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Research report

Functional connectivity of negative emotional processing in adolescent depression

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ABSTRACT

Background: The subgenual anterior cingulate cortex (sgACC) and its connected circuitry have been heavily implicated in emotional functioning in adolescent-onset major depressive disorder (MDD). While several recent studies have examined sgACC functional connectivity (FC) in depressed youth at rest, no studies to date have investigated sgACC FC in adolescent depression during negative emotional processing.

Methods: Nineteen medication-naïve adolescents with MDD and 19 matched healthy controls (HCL) performed an implicit fear facial affect recognition task during functional magnetic resonance imaging (fMRI). We defined seeds in bilateral sgACC and assessed FC using the psychophysiological interaction method. We also applied cognitive behavioral modeling to estimate group differences in perceptual sensitivity in this task. Finally, we correlated connectivity strength with clinical data and perceptual sensitivity.

Results: Depressed adolescents showed increased sgACC-amygdala FC and decreased sgACC-fusiform gyrus, sgACC-precuneus, sgACC-insula, and sgACC-middle frontal gyrus FC compared to HCL ($p < 0.05$, corrected). Among the MDD, sgACC-precuneus FC negatively correlated with depression severity ($p < 0.05$, corrected). Lastly, MDD adolescents exhibited poorer perceptual sensitivity in the task than HCL, and individual differences in perceptual sensitivity significantly correlated with sgACC FC and depression scores ($p < 0.05$, corrected).

Limitations: Subjects were clinically homogenous, possibly limiting generalizability of the findings.

Conclusions: Adolescent depression is associated with biased processing of negative stimuli that may be driven by sgACC dysregulation and may possibly lead to an imbalance among intrinsic functional brain networks. This work also establishes the use of combining neuroimaging and cognitive behavioral modeling methods to investigate cognitive and neural differences between psychiatric and healthy populations.

1. Introduction

Functional magnetic resonance imaging (fMRI) studies have contributed greatly to the understanding of the neural networks in major depressive disorder (MDD). Recent evidence suggests that MDD is partially characterized by dramatic alterations in the functional connectivity (FC) of brain regions involved in emotion processing (Greicius, 2008; Stuhrmann et al., 2011). Since MDD typically begins during adolescence (Avenevoli et al., 2008; Kessler et al., 2001, 2007) and confers a high risk of recurrence into adulthood (Lewinsohn et al., 1999), examining the FC of brain regions during adolescent depression could elucidate the etiology of this disorder in the context of brain changes that occur during this sensitive period of development (Somerville et al., 2010; Pine, 2007).

The subgenual anterior cingulate cortex (sgACC) and its connected circuitry have been heavily implicated in emotion function and in adult depression (Hamani et al., 2011; Mayberg, 1997; Mayberg et al., 1997, 2005; Drevets et al., 2008; Greicius et al., 2007; Johansen-Berg et al., 2008). Given its anatomical connections to subcortical and cortical structures, the sgACC is thought to lie at the interface of affective and cognitive processing, such that aberrant functioning in this region leads to impaired emotional regulation. In adolescents, altered resting-state FC of the sgACC has recently been documented in depressed adolescents and young adults relative to healthy controls (Cullen et al., 2009; Davey et al.,

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2012; Connolly et al., 2013; Gabbay et al., 2013). Specifically, aberrant FC has been observed between the sgACC and the amygdala (Connolly et al., 2013), insula (Cullen et al., 2009, 2013), dorsal medial prefrontal cortex (Cullen et al., 2009; Davey et al., 2012), dorsolateral prefrontal cortex (Connolly et al., 2013), precuneus (Connolly et al., 2013), middle frontal gyrus (Connolly et al., 2013) and striatum (Gabbay et al., 2013). These results suggest an imbalance among salience (which include limbic, paralimbic, and striatal structures), cognitive executive (which include medial and lateral prefrontal and frontal cortices), and resting-state (which include posterior cingulate and precuneus) networks that may be mediated by the sgACC (Seeley et al., 2007; Dosenbach et al., 2008; Vincent et al., 2008; Fransson and Marrelec, 2008). However, these observed FC differences in adolescent and young adult depression have been inconsistent, in part because of the medication status, age range, and comorbidities of the participants recruited. It is therefore important to examine sgACC FC in non-medicated depressed adolescents with no comorbidities so that these factors do not confound interpretation of results.

Additionally, the aforementioned data were measured while subjects were at rest and are therefore unable to answer the question of how sgACC FC patterns among the salience, cognitive executive, and resting-state networks are affected during active emotional processing. Although there has yet to be any published work of sgACC-based functional connectivity during emotion processing in adolescents with MDD, recent neuroimaging work has examined FC differences in depressed adults during processing of negative material (Chen et al., 2008; Carballedo et al., 2011; Matthews et al., 2008; Almeida et al., 2011). These studies focused primarily on the amygdala and found disrupted functional connections with the sgACC and other nodes in the salience and cognitive executive networks. Given that adults (Foland-Ross and Gotlib, 2012; Foland-Ross et al., 2013; Gotlib et al., 2004; Joormann and Gotlib, 2006), adolescents with depression (Hankin et al., 2012), and even youth with a high familial risk for depression (Joormann et al., 2007, 2010; Kujawa et al., 2012; Romens and Pollak, 2012; Lopez-Duran et al., 2013) all exhibit behavioral biases towards affectively negative stimuli, we hypothesize that these sgACC-based FC disruptions among key brain networks may be reflective of the cognitive differences observed between MDD subjects and healthy controls (HCL) during the evaluation of negative material.

Thus, in order to better elucidate the role of the sgACC in adolescent depression as it pertains to negative emotional processing, the aim of the present study was two-fold: (1) investigate possible cognitive differences between MDD and HCL adolescents, and (2) examine and compare sgACC FC between these two groups to determine if and how salience, cognitive executive, and resting-state networks are affected by the processing of negative stimuli. To date, there are no studies of sgACC FC in adolescent depression during processing of negative emotional material. Thus, we applied functional magnetic resonance imaging (fMRI) to investigate sgACC FC in 19 adolescents (13–17 years old) with a current diagnosis of MDD and 19 matched HCL while subjects performed a gender discrimination task of face images exhibiting varying degrees of fear. Importantly, our depressed group was naïve to antidepressants and without psychiatric comorbidities. We defined seeds in bilateral sgACC and assessed FC using a psychophysiological interaction analysis (Friston et al., 1997). Depression severity was measured with the Beck Depression Inventory (BDI-II; Beck et al., 1996). To measure aspects of information processing in addition to simply mean accuracy and response time on the behavioral task, we adopted a commonly used cognitive behavioral model, the Linear Ballistic Accumulator (LBA; Brown and Heathcote, 2008), that allowed us to compute and localize cognitive differences in emotional processing between MDD and HCL adolescents. Based on prior literature in both adult and adolescent depression, we predict finding cognitive processing differences during evaluation of negative emotional stimuli between MDD and HCL adolescents and that these differences would be reflected as alterations in functional coupling between the sgACC and structures in the salience, cognitive executive, and resting-state networks.

2. Methods

2.1. Subjects

Forty-two right-handed adolescents (ages 13–17 years) were recruited for the study. Four subjects were excluded from the final analysis due to excessive motion. We therefore report results for 19 adolescents with a current primary *DSM-IV* diagnosis of MDD (mean age ± SD: 15.8 ± 1.4 years; 8 males) and 19 HCL adolescents (16.1 ± 1.2 years; 8 males). Subject groups were equivalent on major demographic variables (see Table 1). This study was approved by the Institutional Review Boards at the University of California, San Diego, Rady Children's Hospital, and the County of San Diego. Please see *Recruitment and Assessment of Subjects* in Supplementary material for more details.

Exclusionary criteria for adolescents with MDD included any psychiatric comorbidities, left-handedness, being color blind or having less than 20/40 correctable vision, contraindication to MR imaging (e.g., pregnancy, claustrophobia, and metallic implants), a serious medical or neurological illness, a learning disability, prior or present use of antidepressants, the use of medication with CNS effects within the past 2 weeks, evidence of illicit drug use or misuse of prescription drugs, and more than 2 alcoholic drinks per week or within the previous month at the time of scanning. Please see Table 1 for a summary of the clinical characteristics of our depressed subjects.

HCL adolescents were excluded from the study for any of the exclusionary criteria for the MDD group, as well as any current or lifetime Axis I psychiatric disorder, any family history of mood or psychotic disorders in first- or second-degree relatives.

Table 1
Summary of the sociodemographic and clinical data for the MDD and HCL adolescents. Entries are of the form: mean ± standard error of mean (SEM). Statistical analyses were conducted with chi-squared tests (χ^2), Student *t*-tests (*t*), and Wilcoxon Rank Sum test (*U*). MDD=major depressive disorder; HCL=healthy control; *df*=degrees of freedom; and N/A=not applicable.

Characteristic	MDD	HCL	*df*	Statistic	*p*-value
Gender (M/F)	8/11	8/11	1	$\chi^2=1$	0
Age (years)	15.8 ± 1.4	16.1 ± 1.2	36	$t=0.81$	0.42
Ethnicity (African/Asian/Hispanic/Caucasian/Mixed)	1/1/8/6/3	0/2/5/10/2	N/A	$U=206.5$	0.41
Beck Depression Inventory II	23.05 ± 2.6	2.94 ± 1.0	35	$t=7.20$	0.0001
Age of first episode onset (years)	12 ± 0.73				
Duration of MDD (months)	25.8 ± 6.1				
# of MDD episodes	3 ± 1.2				

2.2. Image acquisition

All scanning was carried out on a GE Signa Excite 3T scanner (General Electric, Milwaukee, WI) with Twin Speed gradients and a GE 8-channel head coil. For details on scan parameters, see *Image Acquisition* under Supplementary material. During scanning, subjects lay supine in the bore of the magnet and were instructed to relax but remain awake and as still as possible. Visual stimuli were projected onto a screen and viewed through a small, angled mirror mounted above the subject's head.

2.3. Behavioral task and stimulus

Our behavioral task was adopted from a previously published PET paradigm (Morris et al., 1998) and was created and presented using an in-house Tcl script (⟨http://www.tcl.tk/software/tcltk/⟩). Ten faces (5 female) from a standardized series of facial expressions of fear (Ekman and Friesen, 1976) were morphed using computer graphical manipulation (Morris et al., 1998; Perrett et al., 1994) to represent three graded intensities of fear: strong (100%), moderate (50%), and neutral (0%). Facial stimuli and baseline trials (crosshair fixation) were presented in pseudorandom order. The facial stimuli were presented twice at each level of the fear intensities (see Fig. 1a for faces representative of each fear level), along with 12 baseline trials, for a total of 72 trials. Each trial was presented for 3000 ms, with the inter-trial interval (ITI) randomly varying according to a Poisson distribution (mean ITI=2000 ms). The total duration of the experimental run was therefore 360 s. For each facial trial, subjects were asked to indicate the gender of the face (male or female) by pushing one of two buttons on an MR compatible button box (Current Designs, Philadelphia, PA). These choices were displayed in boxed text on the bottom left and right corners but disappeared once a response was made (see Fig. 1b for an example). Response time (RT) and accuracy of gender decision during scanning were recorded for each trial. However, several behavioral files were lost due to technical difficulties during data transfer. We therefore report behavioral data from 16 MDD and 13 HCL for all analyses involving RT and accuracy.

2.4. Image preprocessing and analysis

All image processing and analyses were conducted with the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). We employed standard steps for fMRI image preprocessing (see *Image Processing* under Supplementary material for details). Briefly, regressors-of-interest modeled for each voxel's time series included the three trial types: FearStrong, FearModerate, and FearNeutral. Six motion parameters and the time points flagged as outliers were considered nuisance regressors to account for motion artifacts. Linear trend was also modeled in the time series of each voxel to account for correlated drift. Finally, the data were converted to percent signal change by dividing the time series of each voxel by the mean global signal, smoothed with a Gaussian filter with a full-width half-maximum (FWHM) kernel of 4 mm, and transformed to stereotaxic coordinates (Talairach and Tournoux, 1998). Since the primary focus of this study was on negative emotion processing, we limited our voxel-based analyses to the linear contrast of FearStrong–FearNeutral to maximize fear-related activation.

2.5. Group and task effects

Regions of significant group differences (MDD versus HCL) were determined by running a voxel-based two-sample *t*-test on the beta weights estimated from the condition of interest (FearStrong–FearNeutral). An analysis of task effect was also conducted by running a one-sample *t*-test on the beta weights for this task condition from all subjects.

2.6. Controlling for multiple comparisons

For all fMRI analyses reported here, significant voxels were required to pass a voxel-wise statistical threshold of $t_{36}=2.029$ ($p=0.05$, uncorrected). To control for multiple comparisons, we computed the minimum number of contiguous voxels passing the voxel-wise threshold that would result in a cluster-wise 5% probability of being due to chance using 10,000 iterations of Monte Carlo simulations based on an average skull-stripped whole

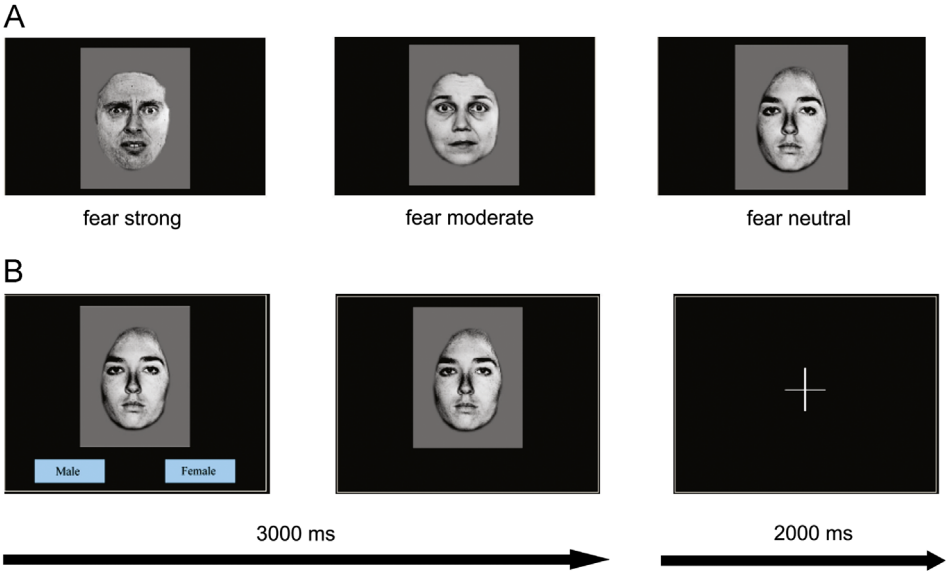

Fig. 1. Implicit fear facial affective recognition paradigm. 60 facial trials and 12 baseline trials (crosshair fixation) were presented in pseudorandom order. Facial stimuli displayed one of three fear levels: FearStrong (FS, 100%), FearModerate (FM; 50%), and FearNeutral (FN; 0%) and were presented twice at each level of the fear intensities (a). Each trial lasted 3000 ms, with an inter-trial interval (ITI) randomly varying according to a Poisson distribution (mean ITI=2000 ms). For each facial trial, subjects were asked to indicate the gender of the face (male or female) by pushing one of two buttons on a button box. These choices were displayed in boxed text on the bottom left and right corners but will disappear once a response is made (b). See *Behavioral task and stimuli* under Section 2 for more details.

brain mask created from all subjects (downsampled to $4 \times 4 \times 4$ mm) and the applied FWHM values of the functional data. According to our simulations, this cluster threshold was 11 voxels (704 μL).

2.7. Region-of-interest (ROI) seed definitions

We defined anatomical bilateral sgACC seeds based on a prior study of cingulate connectivity (Margulies et al., 2007) that were also recently used to examine sgACC connectivity in adolescent depression during resting-state (Connolly et al., 2013). The seeds were converted from MNI to Talairach space and resampled to $4 \times 4 \times 4$ mm, resulting in the following Talairach coordinates for right and left sgACC, respectively: $x=6$, $y=-23$, $z=-8$ and $x=-2$, $y=-23$, $z=-8$. Each seed comprised 7 voxels (448 μL).

2.8. Functional connectivity analysis

Functional connectivity methods were conducted according to previously published work (Simmons et al., 2008; Fonzo et al., 2010; Perlman et al., 2012) using the psychophysiological interaction method (PPI; Friston et al., 1997) adapted for AFNI (http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html). PPI analysis assesses whether connectivity between brain regions change under different psychological task conditions (Friston et al., 1997). Separate analyses were performed for each seed. The individual raw time series data underwent slice-time correction, Gaussian spatial smoothing with a 4.0 mm FWHM kernel, and bandpass filtering ($0.009 < f < 0.08$). Data points were despiked and censored if they differed by more than 2.5 standard deviations from the average EPI signal of the seed. For the first-level analysis, the deconvolved time series were extracted from each seed, multiplied with the condition regressor (FearStrong–FearNeutral), and then convolved with a modified gamma variate function to yield the interaction time series. Next, a multiple regression model was run separately for each seed to estimate the regression coefficient between all voxels and the interaction time series (along with task, movement, and linear drift as nuisance regressors). The strength of association between all voxels and the interaction time series was measured with R^2 values. These coefficients of determination were square-rooted then multiplied by the sign of their respective estimated beta weights to obtain directionality of association. The correlation coefficients of the interaction time series were then converted to z-scores using Fisher's transformation. The resulting statistical maps were then included in a second-level group analysis (MDD versus HCL) by running a voxel-based two-sample t-test on the z-scores of the interaction effect for each seed separately.

2.9. Linear ballistic accumulation (LBA) analysis

The LBA conceives of a two-choice decision as a race between two choice alternatives that begin at a *start point* (a) and accumulate evidence in favor of each respective choice (here, male or female; see Fig. S1 for a schematic of this process). The first accumulator to gather the criterion amount of evidence (*response threshold*, b) determines the subject's choice (e.g., male); the time taken to reach the response threshold (plus an extra constant time for sensory and motor processes, *non-decision time*, t_0) determines the response latency. The average speed at which each accumulator (one representing the correct response and one representing the error response) approaches threshold is termed the accumulator's *drift rate*. The difference between the drift rates of correct (v_c) and error accumulators (v_e) corresponds to perceptual sensitivity and can be thought of as a dynamic version of d' in signal detection theory (Ratcliff and McKoon, 2008). One advantage of a measure like drift rate over d', however, is that RT information is utilized in its calculation, instead of only hit rates and false alarms (Ratcliff and McKoon, 2008; White et al., 2010).

A hierarchical Bayesian method was employed to simultaneously uncover individual-participant parameters (which we used to correlate with individual differences in FC and clinical data) and group-level parameters (which we used to determine differences in cognitive processing between groups). Details of the estimation procedure can be found in *LBA Parameter Estimation* under material (see also Turner et al., 2012). Finally, we computed odds ratios (ORs) to provide a measure of statistical evidence for a difference between the group-level parameter distributions. For each group and each parameter we compared samples exhaustively drawn from the true distribution. A count was produced reflecting when the value drawn from the MDD distribution was larger than the value drawn from the HCL distribution. The mean count was then divided by 1 minus this count. All ORs were therefore calculated to be greater than 1, for ease of interpretation.

2.10. Sociodemographic and clinical scales analysis

Statistical analyses of all demographic and clinical scales were computed with R (R Development Core Team, 2012; http://www.r-project.org/) and Matlab (version 7.10; Natwick, MA). Within the MDD group only, correlations between extracted FC values (i.e., mean Fisher's z-scores) in the significant clusters identified in the PPI analysis and depression severity (i.e., BDI-II scores) were examined using two-tailed tests of Spearman's rank correlation coefficient (r_s). Among all the subjects with behavioral data, participant-level parameter estimates from the LBA model were also correlated with extracted FC values in the significant clusters identified in the PPI analyses, as well as depression severity (two-tailed tests of r_s).

3. Results

3.1. Sociodemographic and clinical scales

The MDD and HCL groups did not significantly differ in age ($t_{36}=0.68$, $p=0.50$), gender ($\chi^2_1=0$, $p=1$), and ethnicity ($U=206.5$, $p=0.42$). MDD adolescents endorsed significantly greater levels of depression as measured by the BDI-II ($t_{35}=7.20$, $p<0.0001$). For more details, see Table 1.

3.2. Behavioral

A two-way ANOVA with group as a between-subject factor and fear level as a within-subject factor was run separately for accuracy and response time (RT) data. Accuracy data showed a main effect of group ($F_{1,23}=5.56$, $p<0.05$), but not of fear level ($F_{2,22}=1.04$, $p>0.05$) nor was there a significant interaction ($F_{2,22}=0.90$, $p>0.05$). RT data showed no main effect of group ($F_{1,23}=1.47$, $p>0.05$), fear level ($F_{2,22}=1.19$, $p>0.05$) nor a significant interaction ($F_{2,22}=0.42$, $p>0.05$). Overall accuracy (mean ± SEM) for MDD and HCL was 81.76% ± 1.9% and 86.96% ± 0.63%, respectively. Overall RT (mean ± SEM) for MDD and HCL was 1358.2 ms ± 67.3 ms and 1252.8 ms ± 44.1 ms, respectively. See Fig. S2 for more details.

3.3. LBA parameter estimates

The LBA model yielded excellent fits to each subject's RT data (see Fig. S3 for more details). Table 2 summarizes the participant-level parameter estimates for each group. Fig. 2 displays the difference between the MDD and HCL groups for each LBA model parameters (and corresponding latent cognitive process). At the

group-level, MDD adolescents showed greater drift rates on trials where they responded correctly compared with HCL (OR=5.9:1), as well as on error trials (OR=18.2:1). As a result, perceptual sensitivity was lower in the MDD group (OR=6.4:1).

3.4. Group and task effects

The MDD group showed reduced activation in the left precuneus, left anterior cingulate cortex, and right precentral gyrus relative to the HCL group in the contrast of interest (FearStrong–FearNeutral; see Fig. S6 and Table S1 for more details). An examination of task effect showed greater activation in bilateral fusiform gyrus on FS compared to FN trials (see Fig. S7 and Table S2 in for more details).

3.5. Functional connectivity

We observed greater mean FC (i.e., Fisher's *z*-score) in the MDD relative to the HCL group between the right sgACC and a cluster in the left amygdala that extends into the striatum (see Fig. 3 and Table 3). We also observed decreased FC in the MDD relative to the HCL group between the right sgACC and left fusiform, right precuneus (extending into posterior cingulate), right middle frontal gyrus, left cingulate, right superior temporal gyrus (extending into the insula), and right middle temporal gyrus, as well as between the left sgACC and the left insula (extending medially into the putamen), left cingulate, right insula, and left middle frontal gyrus, (see Fig. 3, Table 3).

Table 2
Summary of participant-level LBA estimates. Reported here is the mean ± standard error of the median of posterior distributions of each participant-level parameter for each group. For more details on parameter estimation, see Section 2 and *LBA Parameter Estimation* in the Supplementary material. See Fig. S3 for model fits for each individual. For differences in group-level parameters, see Fig. 2.

LBA parameters	MDD	HCL
A (starting point)	2.29 ± 0.41	1.31 ± 0.13
b (response threshold)	1.75 ± 0.12	1.68 ± 0.04
v_c (drift rate for correct responses)	2.70 ± 0.02	2.45 ± 0.008
v_e (drift rate for error responses)	1.23 ± 0.04	0.80 ± 0.007
v_c–v_e (perceptual sensitivity)	1.47 ± 0.02	1.64 ± 0.001
t_0 (non-decision time)	0.22 ± 0.01	0.17 ± 0.03

3.6. Correlations

Within the MDD group only, depression severity correlated negatively with FC between the right sgACC and right precuneus ($r_s=-0.630$, $p=0.004$).

Among all subjects, perceptual sensitivity (based on the participant-level estimates) correlated positively with FC between right sgACC and right middle frontal gyrus ($r_s=0.47$, $p=0.011$) and also FC between right sgACC and left cingulate ($r_s=0.393$, $p=0.036$).

Finally, among all subjects, higher estimates of perceptual sensitivity were significantly associated with lower BDI-II scores ($r_s=-0.46$, $p=0.014$).

4. Discussion

To our knowledge, this study is the first to identify functional connectivity (FC) differences based in the subgenual anterior cingulate cortex (sgACC) during negative emotional processing in adolescents with major depressive disorder (MDD) compared to a sample of healthy controls (HCL). Importantly, all depressed subjects were antidepressant-naïve and with no diagnosed psychiatric comorbidities. We report three primary findings. First, adolescents with MDD showed altered FC in sgACC-based networks when evaluating negative emotional stimuli. Specifically, we found significantly greater FC between sgACC and amygdala and significantly decreased FC between sgACC and insula/putamen, fusiform gyrus, precuneus/posterior cingulate, and middle frontal gyrus in MDD relative to HCL (see Fig. 3 and Table 3). Secondly, among the depressed adolescents only, sgACC-precuneus connectivity strength correlated significantly with depression severity. Lastly, MDD exhibited lower perceptual sensitivity of emotionally negative stimuli than HCL (see Fig. 2 and Table 2). These individual differences in perceptual sensitivity were also significantly associated with sgACC-based functional connectivity, as well as with depression scores.

Based on prior resting-state studies in adolescent depression (Cullen et al., 2009; Davey et al., 2012; Gabbay et al., 2013; Connolly et al., 2013), we hypothesized finding differences in sgACC-based FC among salience, cognitive executive, and resting-state networks between adolescents with MDD and HCL subjects during the processing negative stimuli. However, the functional connectivity results in the aforementioned resting-state studies of adolescent depression are not entirely in agreement with one

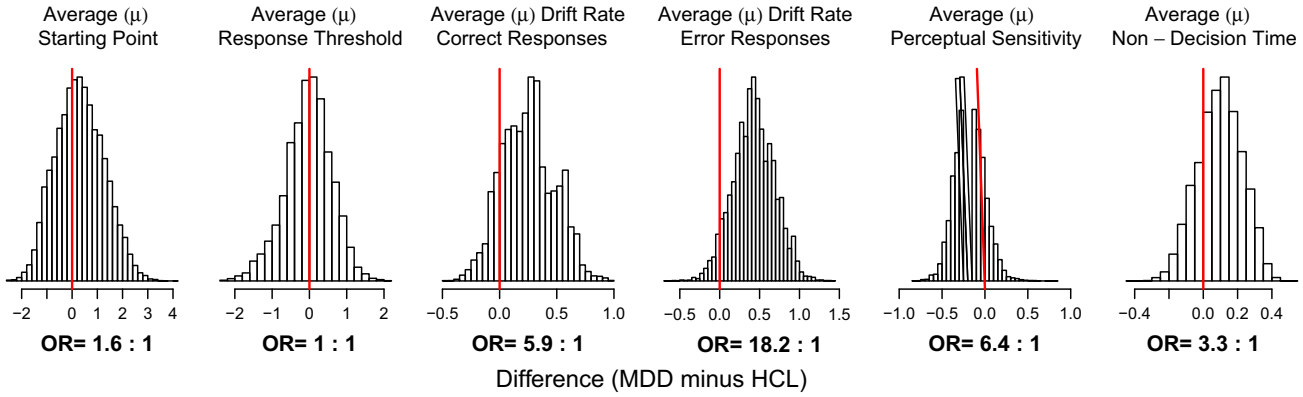

Fig. 2. Group differences in LBA parameters. Each panel shows the posterior predictive distribution of the magnitude (μ) of the difference between the MDD and HCL groups for each parameter of the LBA model. Positive differences indicate larger parameter estimates for the MDD group, while negative differences indicate smaller parameter estimates for the MDD group. A distribution peaking at zero (denoted by the red line at $x=0$) indicates no difference between groups for that parameter. Odds ratios (ORs) indicating amount of evidence in favor of a difference are reported beneath each panel. See Fig. S5 for posterior predictive distributions of the precision (σ) of the estimated group difference for each LBA hyper-parameter. To see posterior predictive distributions of each parameter for MDD and HCL separately, please see Fig. S4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

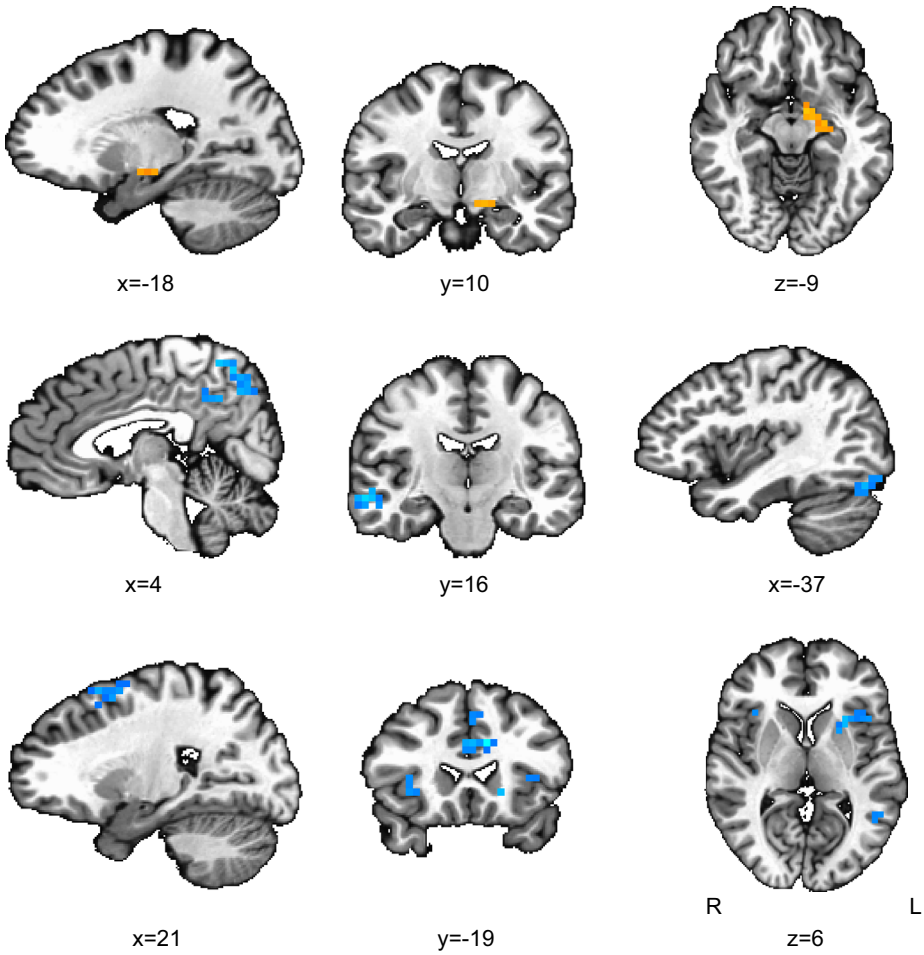

Fig. 3. Group differences in functional connectivity. We employed a psychophysiological interaction (PPI) method of functional connectivity, with bilateral subgenual anterior cingulate cortex (sgACC) defined as seeds and FearStrong–FearNeutral as the condition of interest. This analysis revealed the following clusters with significantly differently functional connectivity with sgACC in MDD relative to HCL (orange = increased, blue = decreased): All coordinates are in Talairach space and results are overlaid over a standardized Talairach template. Significance of each cluster is $p < 0.05$ (see *Controlling for multiple comparisons* under Section 2 for more details). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

Table 3
Location and size of significant clusters from the functional connectivity analysis. Results are based on a psychophysiological interaction (PPI) method of functional connectivity, with bilateral subgenual anterior cingulate cortex (sgACC) defined as seeds and FearStrong–FearNeutral as the condition of interest. Locations are reported according to center of mass of cluster in Talairach coordinates (radiological convention). See Fig. 3 for more details. MDD = major depressive disorder; HCL = healthy controls; and L = left; R = right.

Seed	Direction	Cluster	*x*	*y*	*z*	# of voxels (volume)
R-sgACC	MDD > HCL	L Amygdala/striatum	−16	10	−8	11 (704 μL)
R-sgACC	HCL > MDD	L Fusiform gyrus	−31,	74	−18	32 (2048 μL)
R-sgACC	HCL > MDD	R Precuneus/posterior cingulate	23	64	49	30 (1920 μL)
R-sgACC	HCL > MDD	R Middle frontal gyrus	21	−10	54	26 (1664 μL)
R-sgACC	HCL > MDD	L Cingulate	−3	45	36	17 (1088 μL)
R-sgACC	HCL > MDD	R Superior temporal gyrus/insula	53	45	21	12 (768 μL)
R-sgACC	HCL > MDD	R Middle temporal gyrus	57	16	−9	11 (704 μL)
L-sgACC	HCL > MDD	L Putamen/insula	−28	−14	6	18 (1152 μL)
L-sgACC	HCL > MDD	L Cingulate	−4	−20	26	14 (896 μL)
L-sgACC	HCL > MDD	R Insula/putamen	31	−16	2	13 (832 μL)
L-sgACC	HCL > MDD	L Middle frontal gyrus/cingulate	−5	−13	41	13 (832 μL)
L-sgACC	HCL > MDD	L Middle temporal gyrus	−49	46	11	12 (768 μL)

another, due to differences in medication status (only Connolly et al. (2013) and Gabbay et al. (2013) included medication-free subjects), age range (Davey et al. (2012) and Gabbay et al. (2013) included young adults), and comorbidities of their subjects, as well as differences in data acquisition (Cullen et al., 2009) allowed their participants to listen to music, data preprocessing, and analytical techniques.

Of these, the one by our group (Connolly et al., 2013) is most directly comparable to the present study, due to similar sgACC seed definitions, age range of subjects, and inclusion of an

antidepressant-naïve MDD cohort. Notably, our respective subject pools were completely independent, different MR scanners were used, and distinct preprocessing steps were employed on our respective fMRI datasets. Despite these differences, our results are strikingly similar. Specifically, we both find stronger sgACC-amygdala coupling, along with a decoupling between sgACC and the precuneus, superior temporal gyrus, and middle frontal gyrus in depressed adolescents. We also report both a significant negative correlation between sgACC-precuneus connectivity strength and depression severity. However, while Connolly et al. report greater sgACC-insula FC in their depressed group, we observe reduced sgACC-insula FC in ours. Additionally, we find decoupling between sgACC and fusiform gyrus and superior temporal gyrus in MDD relative to HCL, while no such group differences were seen in the study by Connolly et al. (2013).

Since the present study requires active task engagement, our results collectively suggest that increased FC between sgACC and the amygdala (a component of the salience network) and reduced FC between the sgACC and middle frontal gyrus (a component of the cognitive executive network) and precuneus (a component of the resting-state network) are potential functional identifiers of depression in youth regardless of brain state. This notion is consistent with work from adult depression (Greicius et al., 2007; Sheline et al., 2010; Menon, 2011; Drevets et al., 2008; Mayberg, 1997; Mayberg et al., 2005) suggesting that MDD is associated with sgACC dysregulation of stimulus-driven limbic activation (e.g., amygdala), which in turn may perturb communication with other sites involved in the immediate integration of salient and affective information (e.g., insula) and more higher order cognitive processing relating emotion with the self (e.g., precuneus, and middle frontal gyrus).

However, the decoupling between sgACC and insula that we observe in our depressed adolescents stands in contrast to the increased coupling between these areas observed by Connolly et al. (2013) in their resting-state study. It may be that sgACC-insula FC depends on or even indicates brain state. Indeed, neuroimaging evidence has demonstrated that portions of the insula are responsible for switching between task-negative (rest) and task-positive (non-rest) brain states in healthy controls (Craig, 2009; Sridharan et al., 2008). Nevertheless, the fact that there is a significant difference in sgACC-insula connectivity strength between MDD and HCL in both of our studies (albeit in opposite directions, as we each assessed opposite brain states) suggests that depressed adolescents may have difficulty transitioning between rest and non-rest. As the insula is a major node of the salience network (Menon, 2011), switching between rest and non-rest may be particularly difficult for depressed adolescents during the processing of affective information. Such difficulty could possibly underlie some of cognitive symptoms associated with MDD, including rumination (Hamilton et al., 2011; Berman et al., 2011a, 2011b; Joormann et al., 2011) and trouble disengaging from negative material (Gotlib et al., 2004; Siegle et al., 2002; Joormann et al., 2005).

Unlike Connolly et al. (2013), we also observed FC differences in sgACC-fusiform gyrus and sgACC-superior temporal sulcus between MDD and HCL adolescents. Given that the fusiform gyrus is highly implicated in face processing (Haxby et al., 1994; Kanwisher et al., 1997) and the superior temporal sulcus is sensitive to mouth and eye movements during emotive facial expressions (Puce et al., 1995, 1998; Harris et al., 2012), the sgACC-based FC group differences we see in these areas may be stimulus-dependent. The reduced coupling between sgACC and face-processing areas – in conjunction with greater sgACC-amygdala functional connectivity – may partially explain why our depressed group possessed lower perceptual sensitivity in our task, as the affectively negative value of our facial stimuli may have impacted processing and impaired judgment.

Lastly, the results of our cognitive behavioral model are in line with evidence that both depressed adults (Foland-Ross and Gotlib, 2012; Foland-Ross et al., 2013; Gotlib et al., 2004) and adolescents (Hankin et al., 2012; Hommer et al., 2013) show biased processing to affectively negative material compared to healthy controls. We observed greater drift rates in depressed individuals on both correct and error responses (see Fig. 2 and Table 2). Given that the decision in the task was to determine the gender of facial stimuli, these results suggest that depressed subjects may be more sensitive to or distracted by the negative value of the face and possibly less capable of inhibiting incorrect responses, resulting in poorer behavioral performance overall (i.e., lower accuracy and slower RT; see Fig. S2). Moreover, individual differences in perceptual sensitivity to negative stimuli not only predicted connectivity strength between the sgACC and cingulate, the latter of which is part of the salience network (Menon and Uddin, 2010), but perceptual sensitivity to negative material among all our subjects also correlated negatively with depression severity. These results suggest that depressed adolescents may fundamentally perceive salient, negative affective material differently compared to healthy controls and that differences in functional connectivity which support or reflect these information processing differences may be a potential indicator of illness severity.

One clinical implication of this work is that biased processing of negative material stems from sgACC dysregulation of stimulus-driven responses, which further provokes an imbalance among salience, cognitive executive, and resting-state networks often seen in early-onset depression at rest (Cullen et al., 2009; Davey et al., 2012; Connolly et al., 2013; Gabbay et al., 2013). While studies with remitted or high-risk samples are needed to determine whether this imbalance of functional networks is a trait- or state-marker of MDD, viewing these results within the theoretical framework that they are indeed trait-markers may partially explain why depressed individuals preferentially process negative stimuli, even during remission (Hankin et al., 2012; Joormann and Gotlib, 2007; LeMoult et al. 2009). The results we report here raise the possibility that cognitive therapies which aim to reverse biased processing of negative information (e.g., Lang et al., 2009; Hazen et al., 2009; Joormann et al., 2009, 2005) may help build resilience in those at-risk for developing this disorder by thwarting cognitive mechanisms, such as rumination, that exacerbate negative mood states and possibly maintain depression (Hamilton et al., 2011; Nolen-Hoeksema, 2000). In addition to identifying sgACC-based functional connectivity patterns as potential biomarkers of adolescent MDD, our study also demonstrates that combining cognitive behavioral models with brain measures provides a richer understanding of information processing differences associated with pathologies like depression. Such knowledge could potentially lead to better assessment and treatment of major depression and other affective disorders.

Nevertheless, this study must be interpreted in the context of its methodological limitations. Firstly, functional connectivity is a measure of correlated activity and should not be interpreted as proving the presence of causal connections (McIntosh, 2010). Future studies using effective connectivity (Friston et al., 1997; Friston, 2009; McIntosh, 2010), which test model-based assumptions about the effect of one neural system or region has over another, are needed to assess whether and how sgACC causally affects structures in the salient, cognitive executive, and resting-state networks. However, effective connectivity requires a more focused approach with explicit assumptions on subsections of networks that need to first be identified and validated in fMRI studies using simpler analytical methods, such as functional connectivity (McIntosh, 2010; Buchel and Friston, 2000). As our study is the first to report sgACC-based functional connectivity patterns in adolescent depression during negative emotional

processing, our hope is that these results will inform future effective connectivity studies. A second potential limitation is that we adhered to strict exclusion criteria in our depressed subjects so as to avoid bias from comorbidity when interpreting our findings. Since our MDD sample presented no psychiatric comorbidities and possessed little variability in age of illness onset, our results may not necessarily be generalizable to depressed youth more commonly seen in clinical practice. Investigating sgACC-based FC patterns in other subpopulations of adolescent MDD patients (e.g., prepubertal status, comorbidities, varying age of onset and duration of illness, etc.) is needed to assess the generalizability of our results.

In summary, the present work is the first to examine functional connectivity of the subgenual anterior cingulate cortex (sgACC) in antidepressant-naïve adolescents with major depressive disorder compared to a group of matched healthy controls. Our results join a growing body of resting-state and task-based fMRI research that point to dysfunction in sgACC-based circuits as a potential hallmark of depression in adults (Mayberg, 1997; Mayberg et al., 2005; Drevets et al., 2008; Matthews et al., 2008; Almeida et al., 2011; Pezawas et al., 2005; Chen et al., 2008; Hamani et al., 2011; Greicius, 2008; Stuhrmann et al., 2011; Johansen-Berg et al., 2008), adolescents (Yang et al., 2009; Cullen et al., 2009; Davey et al., 2012; Connolly et al., 2013; Ho et al., 2013; Gabbay et al., 2013), and even children (Gaffrey et al., 2010, 2012; Luking et al., 2011). Our findings therefore support the idea that the sgACC acts as a mediator between emotional and cognitive processing regions. Under this theoretical framework, biased processing of negative information in adolescent MDD may engage sgACC circuitry and possibly result in a greater imbalance among the salience, cognitive executive, and resting-state functional brain networks. Lastly, our study is the first to establish the use of a cognitive behavioral model to examine information processing differences between depressed and healthy populations that can potentially be used to augment understanding of the relationship between cognition and brain activation patterns in affective disorders.

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Conflict of interest

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Appendix A. Supplementary material

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