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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				