNM is that neuropsychiatric disorders, such as depression, might be associated with aberrant functional connectivity (AFC) within and between these three core networks (15).

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Of note, although AFC has been reported in many neuropsychiatric disorders [see (15) for review], DMN “functional connectivity in depression is disproportionately driven by activation in the sgACC” (27).

Investigations of sgACC resting-state functional connectivity (RSFC) have been conducted in adults, adolescents, and children with major depressive disorder (MDD). Studies of adult depression have demonstrated elevated connectivity between the sgACC and dorsolateral PFC (28) that moderates with treatment (29) as well as increased connectivity between sgACC and dorsomedial PFC (30). In adolescents, reduced functional connectivity (FC) between the sgACC and insula as well as the inferior and superior PFC have been reported (31). More recently, increased FC between the sgACC and dorsomedial PFC has also been found in medicated depressed adolescents (32). Finally, in children with preschool-onset MDD, reduced FC between the sgACC and PFC regions has been documented (33). These differences in FC displayed by children (33), adolescents (32), and adults (28,30) might be related to developmental changes. For example, large scale changes in FC have been reported over the course of development from childhood to adulthood (34), with changes in the FC of the sgACC being related to maturation (35). Differences among these studies could also be attributed to medication status. In adults, it has been suggested that antidepressant medication can affect brain activation (11), with recent preliminary evidence indicating that medication might affect the FC of the sgACC (36). Finally, the study by Cullen *et al.* (31) is unique among those reviewed in that they permitted adolescents to listen to music of their choice while being scanned. Therefore it is possible that differences in the “emotional import” of the music selected by each participant might modulate the FC of the sgACC (31).

The RSFC and task-based studies of depression have identified functional changes that are associated with clinical measures of relevance in both adults and adolescents. In adults, sgACC FC was positively correlated with length of depressive episode (27). In adolescents, the strength of correlation between sgACC and dorsomedial PFC was positively correlated with depression severity (32). Finally, in a task-based study using psychophysiological interaction in adolescents with MDD, insula activity was associated with psychosocial function (37). These results suggest that clinical measures of depression and their relationship with FC should be investigated in depressed adolescents, given the role played by the insula and sgACC in depression (37–39).

Rumination is a prominent aspect of depression that might manifest in the resting-state (27). Recent studies have begun to elucidate the neural substrate of ruminative thought processes in adult depression. These studies have shown elevated sgACC activity in the DMN in depressed adults and that the degree of activation is modulated by the level of maladaptive rumination (40–42). The right anterior insula, a component of the SN, has also been associated with maladaptive rumination in depressed adults (40). Furthermore, the amygdala, another element of the SN, has been associated with rumination in depressed adults, with activation positively correlated with rumination (43,44). These observations are important, because the insula and the amygdala are thought to play key roles in depression (37–39). To date, however, no RSFC studies have investigated rumination in adolescents with MDD.

The aim of the present study was to examine the RSFC of the sgACC in a large sample of medication-naïve first-episode depressed adolescents compared with a group of well-matched healthy control subjects. Furthermore, we wished to examine the relationships between depression, rumination, and the FC of the

sgACC. On the basis of the reviewed literature and the triple network model, we hypothesized that AFC within and between the core networks would be observed in the MDD group relative to the healthy control subjects. More specifically, we hypothesized that AFC in the resting state would manifest in the MDD group compared with control subjects in a network of brain regions involving the amygdala and insula. Finally, we hypothesized that these differences in FC in the depressed adolescents would be significantly correlated with clinical measures of depression and rumination.

## Methods and Materials

### Participants

The institutional review boards of University of California San Diego, University of California San Francisco, Rady Children's Hospital, and the county of San Diego all approved this study. Seventy-five participants were scanned for the present study: 45 healthy control subjects; and 30 with MDD. Participants gave written informed assent, and their parent/legal guardian provided written informed consent. Participants were financially compensated for their time.

### Assessment

All healthy adolescents were administered the computerized Diagnostic Interview Schedule for Children version 4.0 (45) and the Diagnostic Predictive Scale (46), to determine the presence of any Axis I disorders.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (47) was administered to all potentially depressed adolescents.

Depressive symptoms were scored by the Children's Depression Rating Scale-Revised (CDRS-R) (48) and Beck Depression Inventory-II (BDI-II) (49). Rumination was assessed by the Ruminative Responses Scale (RRS) of the Response Styles Questionnaire (50). Psychosocial functioning was assessed with the Children's Global Assessment Scale (CGAS) (51).

All participants were right-handed, and the groups were well-matched for IQ, socioeconomic status, age, gender, ethnicity, and pubertal stage. Additional questionnaires and inclusion/exclusion criteria are detailed in Supplement 1.

### MR Data Acquisition and Preprocessing

Scans were acquired on a 3T GE MR750 System (GE Healthcare, Milwaukee, Wisconsin). One 8-min, 32-sec resting-state scan (256 volumes repetition time/echo time = 2 sec/30 msec, flip angle = 90°, 64 × 64 matrix, 3 × 3 × 3 mm voxels, 40 axial slices) was acquired. A high-resolution T1-weighted scan (repetition time/echo time = 8.1 msec/3.17 msec, flip angle = 12°, 256 × 256 matrix, 1 × 1 × 1 mm voxels, 168 sagittal slices) was acquired to permit functional localization.

Analyses were conducted with AFNI (52) and FSL software (53). Detailed methods are in Supplement 1. The T1-weighted images were skull stripped and transformed to MNI152 space (Montreal Neurological Institute, Montreal, Quebec, Canada) with an affine transform (54,55) followed by nonlinear refinement (56,57). Tissue components (gray matter, white matter, and cerebrospinal fluid) were segmented (58). Echo-planar images were motion corrected and aligned to the T1 images (59), convolved with a 4.2-mm full-width-at-half-maximal isotropic Gaussian filter, grand-mean scaled, and transformed to MNI152 space at 3 × 3 × 3 mm resolution. Bandpass filtering (.01–1 Hz), censoring of outlier

volumes and those with excessive motion, and removal of physiological noise (motion and average signal from white matter and cerebrospinal fluid) were accomplished in a single generalized least squares regression step, which required that no fewer than 177 time-points remained after censoring.

### FC Analysis

Four subgenual seed locations, two in each hemisphere, were chosen on the basis of a prior exploration of anterior cingulate connectivity in the resting state (60). Seeds were 3 mm in radius, occupied 189  $\mu\text{L}$ , and located at  $\pm 5$ ,  $-34$ ,  $-4$  and  $\pm 5$ ,  $-25$ ,  $-10$ . For each seed, the Pearson correlation between the whole brain four-dimensional residuals and the average seed time-series was computed. Correlation coefficients were converted to Z scores with Fisher's r-to-z transform (61).

### Group Analysis

Voxel-wise between-group analyses for each seed were accomplished with linear mixed effects models implemented in R software (62) where participant was treated as a random effect. Voxels were thresholded ( $F_{1,58} = 4.01$ ,  $p = .05$ ) and, to control for multiple comparisons, were required to be part of a cluster of at least 2000  $\mu\text{L}$ . Bonferroni correction was used to correct for the number of seeds, and the corrected  $p$  was set to  $.05/4 = .0125$ . A Monte Carlo simulation was used to identify the volume threshold and, together with the voxel-wise threshold, resulted in a 5% probability of a significant cluster surviving due to chance across all four seeds.

### Demographic and Clinical Scales Analysis

All statistical analyses were conducted with R software (62). Between-group differences were assessed by means of Welch  $T$

tests for age, Wechsler Abbreviated Scale of intelligence, BDI-II, and CDRS-R. Group differences in gender and number of participants/group were assessed with  $\chi^2$  test of equal proportions. Effect sizes for these tests were computed with Hedge's  $g$  (63). The Wilcoxon rank-sum test determined group differences in the Hollingshead socioeconomic scale, CGAS, RRS, and Tanner Stage. Effect sizes for these tests were computed with the probability of superiority (PS), which ranges from 0 to 1 and represents the probability that a randomly selected control reports a greater value on the corresponding measure than a randomly selected MDD participant (64).

### Correlational Analysis

Within the MDD group, the relationships between CGAS, CDRS-R, BDI-II, RRS, and the average Z score within each of the regions of interest identified by the between-group whole-brain analyses were examined with Spearman's rank correlation test.

## Results

### Demographic and Clinical Scales

As expected, given the matching criteria, the groups did not significantly differ in age, gender, socioeconomic status, Tanner pubertal stage, or IQ (all  $p > .05$ ). Similarly, all of the depression scales (CDRS-R and BDI-II) showed that the MDD group endorsed significantly greater levels of depression than the control subjects (Hedge's  $g$  for CDRS-R =  $-4.99$  and for BDI-II =  $-2.94$ ). Additionally, on the CGAS, the MDD group demonstrated lower psychosocial function than the healthy adolescents (PS = .99). The MDD adolescents demonstrated greater rumination than the control subjects as measured by the RRS (PS = .06) (Table 1).

**Table 1.** Participant Characterization: Demographic Data and Clinical Rating Scales

Characteristic	Control	MDD	df	Statistic	Effect Size
Number of Participants Recruited (n)	45	30			
Overall Recruitment Gender (M/F)	17/28	11/19	1	$\approx 0$	$\approx 0$
Rejected Due to Excessive Motion and Outlier Count (n) <sup>a</sup>	9	7	1	.0033	$\approx 0$
Number of Participants Surviving Motion and Outlier Correction (n)	36	23			
Gender (M/F) <sup>a</sup>	11/25	7/16	1	$\approx 0$	$\approx 0$
Age at Time of Scan (yrs)	16.1 $\pm$ .2 (13.1–17.9)	16 $\pm$ .3 (13.1–17.8)	41.35	.45	.12
Hollingshead Socioeconomic Score <sup>b</sup>	29 $\pm$ 16.3 (0–77)	33 $\pm$ 26.7 (11–70)	NA	348.5	.42
Tanner Score <sup>b</sup>	4 $\pm$ .7 (3–5)	4 $\pm$ .7 (2.5–5)	NA	446	.54
Wechsler Abbreviated Scale of Intelligence	106.4 $\pm$ 2.1 (84–133)	101.5 $\pm$ 2.2 (85–120)	51.97	1.61	.42
Children's Global Assessment Scale <sup>b,c</sup>	90 $\pm$ 7.4 (75–100)	65 $\pm$ 14.8 (40–85)	NA	817.5	.99
Ruminative Responses Styles Questionnaire <sup>b,c</sup>	22 $\pm$ 13.3 (0–68) [7]	57 $\pm$ 23.7 (14–101) [2]	NA	50.5	.06
Children's Depression Rating Scale (Standardized) <sup>c</sup>	33.4 $\pm$ .9 (30–55)	71.2 $\pm$ 1.8 (55–85)	33.34	–18.96	–4.99
Beck Depression Inventory II <sup>c</sup>	3 $\pm$ .6 (0–12) [1]	27.3 $\pm$ 2.1 (4–47)	25.72	–11.16	–2.94
Comorbid Diagnoses in the MDD Group					
No comorbid diagnoses		5			
Generalized anxiety disorder		12			
Specific phobia		2			
Anxiety disorder not otherwise specified		1			
Posttraumatic stress disorder		2			
Enuresis		1			

Entries are of the form: mean  $\pm$  SEM (minimum – maximum) unless otherwise stated. The optional number in square brackets indicates the number of missing items of data. Effect size is Hedges'  $g$  unless otherwise indicated. Statistical comparisons were by means of Welch  $t$  tests unless otherwise indicated.

Statistic is the W,  $\chi^2$ , or  $t$  value. Statistics for clinical scales and demographics refer only to participants surviving motion and outlier correction.

F, female; M, male; MDD, major depressive disorder; NA, not applicable.

<sup>a</sup> $\chi^2$  test for equality of proportions.

<sup>b</sup>Median  $\pm$  median (minimum – maximum) or median  $\pm$  median absolute deviation (minimum–maximum). The optional number in brackets indicates the number of missing items of data. Wilcoxon rank sum test. The effect size is the probability of superiority.

<sup>c</sup> $p < .001$ .

**RSFC**

The regions identified in the whole-brain between-group analysis (Table 2) were consistent with those identified as being part of the salience, central executive, and default mode networks (15). The left inferior seed demonstrated greater positive connectivity to bilateral inferior frontal gyrus (IFG) and bilateral insula in the MDD group compared with control subjects (Figure 1) as well other regions listed in Table 2. The right inferior seed showed greater positive connectivity in the MDD group than the control subjects to right cuneus, right lentiform nucleus, bilateral superior temporal gyrus, and left claustrum.

The left superior seed showed connectivity differences in only one region in the right cuneus that was more strongly positively connected to the sgACC in the MDD group than the control participants. The right superior seed displayed negative connectivity to the left precuneus and middle frontal and middle occipital gyri in the MDD group relative to the control participants who showed positive connectivity to these three regions. We observed increased positive connectivity between the right superior seed and the right amygdala extending caudally into the parahippocampal gyrus in the MDD group relative to control participants (Figure 2). The right superior seed also demonstrated increased FC

with the left culmen of the cerebellum and the left amygdala extending ventrally into the uncus in the MDD group compared with the control participants (Figure 2). In the case of these three regions (the right amygdala/parahippocampal gyrus, left culmen, and left amygdala/uncus), the MDD group demonstrated positive connectivity to the sgACC, whereas the control group showed positive connectivity for the right amygdala/parahippocampal gyrus and negative connectivity for the left culmen and left amygdala/uncus.

**Correlational Analysis**

Within the MDD group, several regions (Table 3) demonstrated significant relationships with the clinical scales. Those regions showing negative correlations with measures of depression (BDI-II and CDRS-R) included left middle frontal and left occipital gyri, left precuneus, and the left precentral gyrus (all  $p < .05$ ). Positive correlations between the CGAS and regions in the left precuneus and left middle frontal and left occipital gyri were observed (all  $p < .05$ ). One region, the left claustrum, showed a negative correlation with the CGAS ( $p < .05$ ). Negative correlations with RRS were observed in the right middle frontal gyrus (MFG) and right IFG (all  $p < .05$ ).

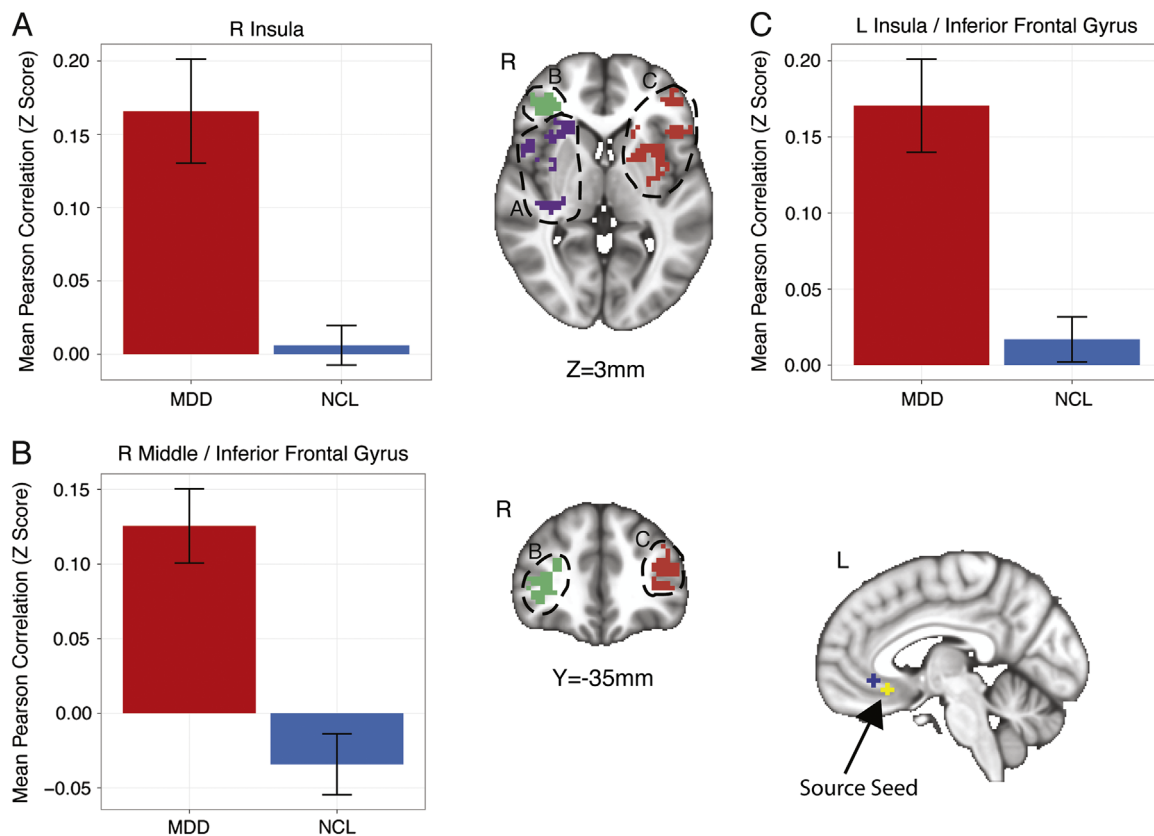
**Table 2.** Seed Locations and Regions Showing Between-Group Differences in Mean RSFC

Structure	Hemisphere	BA	Volume μL	Center of Mass			Mean RSFC	
				X	Y	Z	MDD	NCL
Left Superior Seed			189	5	−34	−4		
MDD > control subjects								
Cuneus	R	19	2052	−13	80	29	.17	.02
Left Inferior Seed			189	5	−25	−10		
MDD > control subjects								
Insula	L	13	19,548	38	−18	8	.17	.01
Insula	R	13	13,905	−37	4	−6	.17	.00
Middle frontal gyrus	R	10	6345	−37	−41	11	.13	−.04
Inferior parietal lobule	L	40	5076	53	42	42	.14	.00
Superior temporal gyrus	R	22	4401	−51	57	14	.19	.04
Inferior parietal lobule	R	40	3780	−58	36	44	.11	−.02
Paracentral lobule	R	31	2673	−4	15	47	.20	.05
Precentral gyrus	L	6	2511	42	−2	37	.19	.03
Inferior frontal gyrus	L	47	2241	34	−33	−9	.24	.08
Right Superior Seed			189	−5	−34	−4		
MDD < control subjects								
Precuneus	L	7	15,228	5	60	51	−.14	.04
Middle frontal gyrus	L	6	4482	28	2	52	−.14	.02
Middle occipital gyrus	L	18	2349	28	92	2	−.09	.09
MDD > control subjects								
Amygdala/parahippocampal gyrus	R	20	3429	−33	4	−29	.17	.01
Culmen	L		3186	16	37	−34	.10	−.04
Amygdala/uncus	L	21	2160	34	6	−31	.15	−.02
Right Inferior Seed			189	−5	−25	−10		
MDD > control subjects								
Cuneus	R	18	14,094	−7	75	12	.18	.02
Lentiform nucleus	R		6777	−21	−9	13	.15	−.01
Inferior frontal gyrus	L	45	6426	48	−21	14	.19	.02
Claustrum	L		4455	27	8	17	.18	.00
Inferior frontal gyrus	R	46	2322	−43	−40	4	.14	−.02
Superior temporal gyrus	R	22	2106	−47	27	0	.21	.04
Superior temporal gyrus	L	22	2106	51	49	12	.22	.04

As measured by Fisher Z-transformed Pearson correlation. Center-of-mass coordinates are in the MNI152 (Montreal Neurological Institute, Montreal, Quebec, Canada) (right anterior inferior) standard and structure labels from the Talairach and Tournoux atlas.

BA, Brodmann area; MDD, major depressive disorder; NCL, normal control subjects; RSFC, resting-state functional connectivity.





**Figure 1.** Regions showing group differences in the correlation with a subgenual anterior cingulate cortex seed in the left hemisphere. Error bars indicate the SEM. L, left; MDD, major depressive disorder; NCL, normal control subjects; R, right.

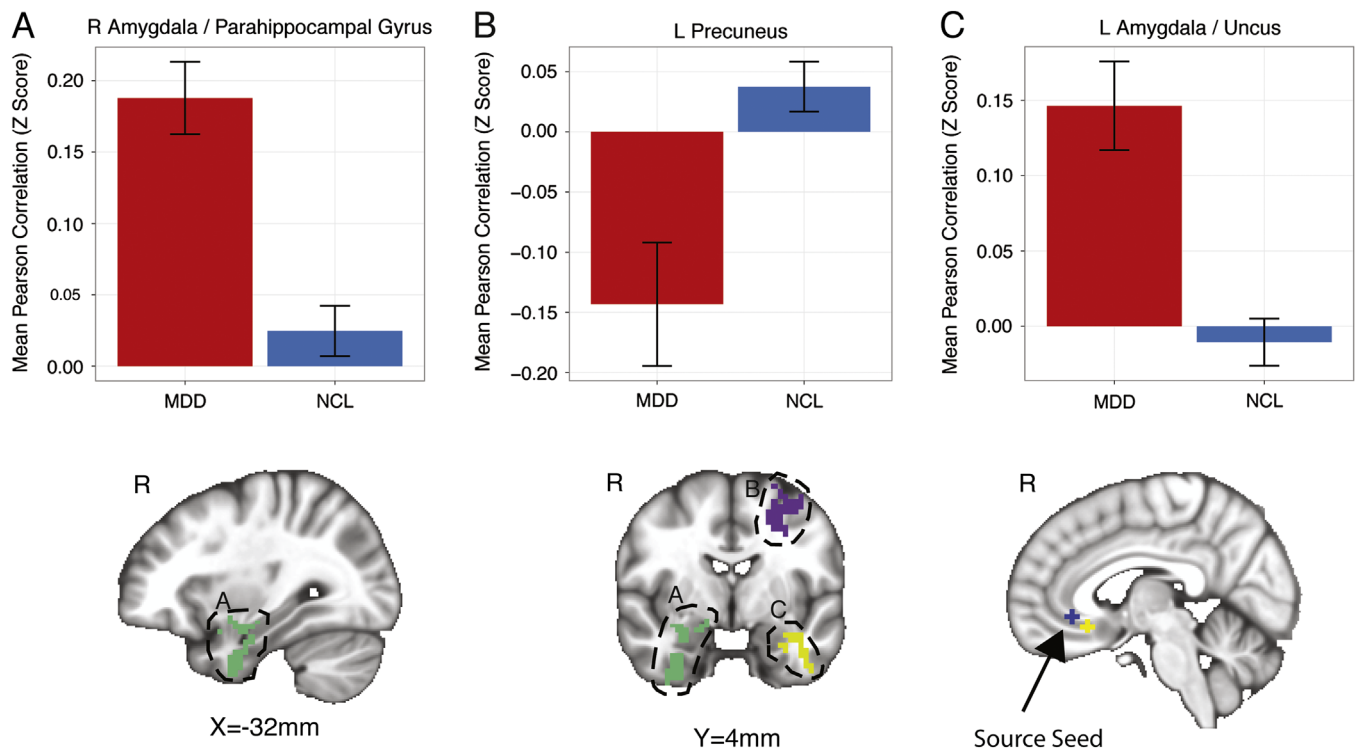
## Discussion

This study compared the RSFC of the sgACC in medication-naïve first-episode adolescents with a primary diagnosis of MDD with a group of well-matched control subjects. Our study yielded four main results. Firstly, we observed several brain regions coactive with the sgACC that are not typically considered part of the DMN. This result might reflect AFC within and between the ICNs of the brain. Secondly, our results further support the body of research indicating that the sgACC is an important node in a network of limbic and paralimbic regions that have previously been shown to be dysfunctional in depressed adults (9,11,65–70), adolescents (31,32), and children (33). Thirdly, our correlational analysis suggests that greater connectivity between regions of the DMN might be associated with better psychosocial function in depressed adolescents and that more severe depression might be related to reduced connectivity between these nodes. Finally, we observed that increased levels of rumination were associated with decreased FC between the sgACC and both the IFG and MFG, which are components of the CEN (15).

We observed elevated positive connectivity with the sgACC in the bilateral insulae (Figure 1) as well as greater negative connectivity between the sgACC and the left precuneus (Figure 2) in the MDD group compared with the control subjects. These observations might reflect FC changes between the ICNs of the brain. In the TNM, the SN is thought to be centered on the anterior cingulate and insular cortex (15). The insula is thought to play a role in the integration of autonomic, visceral, and hedonic information (71). Indeed, the insula has been proposed to be critical to selecting from among internally and externally available

homeostatically relevant information to guide behavior (71). Furthermore, the right anterior insula is thought to play a key role in switching from a predominantly CEN/SN dominated brain state to the default mode state (72). Our observation of increased connectivity between the sgACC and both the right anterior insula and left middle insula (Figure 1) in the MDD group might be significant insofar as it might be indicative of AFC between the SN and DMN. This AFC might be due to the strong connectivity we observed between the sgACC and right anterior insula, which might preclude a successful transition into the pattern of neural activity characteristic of a normal DMN (72).

Although we observed greater positive connectivity between the sgACC and insula in the depressed adolescents compared with control subjects, Cullen *et al.* (31) reported decreased connectivity between these two regions. This difference could be due to issues such as medication status, sample size, or the “emotional import” of the music participants listened to while being scanned (31). In the present study, we examined a larger sample (MDD: 23 vs. 12; control: 36 vs. 14) of medication-naïve first-episode participants who were not permitted to listen to music while being scanned. In the Cullen *et al.* (31) study, participants on several different types of psychiatric medications were scanned while listening to music of the participants’ choice. Although playing music during the scan might be regarded as uncommon (32), recent evidence suggests that this might not appreciably affect the topology of the DMN but rather might enhance connectivity among the nodes thereof (73). Therefore, it is possible that medicated depressed adolescents scanned while listening to music might demonstrate elevated FC between the sgACC and insula, whereas unmedicated depressed adolescents scanned while not



**Figure 2.** Regions showing group differences in the correlation with a subgenual anterior cingulate cortex seed in the right hemisphere. Error bars indicate the SEM. L, left; MDD, major depressive disorder; NCL, normal control subjects; R, right.

listening to music might show reduced FC between these two structures.

We also observed increased FC between the sgACC and right amygdala in the MDD group relative to the control subjects (Figure 2). Previous studies have reported hyperactivation of the amygdala in both adults (39,44,74–76) and adolescents (37,77–81) with major depression. Amygdalar activation has been shown to predict likelihood of positive treatment outcome in depressed adults (82). Consequently, the amygdala has been proposed to play a key role in depression (38,39). Similarly, sgACC hyperactivation has also been observed in both depressed adults (10,66) and adolescents (83). Therefore, it has been hypothesized that the sgACC plays a pivotal role in depression (38,67,84). Effective treatment has been shown to reduce activity levels toward that typical of healthy individuals in both the amygdala (66) and sgACC (11). However, it is unclear whether the FC between these two regions might alter with treatment. Future longitudinal studies are necessary to address this question and identify whether the connectivity between these regions might be a potential biomarker of depression and an apt target for treatment. Our results also suggest that these two regions are functionally connected. Consistent with our FC findings, it has been shown that the amygdala and sgACC are anatomically connected by white matter fibers in the uncinate fasciculus (85). Furthermore, structural alterations in the connection between sgACC and amygdala have been reported in depressed adolescents (86), but whether these predate development of depression and might have a causative effect or are a consequence of the illness is unclear. Future studies in adolescents at risk for depression might help to address these issues.

Within the MDD group, we hypothesized that the clinical measures of depression would be associated with the strength

of connectivity between the sgACC and other brain regions. We observed that higher BDI-II scores were significantly correlated with decreased FC in the MDD group between the sgACC and left precuneus, which are components of the DMN (15,19,87) (Table 3). Consistent with this observation, greater psychosocial function was significantly correlated with increased connectivity between the sgACC and left precuneus. We also observed that greater CDRS-R scores were significantly correlated with decreased connectivity between the sgACC and left MFG in the MDD group. Because the MFG is a component of the CEN (15), this observation might indicate an impairment of top-down regulation of emotion by the CEN. These findings suggest that increased depression and decreased psychosocial functioning are associated with AFC of the sgACC and are consistent with our hypothesis that differences in FC within the depressed adolescents would be significantly correlated with measures of clinical depression. Overall, the MDD group displayed more negative connectivity than the control subjects, with respect to the sgACC-left MFG connectivity. We also found negative correlation between depression scores (CDRS-R, BDI-II) and sgACC-left MFG FC in the MDD group. These results suggest that the CEN of depressed adolescents with less negative FC between these regions might be more effective at regulating depressive symptoms. Conversely, more negative sgACC-left MFG FC might indicate inadequate regulation of depressive symptoms.

Finally, within the MDD group, we investigated whether rumination correlated with connection strength from the sgACC. As shown in Table 3, increased rumination was associated with decreased FC between the sgACC and both the right MFG and right IFG. Both the MFG and IFG are thought to be components of the CEN (88–92), with right IFG important to emotion regulation in both healthy and depressed adults (93–95). Overall, the MDD

**Table 3.** Table of Regions Showing Correlations with Clinical Rating Scales

Cluster	Regression Variable	S	$\rho$	$p$
Superior Right Seed				
L precuneus	Children's Global Assessment Scale	948.94	.53	<.01
L middle frontal gyrus	Children's Global Assessment Scale	769.10	.62	<.01
L middle occipital gyrus	Children's Global Assessment Scale	649.53	.68	<.001
L middle frontal gyrus	Children's Depression Rating Scale-Revised (Standardized)	2937.71	-.45	<.05
L middle occipital gyrus	Children's Depression Rating Scale-Revised (Standardized)	3183.44	-.57	<.01
L precuneus	Beck Depression Inventory II	2880.06	-.42	<.05
L middle frontal gyrus	Beck Depression Inventory II	3081.31	-.52	<.05
Inferior Left Seed				
R middle frontal gyrus	Ruminative Responses Scale	2370.27	-.54	<.05
L precentral gyrus	Children's Depression Rating Scale-Revised (Standardized)	3108.22	-.54	<.01
Inferior Right Seed				
L claustrum	Children's Global Assessment Scale	2925.24	-.45	<.05
R inferior frontal gyrus	Ruminative Responses Scale	2227.22	-.45	<.05

L, left; R, right;  $\rho$ , Spearman's correlation coefficient; S, Spearman's rank sum.

group displayed greater positive sgACC-MFG and sgACC-IFG connectivity than the control subjects. We also observed a negative correlation between rumination and sgACC-MFG and sgACC-IFG connectivity in the MDD group. These results suggest that the CEN of depressed adolescents with lower FC between these regions might be inadequately regulating negative emotional thoughts (96). Conversely, individuals with greater sgACC-MFG and sgACC-IFG connectivity might be better regulating negative emotional thoughts.

The results of this study must be interpreted in light of its limitations. The current study is cross-sectional and therefore cannot address whether or not these observations are a consequence of MDD. Future longitudinal studies should be performed to address this question. Given the high rates of comorbid diagnoses in this sample of depressed adolescents, future studies are still required to investigate the specificity of these findings and how they might be influenced by comorbidity. Notwithstanding, adolescent depression is a highly comorbid disorder (97–99), and inclusion of participants with comorbid diagnoses arguably makes our sample more representative of the patients typically seen in clinics and thus contributes to the generalizability of our results. The issue of gender differences is important, especially given the higher rates of depression in female adolescents than male adolescents (1,100). Although we conducted a preliminary investigation of the effect of gender in the current sample (Supplement 1), we were limited in this investigation by the small number of depressed male adolescents ( $n = 7$ ). Future studies are required to investigate whether and, if so, how FC varies by gender in depressed adolescents. Finally, we used the TNM as a theoretical basis to explain our findings. However, it is possible that other theories might be equally applicable to the results reported herein. Although we have attempted to explain most of our findings with the TNM, the FC of the depressed adolescent brain might be more complex and involve additional networks than the three central to the TNM. The application of the TNM might therefore be regarded as preliminary, and future studies are required to confirm the applicability of the TNM to the study of adolescent depression.

In summary, the present study examined the RSFC of the sgACC in medication-naïve first-episode adolescents with MDD compared with a group of well-matched healthy control participants. Relative to control participants, the depressed adolescents demonstrated greater sgACC-amygdala and sgACC-insula

connectivity, suggesting AFC between the SN and DMN in the resting state. Furthermore, adolescents with greater levels of depression and lower levels of psychosocial function demonstrated weaker sgACC-precuneus connectivity. Taken together, these results suggest that adolescent depression might be related to or accompanied by AFC between the DMN and SN that might be underpinned by elevated connectivity between the sgACC and both the insula and amygdala. Our results are consistent with and further support prior reports of elevated FC in depressed adolescents (32) and adults (27,28,30) rather than reduced connectivity (31). We also observed increased rumination as a function of decreased connectivity between the sgACC and both the right MFG and right IFG, suggesting impaired top-down modulation by the CEN of negative emotional thoughts. Finally, our findings further support the model that the sgACC plays a key role in major depression (4,5) and are consistent with the TNM of neuropsychiatric disorders (15). Collectively, our results raise the possibility that potential therapeutic interventions that can restore the FC within and between the SN, CEN, and DMN to that typical of healthy adolescents might be a fruitful avenue for future research in the treatment and prevention of adolescent depression.

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