Published in final edited form as:

Neuroreport. 2009 March 4; 20(4): 440–444. doi:10.1097/WNR.0b013e3283262e10.

Depressed adolescents demonstrate greater subgenual anterior cingulate activity

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Abstract

Neuroimaging studies implicate the subgenual anterior cingulate cortex (sgACC) as a critical brain region in adult depression. However, unlike adult depression, little is known about the underlying neural substrates of adolescent depression, and there are no published data examining differences in sgACC activation between depressed and healthy adolescents. This study used functional magnetic resonance imaging to examine sgACC activity in twenty-six depressed and normal 13- to 17-year olds during the performance of a stop-signal task. Significantly greater sgACC activation was found in the depressed adolescents relative to controls. These results establish for the first time abnormal functioning of the sgACC in depressed adolescents and have important implications for understanding the underlying neural correlates and potential treatments of adolescent depression.

Keywords

adolescent; depression; FMRI; subgenual anterior cingulate cortex; prefrontal cortex; major depressive disorder; functional neuroimaging; functional MRI; pediatrics; mood disorder

INTRODUCTION

Adolescent depression is a major and costly problem. Epidemiological studies have demonstrated that up to 8.3 percent of adolescents in the United States suffer from depression [1]. By the time they enter their early adult years, at least 20% of adolescents have experienced at least one depressive episode [2]. The physical, social, and psychological changes taking place during adolescence make this time period a high risk for the development of depression.

Functional neuroimaging studies have begun to uncover the underlying neural correlates of depression. Several functional neuroimaging studies have clearly demonstrated the subgenual anterior cingulate cortex to be one brain region that is a part of an extended and complex cortical and subcortical network which is dysfunctional in depressed adults. In a positron emission tomography (PET) study of depressed adults, Mayberg et al. [3] reported that with sadness,

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there were increases in blood flow within the subgenual anterior cingulate cortex. With recovery from depression, decreases in blood flow within the subgenual anterior cingulate cortex were observed. Similarly, functional magnetic resonance imaging (fMRI) studies have found the anterior cingulate to be an important brain region in adult depression. In one fMRI study comparing depressed and non-depressed adults, the authors discovered the depressed adults exhibited increased activation in the subgenual anterior cingulate cortex [4]. To test the hypothesis that an inability to self-regulate negative emotions plays a pivotal role in the genesis of major depressive disorder (MDD), another fMRI study scanned depressed adults and controls [5]. The researchers found greater activation in the anterior cingulate cortex in the depressed adults relative to the controls.

While adult depression has been extensively studied, investigation of the underlying neural substrates of adolescent depression is very limited. To our knowledge, there are no published fMRI studies examining differences in brain activation within the subgenual anterior cingulate cortex between adolescents with major depression compared to matched, healthy controls. Thus, the main purpose of this 3-Tesla fMRI study was to examine subgenual anterior cingulate cortex activity in depressed adolescents relative to matched, normal adolescents. To this end, we used blood oxygenation level dependent fMRI (BOLD-fMRI) in combination with a fast event-related, parametric, stop-signal paradigm that has been shown to reliably activate the subgenual anterior cingulate cortex in both healthy adult [6] and adolescent [7] populations. Based upon the reviewed adult functional neuroimaging literature, we hypothesized that the subgenual anterior cingulate cortex would be more active in the depressed adolescents relative to the matched, healthy controls during the performance of the stop-signal task.

METHODS

Subjects

A total of 26 adolescents participated in this study. 13 adolescents (mean $\pm$ SD, 16.0 ± 1.5 years; range, 13-17 years; 7 girls, 6 boys) with a DSM-IV diagnosis of major depressive disorder were compared with a matched group of 13 healthy adolescents (mean $\pm$ SD, 15.8 ± 1.5 years; range, 13-17 years; 7 girls, 6 boys). All adolescents were right-handed. The depressed and healthy adolescents did not significantly differ in estimated IQ [$t(24) = -1.21$, $p = 0.273$], socioeconomic status ($X^2(8, n = 26) = 7.33$, $p = 0.501$), pubertal developmental stage (Tanner Stage) ($X^2(6, n = 26) = 4.200$, $p = 0.650$), age [$t(24) = 4.59$, $p = 0.650$], gender ($X^2(1, n = 26) = 0.000$, $p = 1.00$), ethnicity ($X^2(3, n = 26) = 0.000$, $p = 1.000$), and anxiety [$t(24) = 1.618$, $p = 0.119$]. Relative to the healthy controls, the depressed adolescents were significantly higher on the Children's Depression Rating Scale-Revised (CDRS-R) [$t(24) = 11.401$, $p = 0.00$] and lower on the Children's Global Assessment Scale (CGAS) [$t(24) = -13.984$, $p = 0.00$].

Healthy adolescents were recruited from all regions of San Diego through the use of posted flyers, e-mail, and the internet. Depressed adolescents were recruited from clinics in San Diego when they sought treatment.

Healthy adolescents were screened using the Computerized Diagnostic Interview Schedule for Children (DISC) version 4.0 [8] and the Diagnostic Predictive Scale (DPS) [9] to assess for the presence of any Axis I diagnoses.

For the potentially depressed adolescents, psychiatric diagnosis was determined through the administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [10] to both the adolescent and parent (s) by an experienced child and adolescent psychiatrist. Using the K-SADS-PL, all adolescents met criteria for current major depressive disorder. None of the depressed adolescents had psychotic features.

All participants were administered the following items: (1) Wechsler Abbreviated Scale of Intelligence (WASI) [11], (2) Customary Drinking and Drug Use Record (CDDR) [12], (3) Standard Snellen Eye Chart, (4) Ishihara Color Plates Test (8 plate, 2005 edition), (5) Family Interview for Genetics Studies (FIGS) [13], (6) Edinburgh Handedness Inventory [14], (7) Children's Depression Rating Scale-Revised (CDRS-R) [15], and Children's Global Assessment Scale (CGAS) [16]. The CDRS-R and CGAS were administered by an experienced child and adolescent psychiatrist. In addition, each participant completed the following self-administered questionnaires: (1) Tanner Stage [17], (2) demographics questionnaire, (3) medical and developmental history form, and (4) Multidimensional Anxiety Scale for Children (MASC) [18].

Adolescents ages 13 to 17 years with major depressive disorder from all ethnicities and both genders were allowed to participate. All patients were medication-free and symptomatic. Exclusionary criteria for the depressed adolescents included: (1) having a full IQ score of less than 80 on the WASI; (2) being color blind or having less than 20/40 correctable vision as determined by the Ishihara color plates and Snellen eye chart; (3) any contraindication to MRI imaging (ferromagnetic implants, braces, claustrophobia); (4) any history of neurological disorder (e.g., meningitis, migraine, HIV), head trauma with loss of consciousness >2 minutes, learning disability, serious physical health problem, or a complicated or premature birth <33 weeks of gestation (exclusionary due to potentially abnormal neurodevelopment); (5) being pregnant or suspect being pregnant; (6) any evidence of illicit drug use, misuse of prescription drugs, or more than 2 alcohol drinks per week either currently or within the past 6 months as determined by the CDDR; (7) left-handedness; (8) prepubertal status (Tanner stages 1 or 2); (9) inability to fully understand and cooperate with the study procedures; (10) a current diagnosis of PTSD; (11) present or past diagnosis of anorexia nervosa, bipolar disorder, autism, or schizophrenia; (12) use of medication with central nervous system effects within the past 2 weeks prior to scanning; (13) CDRS-R score less than 55.

Healthy adolescents were excluded from the study for any of the items listed for the depressed adolescents and for any of these additional reasons: (1) any current or lifetime DSM-IV Axis I psychiatric disorders as determined by the DISC and DPS; (2) any family history of mood or psychotic disorders in first- or second-degree relatives as assessed by the FIGS.

This study was approved by the University of California at San Diego (UCSD) and Children's Hospital and Health Center (CHHC) Institutional Review Boards. All subjects provided written assent, and their parent/legal guardians provided written informed consent to participate. All subjects were financially compensated.

Experimental Task

The visual stimuli, an "X" or an "O", in white capital letters appeared on a black background back-projected to the MRI room subtending a visual angle of approximately 6°. Subjects were told to press as quickly as possible the right button whenever an "O" appeared and the left button when an "X" appeared. Additional details of this task have been published elsewhere [6]. Subjects were also told that when they heard a tone delivered through headphones during a trial, they were not to press either button. Stimuli appeared at the beginning of each of the trials. Each trial lasted 1300 ms or until the subject responded. Trials were separated by 200 ms interstimulus intervals (blank screen). The individual response latency was used to denote the period of inhibitory processing and provided a naturally jittered reference function. Subjects performed seventy-two total stop trials which were pseudo-randomized throughout the task and counterbalanced. Six blocks were performed, each containing 48 total trials (12 stop and 36 non-stop trials in each block). Task instructions were presented for 12 seconds between blocks.

Just prior to scanning, each subject performed the stop task in a behavioral testing session to determine their mean reaction time (RT). Based upon this data, 6 different trial types were designed based on the amount of time after the beginning of the trial (when an “X” or “O” stimuli first appeared) when the stop signal was delivered: those when the stop signal was delivered at the subject’s mean RT, and those when the stop signal was delivered at 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial. Behavioral response data were collected on all subjects during the scan.

Image Acquisition

A fast event-related fMRI design was employed. Images were acquired on a 3-T GE scanner (General Electric, Milwaukee, WI) with Twin Speed gradients using a GE 8-channel head coil. Each session consisted of a three-plane scout scan, high-resolution anatomical scan, T2*-weighted echo-planar imaging (EPI) scan to measure the blood oxygen-level dependent (BOLD) response, and EPI-based field maps to correct for susceptibility-induced geometric distortions. Functional scans covering the entire brain were acquired parallel to the anterior and posterior commissure (T2*-weighted EPI, TR = 2000 ms, TE = 32 ms, FOV = 23 × 23 cm, 64 × 64 matrix, thirty 2.6 mm oblique slices parallel with the ac-pc axial plane with a 1.4 mm gap, 256 repetitions, 512 seconds). During the same experimental session, a T1-weighted image with an inversion time of TI = 450 ms to null the CSF (FSPGR, TR = 8.0 ms, TE = 3.1 ms, flip angle = 12°, FOV = 25 cm, matrix = 256 × 256, 0.98 × 0.98 × 1.0 mm³ voxels) was collected in the sagittal plane for anatomical reference.

Statistical Analysis of Imaging Data

All functional and structural image processing and analyses were conducted with the Analysis of Functional NeuroImages (AFNI) software [19]. Details of the image analysis pathway have been published elsewhere [6,20]. To minimize motion artifact, an AFNI 3D-coregistration algorithm (3dvolreg) was used to realign all echoplanar images. Data were time-corrected for slice acquisition order, and the time series data for each individual were analyzed using a multiple regression model (3dDeconvolve).

For the analysis of task difficulty, three task regressors of interest: “easy” (MRT-400ms and MRT-500ms), “medium” (MRT-200ms and MRT-300ms), and “hard” (MRT and MRT-100ms), and five nuisance regressors: roll, pitch, yaw (to account for residual motion), baseline (which included block instructions), and linear trend (to eliminate slow signal drifts) were entered into a linear multiple regression. Prior to inclusion in the regression model, the task-related regressors were convolved with a modified gamma variate function to account for the hemodynamic delay and the slow rise and fall of the hemodynamic response. Activation in each voxel during each specific task condition was divided by the baseline activation to obtain the percent signal difference for each task condition.

A 4-mm full width half maximum Gaussian filter was applied to the voxel-wise percent signal difference data to account for individual variations in anatomical landmarks. After smoothing, each subject’s data were normalized to Talairach coordinates and a whole-brain mask screened out non-brain voxels.

The ANFI program 3dttest was used to examine differences in brain activation between the depressed and non-depressed adolescents for the all-stop minus non-stop condition.

A threshold/cluster method was then applied. This threshold adjustment method was based on Monte-Carlo simulations and was utilized to guard against identifying false positive areas of activation using a 4 mm FWHM Gaussian filter. Based on these simulations, it was determined

that a minimum volume of 704 μl and a connectivity radius of 4.0 mm was necessary to ensure that a voxel-wise a-priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05. Percent signal change values for the contrasts were extracted from significant brain clusters for further analysis.

Statistical Analyses of Behavioral and Clinical Scales Data

All behavioral and correlational statistical analyses were carried out with SPSS 14.0 [21]. Correlational analyses of the task-related activation in the subgenual anterior cingulate cortex and bilateral medial frontal gyrus with the Children's Depression Rating Scale-Revised and Children's Global Assessment Scale were conducted for both groups combined.

RESULTS

Behavioral Data

The depressed (mean=665ms; SD=103ms) and healthy (mean=696ms; SD=142ms) adolescents were not different in their mean reaction times ($F(1,24)=0.387$, $p=0.540$) during the non-stop trials, indicating that the two groups did not differ in vigilance during the task. By design, both groups committed significantly more errors during the hard (Depressed: mean=93%; SD=11%. Controls: mean=91%; SD=18%) than easy trials (Depressed: mean=34%; SD=21%. Controls: mean=44%; SD=27%), ($F(2,23) = 104.5$, $p<0.001$). No significant group ($F(1,24) = 0.437$, $p = 0.515$) or group by task ($F(2,23) = 1.424$, $p = 0.261$) effects on error rate were found indicating that the depressed and healthy control groups were not significantly different in their accuracy during any of the trials.

Functional Neuroimaging Whole-Brain Analysis

The whole-brain analysis revealed several brain regions that were significantly different in activation between the depressed and healthy adolescents. For the all-stop minus non-stop condition, the depressed adolescents demonstrated greater activation than did the healthy control subjects in the subgenual anterior cingulate cortex (Brodmann Areas 24, 25, 32; $x = -11.8$, $y = 35.0$, $z = -5.4$; cluster volume = 2176 μl ; $t[25] = 4.024$). In comparison, the depressed adolescents showed less activation than did the healthy controls bilaterally in the medial frontal gyrus (Brodmann Area 10; $x = -0.5$, $y = 51.6$, $z = 7.2$; 2240 μl ; $t[25] = 3.972$) and visual cortex (Brodmann Areas 17, 18; $x = -2.3$, $y = -71.1$, $z = 5.3$; 960 μl ; $t[25] = 3.490$) for the same contrast (Figure 1). All coordinates are Talairach coordinates (x , y , z).

Correlational Analysis

Greater subgenual anterior cingulate cortex activation was associated with higher scores on the Children's Depression Rating Scale-Revised (Spearman's $\rho = 0.57$, $p = 0.002$, two-tailed) and lower scores on the Children's Global Assessment Scale (Spearman's $\rho = -0.60$, $p = 0.001$). In contrast, greater bilateral task-related medial frontal gyrus activation was associated with lower scores on the Children's Depression Rating Scale-Revised (Spearman's $\rho = -0.60$, $p = 0.001$) and higher scores on the Children's Global Assessment Scale (Spearman's $\rho = 0.62$, $p = 0.001$).

DISCUSSION

The present study is the first one to use a fast, event-related, parametric, individualized stop-signal task design to examine differences in brain activation between depressed adolescents and matched controls. The whole-brain analysis yielded two important main findings: (1) depressed adolescents demonstrated greater activation of the subgenual anterior cingulate

cortex relative to the normal adolescents, and (2) depressed adolescents showed less activation of the medial frontal gyrus compared to the healthy controls.

To our knowledge, this study is the first to report fMRI whole-brain findings of significant differences in activation between depressed adolescents and matched, healthy controls in the subgenual anterior cingulate cortex and medial frontal gyrus. The adult functional neuroimaging studies implicate the subgenual anterior cingulate cortex as one of several critical brain regions in depression. Our finding of significantly greater subgenual anterior cingulate cortex activation in the depressed adolescents relative to the matched, healthy controls is consistent with several adult depression studies using PET [3] and fMRI [4,5]. Additionally, our finding of decreased medial frontal gyrus activation in the depressed adolescents compared to the controls is consistent with the much larger adult functional neuroimaging literature examining the prefrontal cortex in depression. A comprehensive review of PET studies in depression found that decreased prefrontal cortex blood flow and metabolism in depressed adults are the most consistently replicated findings in the PET literature [22]. Similar to the PET findings, results from fMRI studies in adults have also shown decreased prefrontal cortex activity in depressed adults compared to never-depressed, healthy controls [23]. Of particular note, our results are consistent with Mayberg and colleagues' model of adult depression in which the prefrontal cortex and subgenual anterior cingulate cortex play a crucial role [3]. In their model, decreases in blood flow to the prefrontal cortex and increases in blood flow to the subgenual cingulate are associated with sadness whereas the reverse pattern involving the same brain regions is seen in the recovery from depression. Although preliminary, our findings suggest that perhaps Mayberg and colleagues' model of adult depression might be extended to include depressed adolescents as well.

The results of the present study may have important clinical implications for the treatment of adolescent depression. Several functional neuroimaging studies in depressed adults have shown that the subgenual anterior cingulate cortex is important both as a specific target site for the application of deep brain stimulation in treatment-resistant depression [24] and as a brain region associated with the successful response to treatment using antidepressants or cognitive behavioral therapy [25]. While several such functional neuroimaging studies have been done in adults, no such similar research has been performed in depressed adolescents. Our findings suggest that future studies may wish to focus on the subgenual anterior cingulate cortex as a potential target site for the treatment of adolescent depression. Finally, given that adults and adolescents differ from one another in clinically important areas such as medication response, future studies should include both depressed adults and depressed adolescents to directly compare these two groups for any significant differences in brain activation.

CONCLUSION

By using a fast, event-related, parametric, individualized stop-signal task design to study potential differences in brain activation between depressed adolescents and matched healthy controls, we demonstrated for the first time that depressed adolescents showed significantly greater subgenual anterior cingulate cortex activity than normal adolescents. Our results have important implications for both the understanding of the underlying neural correlates and the potential clinical treatment of adolescent depression.

ACKNOWLEDGEMENTS

We would like to acknowledge the invaluable help of Dr. Rebecca Theilmann, Dr. Scott Roesch, Dr. Don Slymen, Kevin Hahn, and Sarah Jurick.

Support: This work was supported by grants from NIMH (K23MH70791) and NARSAD Foundation to TTY.

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Figure 1.

Sagittal image showing whole-brain results of significant activation differences between the thirteen depressed adolescents and thirteen matched, healthy controls in the bilateral medial frontal gyrus (A), subgenual anterior cingulate cortex (B), and bilateral visual cortex (C). Bar graphs on the right side show the percent signal change in the medial frontal gyrus (A) and subgenual anterior cingulate cortex (B) for the Easy and Hard conditions in the depressed (MDD) adolescents and healthy controls (CTL). Error bars indicate Standard Error (SE).