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Depressed Mood and Lateralized Prefrontal Activity During a Stroop Task in Adolescent Children

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Abstract

Negative affective style and depressive disorders share a common pattern of brain activation asymmetry in adults, characterized by reduced left relative to right prefrontal activation. It is not clear whether a similar pattern of asymmetry is related to depressive mood state during the period of adolescence, an important stage of emotional and brain development. We correlated Beck Depression Inventory (BDI) scores from 16 adolescents with prefrontal, anterior cingulate, and amygdala activity during functional magnetic resonance imaging (fMRI) of the Stroop Interference task. Depressed mood correlated positively with activity in the left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate gyrus, and negatively with activity in the right DLPFC. When interpreted from a compensatory recruitment perspective, findings suggest that affective lateralization in adolescents is consistent with that seen in adulthood.

Keywords

fMRI; Neuroimaging; Adolescence; Depression; Mood; Dorsolateral Prefrontal Cortex; Anterior Cingulate; Amygdala; Limbic System; Development

The neurobiological systems responsible for affective processing and mood regulation appear to be differentially lateralized across the two cerebral hemispheres [4]. Differences in the balance of activity between the left and right prefrontal cortices may account for differences in affective style, the trait-like variability among individuals in mood and emotional responsiveness [6]. Electroencephalographic (EEG) studies suggest that individuals with relatively greater baseline activation of the left prefrontal cortex are more prone toward approach-related behavior and positive affect, whereas those with relatively greater right prefrontal cortex activation are more likely to show withdrawal-related behavior and negative affect [3]. Moreover, a right-lateralized pattern of EEG asymmetry often appears to be a stable trait marker for depression, as it is present even in previously depressed patients following recovery [14].

Though mostly studied in adults, some limited evidence suggests that similar affect-related cerebral asymmetries may also be present in infants and children [5]. At present, however, there remains a dearth of information regarding the lateralization of affective processes during adolescence and it is not clear whether these patterns change with maturation. Adolescence is

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a period of rapid development, involving changes in physical appearance, secondary sexual characteristics, and social and emotional awareness. Moreover, these changes occur in conjunction with significant developmental re-organization of the brain [9]. A comprehensive understanding the development of affective neural systems during adolescence is particularly important because affective experiences at this stage are predictive of clinical mood disorders during adulthood [30], and may lead to more targeted approaches to prevention and treatment of mood disorders. Therefore, in the present study, we examined the relationship between adolescent self-ratings of depressive mood and functional responses within left versus right dorsolateral prefrontal cortex during a cognitively demanding Stroop Interference task. The Stroop task relies heavily upon the anterior cingulate gyrus and has been shown to draw upon the resources of the prefrontal cortex [21], particularly as cognitive demands are increased. The compensatory recruitment hypothesis suggests that when a region of the brain is temporarily fatigued or otherwise compromised, the brain compensates with an increased Blood Oxygen Level Dependent (BOLD) response in the affected and adjacent regions in order to sustain roughly equivalent levels of performance on cognitively demanding tasks [8]. Assuming depressed mood or negative affective style is associated with greater left hemisphere dysfunction, as suggested by the literature, we hypothesized that this region of the brain would compensate during a demanding Stroop Interference task via increase task-related BOLD activity. This increase was hypothesized to correlate positively with simple ratings of depressive mood in the left but not the right DLPFC in a sample of adolescents.

Methods

Subjects

Sixteen healthy adolescent children (9 male; 7 female) ranging in age from 8 to 15 years ($M = 11.6$, $SD = 2.1$) participated (15 right-handed). We have previously reported data for a different fMRI task on these same children [17]. They were without significant history of psychiatric or neurologic illness, were free of any history of alcohol or illicit drug use, and possessed normal or corrected normal visual acuity. Participants were recruited by newspaper advertisements within the local community of Belmont, MA. Prior to participation, procedures and potential risks were explained in full to the children and their parents. Assent was obtained from all children and parents provided written informed consent prior to enrollment. Small financial compensation was provided.

Beck Depression Inventory

Prior to scanning, each child underwent a battery of psychometric tests and questionnaires assessing social and emotional functioning. Of interest here, participants completed the Beck Depression Inventory (BDI), a well-validated and extensively used measure of depressed mood [2]. Although originally designed for use with adult populations, a number of studies have demonstrated the utility and validity of the BDI with young adolescents [15,16,27].

FMRI Stimulation Paradigms

The children underwent several functional neuroimaging scans designed to test a variety of cognitive and affective processes. For this investigation, participants completed a version of the Stroop Color-Word Interference Test. Detailed descriptions of this paradigm have been published elsewhere [11]. Briefly, the task was completed in a series of three 2.5 minute scans: 1) Color Naming, which consisted of a series of 10 screens each presenting a line of six red, green, and blue colored rectangles (2500 msec stimulus; 500 msec inter-stimulus interval); 2) Word Naming, which consisted of a series of 10 screens each presenting a line of text comprising six randomly ordered words of “red”, “green”, and “blue” printed in black ink (2500 msec stimulus; 500 msec inter-stimulus interval); 3) Color-Word Interference, which consisted of a series of six screens each presenting a line of text comprising six printed words

of “red”, “green”, and “blue” printed in an incongruent color (4500 msec stimulus; 500 msec inter-stimulus interval). Each run consisted of five alternating 30-second stimulus/rest periods lasting 150 seconds (i.e., rest, naming, rest, naming, rest). Rest periods consisted of a simple fixation point. The visual stimuli were projected onto a translucent screen located at the foot of the scanning bed via a magnetically shielded LCD video projector and observed through a mirror mounted on the head coil. For Color-Naming, participants named aloud the color of the ink in which the rectangles were printed. For Word Naming, participants read aloud the words on the screen as quickly as possible. For the Interference task, participants were instructed to ignore the printed words and to name aloud the color of the ink in which the words were printed. Responses were made vocally through a microphone and recorded by a technician.

Neuroimaging Methods

Following a standard acquisition sequence published previously [19], functional data were acquired using a 1.5 Tesla GE LX MRI scanner fitted with a quadrature RF head coil (TR = 3 sec, TE = 40 msec, flip angle = 90 degrees). At the outset of each scan, three dummy images were acquired and discarded prior to analysis. For each scan, fifty echoplanar images were acquired over 20 coronal slices (7mm, 1mm gap), with a 20 cm field of view and a 64×64 acquisition matrix with in-plane resolution of $3.125 \times 7 \times 3.125$ mm. In addition to functional images, matched T1-weighted high-resolution images were collected at the beginning of each session.

Image Processing

The data were preprocessed in SPM99 [10]. Using standard algorithms, the data were motion corrected in three axes, normalized to the three-dimensional space of the Montreal Neurological Institute (MNI), spatially smoothed using a non-isotropic Gaussian kernel (full width half maximum [FWHM] = 8 mm), and resliced to $2 \times 2 \times 2$ mm isotropic voxels using sinc interpolation. Data were convolved to a boxcar waveform derived from the experimental design and the hemodynamic response function implemented in SPM99, subjected to a high-pass filter to remove low frequency confounds, and globally normalized.

Statistical Analysis

Statistical parametric mapping followed a two-step random-effects approach [25]. At the first stage, the Color Naming and Interference conditions were concatenated to form a single design matrix permitting a direct contrast between the functional of these two conditions (i.e., [Interference – Fixation] – [Color Naming – Fixation]). These contrast images isolated the activity unique to the interference condition minus the activity associated with the process of verbally naming colors. In the second stage, contrast images were then used as the dependent variables in a random-effects multiple regression analysis in SPM99 [25]. BDI scores were entered as the covariate of interest and participant age was entered as a nuisance variable. The analysis was restricted to the dorsolateral prefrontal cortex, anterior cingulate gyrus, and amygdala by constructing a region of interest (ROI) that included the superior, middle, and inferior frontal gyri (trigone region), the anterior cingulate gyrus, and the left and right amygdala, as defined by the published anatomical atlas of Tzourio-Mazoyer and colleagues [28] as implemented in the Wake Forest University PickAtlas Utility [22]. Regions of activation within the ROI were evaluated at an uncorrected threshold of $p < .005$, and k (extent) = 20 contiguous voxels.

Results

Behavioral Data

Beck Depression Inventory—Scores on the BDI ($M = 5.33$, $SD = 4.03$) ranged from 0 to 12, generally falling within the normal to minimally depressed range based on previous studies [2,18]. For further analysis, BDI scores were transformed into z-scores based on the sample mean and standard deviation. All scores were within 2 SD of the sample mean, suggesting that there were no statistical outliers.

Stroop Task—For each task, the percent of correct responses was calculated and compared using a repeated-measures analysis of variance with Greenhouse-Geisser correction.

Performance differed across the three tasks, $F(1.4, 20.9) = 5.33$, $p = .022$, with mean scores on Color Naming ($M = 83.4$, $SD = 15.4\%$) and Interference ($M = 83.9$, $SD = 16.3\%$) significantly lower ($p < .05$, Bonferroni corrected) than Word Reading ($M = 91.8$, $SD = 11.2\%$). Scores on Color Naming ($r = .05$, $p = .87$), Word Reading ($r = .02$, $p = .93$), and Interference ($r = -.31$, $p = .24$) tasks were not significantly correlated with BDI scores.

Functional Imaging

Regression Analysis—BDI scores were entered into a random-effects multiple regression analysis within SPM99 to predict activity in the *a priori* defined ROI, with age entered as a covariate. Controlling for age, three clusters within the ROI showed positive correlations with BDI score (see Table 1). Specifically, there was a significant positive correlation between BDI scores and activity within the left middle frontal gyrus ($r = .78$, $p < .001$) and the trigone of the left inferior frontal gyrus ($r = .73$, $p = .001$; see Figure 1). BDI scores were also positively correlated with activity within the left anterior cingulate gyrus ($r = .72$, $p = .002$). In contrast, BDI scores were negatively correlated within a region of the middle frontal gyrus within the right hemisphere ($r = -.78$, $p < .001$; see Figure 1 and Table 1). Functional responses were not correlated with depressed mood in either the left or right amygdala.

Laterality Index—We calculated an index of lateralized activation for the baseline Color-Naming and Stroop Interference conditions. Two functionally defined lateralized ROIs were created from the significant voxel clusters yielded by the regression analysis and saved as region masks in SPM. For each subject, we then re-ran the individual SPM contrast of Stroop Interference – Color Naming at a height threshold of $p < .05$, $k = 0$, and calculated the number of suprathreshold voxels in the left and right hemisphere ROIs. Each hemispheric ROI was corrected for total volume by dividing the number of suprathreshold voxels in that region by the total number of voxels comprising the ROI (Left = 513 voxels; Right = 82 voxels). Thus, for both ROIs, a proportion of active voxels was obtained (ranging from 0 to 1.0). Subtracting the proportion of active voxels in the ROI on the left from those on the right yielded a laterality index that ranged from -1.0 (indicating total left lateralized suprathreshold activity) to $+1.0$ (indicating total right lateralized suprathreshold activity). This procedure was conducted for the baseline (i.e., Color-Naming) and the experimental (i.e., [Interference]-[Color-Naming]) contrasts separately. For Color-Naming, the laterality index ($M = +0.15$, $SD = 0.36$) did not differ significantly from zero, $t(15) = 1.65$, $p = .12$, but did show a positive correlation with BDI scores ($r = .56$, $p = .023$; see Figure 1d), suggesting that higher depressive mood was associated with greater right lateralized activity. This laterality index was not significantly correlated with performance measures on the Stroop, including Color-Naming ($r = -.30$, $p = .26$), Word-Reading ($r = -.22$, $p = .42$), or Interference ($r = -.12$, $p = .67$) subtests. For the more cognitively demanding Stroop Interference – Color-Naming contrast, this index ($M = -0.12$, $SD = 0.32$) also did not differ significantly from zero, $t(15) = -1.55$, $p = .14$. Consistent with predictions, however, the laterality index was significantly negatively correlated with scores on the BDI ($r = -.84$, $p < .001$; see Figure 1d), suggesting that higher depression was associated

with relatively greater left lateralized activity. This laterality index was also not correlated with performance measures on the Stroop, including Color-Naming ($r = .15$, $p = .58$), Word-Reading ($r = .06$, $p = .83$), or Interference ($r = .32$, $p = .23$) subtests.

Discussion

During a cognitively demanding Stroop Interference task, BOLD responses within the left and right DLPFC showed opposite patterns of correlated activity with self-ratings of depressed mood in a sample of young adolescent children. Higher scores on the BDI were associated with greater task related BOLD responses in the left middle and inferior frontal gyri, and the left anterior cingulate gyrus, suggesting greater compensatory responsiveness to overcome the presumed reduction in left prefrontal cortex baseline activity that is commonly demonstrated among individuals with a negative affective style and withdrawal related tendencies [3], dysphoric mood [7], and/or depressive disorder [13]. In contrast, higher scores on the BDI were associated with reduced responsiveness of a similar region within the right prefrontal cortex. The hypothesis was further supported by the calculation of a laterality index to show the relative activation of the ROIs in each hemisphere. While higher BDI scores were associated with greater left lateralized activity during the highly demanding Interference condition, greater right lateralized activity was correlated with depressed mood for the less demanding baseline Color Naming condition. Thus, each hemisphere showed opposing patterns of task-related activity that was directly related to the severity of BDI score. Interestingly, we found no significant relationship between BDI scores and amygdala activity during any condition.

Davidson [4] has proposed that individuals showing trait-like asymmetry of anterior EEG activity also show reliable trait-like differences in affective style. Those with relatively lower left than right prefrontal EEG activity tend to exhibit a negative affective style and this asymmetry appears to serve as a diathesis toward developing a depressive disorder [4]. The present findings are consistent with this position, suggesting that more resources within the left hemisphere were recruited to sustain performance in those adolescents with the most severe depressive mood. Similar compensatory responses occur when prefrontal blood flow is temporarily reduced due to sleep-loss [8]. These findings are also consistent with neuroimaging research showing decreased left prefrontal resting baseline activity in patients with current [13] or remitted depression [14].

The Stroop Interference task relies heavily upon the resources of the anterior cingulate gyrus in healthy adult individuals [20]. Because depression is disruptive to normal cognitive function [23], additional brain resources may need to be recruited for depressed patients to achieve comparable performance, resulting in hyperactivity in left prefrontal circuits in these patients when performing highly demanding cognitive tasks [12]. These results are similar to findings in non-medicated depressed adults who show increased activity in the left dorsolateral prefrontal cortex and rostral anterior cingulate gyrus during the Stroop task when compared to healthy controls [29]. When viewed from a compensatory recruitment perspective, the present findings suggest that elevations in depressive mood may disrupt left anterior frontal regions, necessitating the recruitment of additional cortical resources to sustain performance. Furthermore, greater depressive mood appeared to reduce the utilization of right prefrontal regions during the Interference task but not during the baseline Color Naming task. These findings extend the theory that negative mood states and depression are associated with an alteration in the relative balance of baseline activation between the anterior regions of the left and right hemispheres [3] to include young adolescents.

It should be pointed out that the lateralized model of resting EEG developed by Davidson and colleagues is not universally supported, as some studies find either no relationship between frontal EEG asymmetry and the severity of depression [1,26] or even a reversed pattern of

asymmetry during negative mood states (i.e., greater left than right) [24]. Consequently, it could be argued that the present findings, rather than reflecting compensatory processes, may simply reflect that depressive mood state is actually characterized by greater left lateralized activity. While we acknowledge such a possibility, our finding of a correlation between greater right lateralized activity and BDI scored for the baseline Color-Naming condition argue against this possibility by suggesting that greater rightward asymmetry is observed during a less demanding task, but shows compensatory activity during a more demanding one. As with any correlational study, it is possible that the findings may have been influenced by uncontrolled factors, such as individual differences in personality, hormone levels, nutritional status, sleep status, or familiarity with similar tasks. Replication of these findings with independent samples will be necessary to disconfirm such possibilities.

Together, the findings from the present study and our previous report [17] suggest that the neurobiological aspects of depressive mood severity, including ventromedial increases during affective face processing and left dorsolateral compensatory increases during a demanding cognitive task are consistent with findings in adults, suggesting a continuity of these processes from adolescence through adulthood. It should be pointed out, however, that the range of mood scores in the present sample were all within the non-clinical range. It is, therefore, not certain whether the observed hemisphere specific relationships would be sustained as the level of depressed mood approaches the range of clinical depression.

Conclusion

During the Stroop Interference task, depressive mood scores in adolescent children were positively correlated with BOLD activity in the left dorsolateral prefrontal cortex and anterior cingulate gyrus, while correlating negatively with activity in a homologous region of the right hemisphere. When considered in light of the compensatory recruitment hypothesis, these findings are consistent with adult models of the relationship between hemispheric asymmetry of resting prefrontal brain activity and negative affective style, suggesting a continuity of affective brain function from adolescence into adulthood.

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Figure 1.

Beck Depression Inventory (BDI) scores were significantly correlated with activity in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate (AC) gyrus ($p < .005$, uncorrected) during the Stroop Color Word Interference task. Furthermore, the direction of correlated activity differed as a function of hemisphere. (a) Maximum intensity projections show that the left DLPFC and AC were positively correlated with scores on the BDI, whereas (b) activity in the right DLPFC was negatively correlated with BDI severity. (c) Scatterplots show the relationship between BDI (z-score units) and the age adjusted fMRI response at the local maxima in the left DLPFC (left), left AC (middle) and right DLPFC (right). (d) Scatterplots show the positive correlation between the laterality index and BDI z-scores for the Color-Naming (left) condition and the negative correlation for the same variables in the Interference-Color Naming (right) condition.

Significant Correlations between Beck Depression Inventory Scores and BOLD Signal Intensity in the Dorsolateral Prefrontal Cortex and Anterior Cingulate Gyrus ROIs

Table 1

Region of Activation	Brodman Area	Active Voxels	x	y	z	z-score
Positive Correlations						
L. Middle Frontal Gyrus	9/44/46	401	-40	26	36	3.75
L. Inferior Frontal Gyrus (trigone)	48	60	-48	20	22	3.34
L. Anterior Cingulate Gyrus	10/11/32	52	-6	44	2	3.29
Negative Correlations						
R. Middle Frontal Gyrus	45/46	82	42	40	36	3.75

Note. L = left hemisphere, R = right hemisphere. Atlas coordinates are listed in the standard space of the Montreal Neurological Institute (MNI). All activated voxels within the ROI are significant at $p < .005$, uncorrected. k threshold (extent) = 20.