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An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder

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Abstract

The pathophysiology of pediatric bipolar disorder impacts both affective and cognitive brain systems. Understanding disturbances in the neural circuits subserving these abilities is critical for characterizing developmental aberrations associated with the disorder and developing improved treatments. Our objective is to use functional neuroimaging with pediatric bipolar disorder patients employing a task that probes the functional integrity of attentional control and affect processing. Ten euthymic unmedicated pediatric bipolar patients and healthy controls matched for age, sex, race, socioeconomic status, and IQ were scanned using functional magnetic resonance imaging. In a pediatric color word matching paradigm, subjects were asked to match the color of a word with one of two colored circles below. Words had either a positive, negative or neutral emotional valence, and were presented in 30 second blocks. In the negative affect condition, relative to the neutral condition, patients with bipolar disorder demonstrated greater activation of bilateral pregenual anterior cingulate cortex and left amygdala, and less activation in right rostral ventrolateral prefrontal cortex (PFC) and dorsolateral PFC at the junction of the middle frontal and inferior frontal gyri. In the positive affect condition, there was no reduced activation of PFC or increased amygdala activation. The pattern of reduced activation of ventrolateral PFC and greater amygdala activation in bipolar children in response to negative stimuli suggests both disinhibition of emotional reactivity in the limbic system and reduced function in PFC systems that regulate those responses. Higher cortical cognitive areas such as the dorsolateral PFC may also be adversely affected by exaggerated emotional responsivity to negative emotions. This pattern of functional alteration in affective and cognitive circuitry may contribute to the reduced capacity for affect regulation and behavioral self-control in pediatric bipolar disorder.

Keywords

Functional magnetic resonance imaging (fMRI); attention; emotion; affect; cognition; child; adolescent

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1. Introduction

Affect disturbance, characterized by rapid mood swings and chronic morbidity, is central to pediatric bipolar disorder (PBD) (Geller et al., 2004; Pavuluri et al., 2005). However, the pathophysiology underlying this disturbance remains unknown. In addition, cognitive dysfunction, including deficits in attention, memory and executive functions, are also prevalent in this disorder, regardless of medication or illness status (Dickstein et al., 2004; Pavuluri et al., 2006b). While affective disturbance and cognitive deficits can manifest independently and have different pathophysiologies, they may have important functional interactions. Unmodulated emotions could disrupt cognitive operations, and reduced cognitive control could reduce top-down modulation of the intensity and duration of emotional experiences.

Non-human primate studies (Goldman-Rakic, 1988; Barbas, 1995, 2000), clinical studies of human patients with focal lesions (Manes et al., 2002), and functional magnetic resonance imaging (fMRI) studies in healthy adults (Walker, 1940; Goldman-Rakic, 1996; Petrides and Pandya, 2002) provide a framework for translating the understanding of prefrontal cortex (PFC) in affect regulation. Petrides and Pandya (2002) described the reciprocal connectivity between rostral mid-lateral convexity of PFC at the junction of Brodmann Areas (BA) 45, 47 and 9/46 and the amygdala. The rostral mid-lateral convexity of PFC (Goldman-Rakic, 1996) consisting of ventrolateral PFC (VLPFC or inferior frontal gyrus/BA 47 and 45) and dorsolateral PFC (DLPFC/BA 9 and 46/middle frontal gyrus) appears especially important as a junction where inputs from executive cognitive systems are integrated with inputs from emotional processing areas (Petrides and Pandya, 2002). This PFC area, specifically VLPFC, is believed to be involved in top-down regulation of emotional responses by providing information about reward and punishment through evaluation of affective stimuli (Barbas and Pandya, 1989; Cools et al., 2002; Goel and Dolan, 2003). This way, and via interaction with other brain regions, it contributes to experience and regulation of affective states. It has been established that DLPFC (BA 9 and 46) is involved in higher level functions including shifting attention, working memory, and voluntary response inhibition. It regulates emotional responses in a context-dependent manner via its rich connectivity to the dorsomedial PFC (DMPFC or superior frontal gyrus) and pregenual cingulate, as well as via interactions with immediately adjacent VLPFC (Manes et al., 2002; Phillips et al., 2003; Fichtenholtz et al., 2004). This systems-level understanding of prefrontal circuitry in relation to emotional processing provides an important framework for developing models of pathophysiology in PBD.

fMRI studies in adult bipolar disorder have added insights into functional abnormalities in cognitive and affective brain systems in this disorder, further placing the emphasis on frontolimbic dysfunction (Strakowski et al., 2004; Altshuler et al., 2005; Malhi et al., 2005). Studies using affective and non-affective Stroop paradigms found under-activation of the left VLPFC (BA47) (Strakowski et al., 2004; Altshuler et al., 2005) that appears to be a “trait” deficit in adult bipolar disorder. Similar to the studies in adult bipolar disorder that used varied tasks (Blumberg et al., 2003b; Malhi et al., 2005), two studies that directly probed frontolimbic circuitry in PBD (Pavuluri et al., 2006a; Rich et al., 2006) showed VLPFC dysfunction with increased activation in amygdala in response to emotional faces in PBD. The nature of VLPFC dysfunction varied across PBD studies with decreased activation in response to emotional faces (Pavuluri et al., 2006a) and increased activation in response to neutral faces (Rich et al., 2006). It is yet to be determined if emotional stimuli result in decreased activity in VLPFC and thereby, its ability to modulate amygdala. Further, in conjunction to greater activation of amygdala in PBD patients in functional imaging studies, structural imaging studies point to smaller amygdala in pediatric patients relative to healthy controls (Blumberg et al., 2003a; DelBello et al., 2004; Chen et al., 2004; Dickstein et al., 2005; and Chang et al., 2005). However, the size of the amygdala is larger or normal in adult bipolar patients (Strakowski et al., 1999; Altshuler et al., 2000; Brambilla et al., 2003). These findings suggest potential

intrinsic abnormalities of the amygdala in PBD and its role in developing affective circuitry disturbance.

It is also vital to understand the impact of emotional valence on the interfacing affective and cognitive circuitry function. In healthy adults, negative emotional regulation recruits cognitive regions known to serve the attention and executive function such as DLPFC and also the higher cortical region responsible for affect regulation, the VLPFC (Fossati et al., 2003; Ochsner et al., 2004). These PFC regions may not be efficiently functioning in PBD patients given excessive reactivity and bias to negative emotions (Brotman et al., 2007; Rich et al., 2004) and were shown to reduce activation in DLPFC and VLPFC (Pavuluri et al., 2006a). However, the behavioral data on positive emotions is divided, indicating improved (Ashby et al., 1999; Davidson et al., 1990) or impaired (Phillips et al., 2002) working memory and attention in healthy adults. In order to understand emotional reactivity to these emotions and design effective treatment strategies, we aim to study the effect of negative and positive emotions on the affective and cognitive circuitry.

Therefore, based on models developed in basic affective neuroscience research and preliminary evidence from bipolar patients, we hypothesized that while making a simple perceptual decision about affective vs. emotionally neutral stimuli, PBD patients relative to healthy controls will show: (1) greater amygdala activation, (2) reduced activity in VLPFC, and (3) reduced activation in DLPFC. Further, we hypothesized that, within PBD group, negative word matching will result in decreased activation in the PFC regions, and positive word matching may not affect the neural circuitry to the same degree as negative emotions.

To test these hypotheses, a pediatric color word matching paradigm was developed to assess frontal lobe and amygdala responses during a task with concurrent cognitive and emotion processing demands. In order to understand the pathophysiology of more trait-like disturbances in PBD that are less influenced by acute illness states or treatment effects, euthymic unmedicated PBD patients were recruited for this study.

2. Methods

2.1 Subjects

Subjects between 12 and 18 years of age were recruited from the University of Illinois at Chicago (UIC) Pediatric Mood Disorders Clinic and from the surrounding community. Six subjects from an initial pool of 16 PBD subjects and four subjects from an initial pool of 14 healthy subjects were excluded due to motion artifacts. Informed consent was obtained from at least one parent, and assent was obtained from each subject. The study was approved by the Institutional Review Board at the UIC.

Inclusion criteria for PBD subjects were diagnosis of bipolar type I disorder, euthymic phase, and agreement to be scanned in a medication-free state. PBD patients were euthymic for a minimum of four months prior to testing. Euthymia was defined by the subject not meeting DSM-IV criteria for major depression, dysthymia, mania, or hypomania. Presence of current comorbid DSM-IV diagnoses was an exclusion criterion, with exception of attention deficit hyperactivity disorder (ADHD). Each child and a parent were interviewed using the Washington University Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS; Geller et al., 1998). Current and life-time unmodified DSM-IV diagnosis was made based on consensus decision from information gained from an independent clinical interview, other available clinical data, and ratings on the WASH-U-KSADS. Patients were medication free by choice of patient or parents, or because they were participating in a medication free trial under medical supervision in our pediatric mood disorders program. All patients were previously on mood stabilizers and/or second generation antipsychotics, with or without

stimulants. They were not receiving CNS-active medications for at least seven days prior to the scan. None of them were on aripiprazole or fluoxetine that would have required a longer wash-out period. Medication dosages were reduced gradually over a three week duration prior to the drug-free period. The last medications withdrawn were stimulants. Healthy controls were interviewed using the WASH-U-KSADS to ensure the absence of mental disorder. Exclusion criteria for all subjects included presence of a neurological condition, history of head trauma with loss of consciousness exceeding 10 minutes, substance use disorder, use of medication altering cerebral blood flow (i.e., medication for migraine or blood pressure), IQ < 80, or the presence of metallic implants, retractors or braces. IQ was estimated using Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999).

2.2 Pediatric color word matching paradigm

A pediatric color word matching paradigm was designed to examine brain activity associated with processing emotional words during a cognitive task. The task assessed the ability to attend and respond to target words by matching the color of the words to one of two colored dots presented beneath the word on the display screen. Trials were balanced for correct responses (left or right dots) and colors used. Affective words targeted affective domains relevant to PBD. Positive words reflected feelings of happiness, energy, accomplishment, and success. Negative words reflected feelings of depression, disappointment, and rejection. Words were at an eight-year-old reading level, and were equivalent across affect conditions in frequency of usage (Klein, 1964; Kucera and Francis, 1967; Gilhooly and Logie, 1980; Bradley and Lang, 1999). No word was repeated during the task.

Subjects were presented with separate blocks (30 seconds each) of positive, negative, and neutral words in a pseudo-random order. Each block was separated by a 10 second fixation period to provide rest periods during testing, and to allow for hemodynamic responses to return toward resting level before the next block of trials. A block consisted of 10 word presentations. Each word was presented for 200 milliseconds, followed by a response period of 2.8 seconds. Two colored dots were presented beneath the word throughout the 3 second trials. Participants were instructed to press the button (left or right) to match the color of the word to the correct color dot as illustrated in Figure 1, and to “respond as quickly as possible”. This task had three noteworthy characteristics. First, it directed attention to a simple perceptual characteristic of the words (color) rather than to their semantic meaning. Second, words were presented only briefly (200 milliseconds). Third, it required a simple cognitive operation and response choice (color matching) that could be easily performed by all subjects. Together, these features maximize the impact of automatic affective responding rather than deep semantic processing of words.

A color high-resolution LCD projector projected visual stimuli onto a rear projection screen that was viewed via an angled double mirror system mounted on a standard GE head coil. During the scan, a camera monitored subject's right eye to ensure attention to visual stimuli. The accuracy and reaction time (RT) of button press responses were averaged within each condition for each participant. Prior to imaging studies, participants spent approximately 20 minutes in a mock scanner to acclimate them to the scanner environment.

2.3 Image acquisition

MRI studies were performed using a 3.0 Tesla whole body scanner (Signa, General Electric Medical System, Milwaukee, WI). Functional images were acquired using gradient-echo echo-planar imaging, which is sensitive to regional alterations in blood flow via blood oxygenation level dependent (BOLD) contrast effects (Kwong et al., 1992). Twenty-five axial slices were acquired (TE=25ms; flip angle = 90°; field of view = 20x20 cm²; acquisition matrix = 64x64; TR=2.5s; 5mm slice thickness with 1mm gap). Anatomic images were acquired in the axial

plane from all subjects (three-dimensional spoiled gradient recalled [SPGR], 1.5mm thick contiguous slices) for co-registration with the functional data.

2.4 Image processing and data analysis

FIASCO software (Functional Imaging Analysis Software – Computational Olio; Eddy et al., 1996) was used to estimate and correct for head motion. Individual volumes from the time series were excluded from analysis if head displacement from the median head position in the time series was greater than 1.5mm or if head rotation from the median head position was greater than 0.5 degrees. The number of volumes retained after discarding those with motion artifact did not differ across groups. For each subject, voxelwise *t*-maps were computed by separately comparing images acquired during the two emotion conditions (positive and negative) each with the neutral word condition. As an additional approach for characterizing within-subject activation effects, voxelwise effect size (*r*) maps were calculated for each subject for each pairwise condition contrast, and then Fisher *z* transform was applied to normalize the data (*zr*; Rosenthal, 1991).

AFNI software (Analysis of Functional Neuroimages; Cox, 1996) was used to transform individual subjects' *t*-maps, *zr*-maps (effect size) and SPGR anatomical images into Talairach space using AFNI's automated Talairach procedure (Talairach and Tournoux, 1988). Functional maps were resampled to an isotropic 3x3x3 grid, which has a size similar to that of the in-plane resolution of acquired data. Primary analyses were voxelwise between group *t*-tests on the effect size maps. Interpretation of group comparisons were supplemented by within group average *zr*-maps used to identify brain areas where significant task-related activation and deactivation occurred in each group.

For within-group contrasts of affect conditions (positive and negative each vs. neutral) and for between-group contrasts, significant effects were identified with a contiguity threshold which maintained an experiment-wise protected Type 1 error rate of $P < 0.05$ based on AFNI's AlphaSim Monte Carlo simulations. This procedure determines the number of contiguous voxels with activation above a given voxelwise threshold required to identify activation in a brain region. The contiguity threshold approach identifies clusters of voxels with activation over a threshold, rather than performing independent voxelwise comparisons. The rationale for contiguity analyses is that in neocortical areas, real activation is expected in larger areas of adjacent tissue than the size of a single voxel. Looking only for clusters of active voxels minimizes false positive errors in isolated single voxels, while simultaneously minimizing false negative misclassifications resulting from extremely conservative Type 1 error protection required by voxelwise approaches.

In addition to whole brain analysis, activation within smaller brain structures of interest were assessed separately, as effects within smaller structures could not be expected to survive a contiguity threshold determined for the whole brain analysis. For these analyses, individual *zr*-maps were used to count the number of voxels with activation above a threshold of $P < 0.05$ threshold in specified regions (unprotected; $zr = 0.18$). Voxel counts in these smaller 'a priori' regions of interest were subjected to non-parametric statistics comparing the subject groups. The smaller ROIs included *limbic regions such as amygdala, hippocampus, and parahippocampal gyrus*. These regions as defined in AFNI format as well as the rationale for ROI definitions are available at

http://ccm.psych.uic.edu/Research/NormalBrain/ROI_rules.htm and

http://ccm.psych.uic.edu/Research/ResearchProgram/NormalBrain/ROIaffect_rules.aspx

3. Results

3.1 Clinical and demographic data

Demographic and clinical data are summarized in Table 1. On the Young Mania Rating Scale (YMRS) and the Child Depression Rating Scale-Revised (CDRS-R), the PBD group's ratings were 6.1($SD=3.7$) and 21.7($SD=6.8$), respectively. Healthy subjects were rated significantly lower on the YMRS than PBD subjects ($t [df_{18}] = 4.58$; $P<0.001$) but the groups did not differ on CDRS-R ratings. Six subjects with PBD met criteria for lifetime diagnosis of ADHD.

3.2 Behavioral data

Response time (RT) and accuracy data were analyzed in separate repeated measure ANOVAs with word type (neutral, negative, positive) as a within-subjects factor. For RT data, there was not a significant main effect of diagnosis ($F(1, 18) = 2.24$, ns) or a diagnosis by word type interaction ($F(2, 36) = 0.67$, ns). There was, however, significant main effect of word type ($F(1,36) = 5.61$, $P<0.05$), with both groups showing longer latencies for negative than positive words ($t [df_{19}] = 2.74$, $P<0.05$). For mean accuracy measures, there was no significant main effect of word type ($F(2,36) = 0.68$, ns) nor diagnosis by word type interaction ($F(2,36) = 1.81$, ns). However, there was significant main effect of diagnosis ($F(1,18) = 4.81$, $P<0.05$), with the PBD group performing less accurately than the healthy group for positive ($F(1,19) = 5.07$, $P<0.05$), neutral ($F(1,19) = 4.63$, $P<0.05$) and negative words ($F(1,19) = 4.37$, $P<0.05$). Median RT and mean accuracy measures for each group for each word type are summarized in Table 2.

3.3 Imaging data

3.3.1 fMRI activity for negative vs. neutral conditions—The healthy group's activation during the negative condition, relative to the neutral condition, was characterized by significant signal increases in bilateral DMPFC and posterior cingulate as well as in the left VLPFC and left insula.

The pattern of activation in PBD patients during the negative (vs. neutral) condition was characterized by significant signal increases in left DMPFC, left insula and left pregenual anterior cingulate (Figure 3). In contrast, there was decreased activation bilaterally at the rostral aspect of the junction between right VLPFC and DLPFC which includes the putative interface of the cognitive and emotional processing regions. This effect was bilateral, but especially prominent in the right hemisphere. Decreased activity was observed in right middle temporal gyrus.

Between-group comparison of the differences between negative and neutral conditions revealed a greater activation for PBD group in bilateral pregenual anterior cingulate. There was also less activation in right rostral VLPFC and DLPFC in PBD patients due to a relative signal reduction in the PBD group not seen in healthy individuals. The PBD group also displayed reduced activation in bilateral DMPFC.

3.3.2 fMRI activity for positive vs. neutral conditions—In the healthy group, activation in response to positive words (vs. neutral) was characterized by greater activation bilaterally in DMPFC and posterior cingulate. There were also unilateral increases in response to positive words in the right anterior cingulate, right VLPFC, right DMPFC, right DLPFC and the left middle temporal gyrus.

In the PBD group, increased activation in bilateral DMPFC was observed in the positive condition. Decreased activation was noted in the right insula and right superior temporal gyrus.

Significant signal changes were not evident in the rostral VLPFC/DLPFC junction in contrast to the effect observed with negative words.

Between-group comparisons revealed less activation in the PBD group relative to the healthy group in posterior cingulate, DMPFC bilaterally in response to positive words. Additionally, the PBD group had less activation than the healthy group in insula, and VLPFC/orbito frontal cortex region, due primarily to less activation in positive than neutral words in the PBD group.

The decrease in activation within VLPFC region in PBD group appeared much smaller with positive words relative to neutral words than with negative words relative to neutral words. In order to directly examine this potential difference between positive versus negative word matching within PBD group, we compared the two conditions. There was a significantly greater activation in the bilateral DLPFC and VLPFC and right superior temporal gyrus, fusiform gyrus and occipital gyrus in response to positive words relative to negative words. There was also decrease in activation in DLPFC in response to negative words relative to positive words within the PBD group. A similar comparison among healthy subjects did not show such discrepancy in activation in response to the negative and positive words. These results are illustrated in Figures 2 and 4.

3.4 Analysis of smaller Regions of Interest

Mann-Whitney *U* tests of the number of active voxels for each subject within the amygdala, hippocampus, parahippocampal gyrus, and caudate nucleus were conducted for the negative and positive word conditions (each vs. neutral). Between group differences were found only in the left amygdala ($U = 24.50, P < 0.05$) in response to negative words, with the PBD group displaying a greater number of active voxels. There was also a similar trend for the right amygdala ($P = 0.08$) and left hippocampus ($P = 0.08$). No significant group differences were found in response to the positive relative to neutral words for any of the regions. Counts of significant voxels in these regions are summarized in Table 3.

4. Discussion

This study examines the interface between cognitive and affective neural circuitry. The current study used unmedicated euthymic PBD patients, removing potential confounds of acute symptoms (mania or depression) or medication effects. We excluded comorbid disorders, other than lifetime diagnosis of ADHD, to reduce diagnostic confounds. Our central findings indicate overactivation of amygdala and reduced activation of VLPFC in response to negative stimuli in PBD patients. This suggests a pattern of excessive emotional arousal in limbic areas coupled with reduced activation in PFC regions believed to regulate those responses. In addition, PBD patients showed reduced activation in DLPFC, suggesting that cognitive activation supporting trial-dependent response choices was reduced in PBD patients in the context of negative affect. This pattern of excessive activation of amygdala and reduced activation in DLPFC was not as evident in response to positive stimuli in PBD patients, although very minimally reduced in VLPFC region. However, in adult bipolar patients, mild happy faces elicited increased response in subcortical and VLPFC regions relative to healthy controls, but healthy controls showed greater activation to intense happy faces (Lawrence et al., 2004). The variability in response to differing degrees of positive stimuli could be due to developmental differences in pathophysiology of bipolar disorder or due to task related differences with varying intensity of emotional stimuli.

Our behavioral data did not show a greater slowing of reaction times for the affect conditions in PBD patients when compared to healthy individuals. This could be due to our relatively small sample size, but fMRI methods were sensitive to detect regional differences in neural functioning during trials with emotional words.

4.1 Overactivity of the amygdala

The amygdala plays a crucial role bestowing emotional valence to experiences that is critical for appropriate multimodal information processing by PFC (Altshuler et al., 2005; Blumberg et al., 2005). In the current study, increased amygdala activation was observed in PBD patients in response to only the negatively valenced emotional information. This heightened amygdala response could result from intrinsic disturbances to the amygdala, such as arrested development of amygdala given that smaller amygdala volumes have been reported in PBD previously (DelBello et al., 2004; Dickstein et al., 2005; Chang et al., 2005). However, another possibility is that this hyperactivation is a result of reduced top-down input from areas of PFC believed to modulate amygdala activity and that were observed to have reduced activation in the PBD patients.

Similar to our findings, Rich and colleagues (2006) reported greater left amygdala activation in PBD patients rating neutral facial expressions on their hostility and fearfulness. Even with neutral faces, attention to potential negative emotions triggered a heightened amygdala response. Additionally, as has been demonstrated in PBD (Pavuluri et al., 2006a), there are reports of amygdala overactivation in adult bipolar patients in response to facial emotional stimuli (Yurgelun-Todd et al., 2000; Lawrence et al., 2004; Altshuler et al., 2005; Blumberg et al., 2005). Thus, excessive limbic reactivity to emotional stimuli in bipolar disorder appears to occur across pediatric and adult patients. The present findings in euthymic patients suggest that this disturbance in PBD may be a trait deficit.

The extent to which this increased amygdala response is related to intrinsic disturbances in amygdala vs. reduced modulation by neocortical systems remains an important question for future studies. There are important reciprocal connections between amygdala and neocortex in regions that our data suggest are functioning in an abnormal way in PBD. This functional reciprocity includes not only top-down generation and regulation of amygdala responses from neocortex, but the regulation of neocortical systems by the amygdala. For example, there is strong amygdalofugal inhibitory input onto neocortical γ -aminobutyric acid (GABA) interneurons (Cunningham et al., 2002) arising from the basolateral nucleus (Vogt et al., 1992). These amygdalo-cortical connections continue to mature throughout the adolescence and influence emotional development (Benes et al., 1994).

4.2 Underactivity of the VLPFC: Impaired top-down regulation

Amygdala overactivity may also be, in part, a result of the observed dysfunction in VLPFC. This region provides top-down regulation of affective responses in the amygdala. We recently demonstrated a pattern of decreased activation of right VLPFC and increased amygdala activity (Pavuluri et al., 2006a) using a passive facial affect processing task with PBD patients. The present findings indicate a similar pattern during a behavioral paradigm in which cognition-affective interactions were examined. Both positive and negative emotions may impact the higher cortical centers of emotion regulation in PBD. But it appears that the negative emotions have greater effect than positive emotions. The VLPFC activation is reduced in response to both negative and positive conditions relative to healthy controls, showing that the PBD patients are affected by emotional stimuli. However, within PBD group, VLPFC and DLPFC activation is much greater and less affected by positive emotions while this is relatively reduced with negative emotions that appear to have greater impact on the regulatory higher cortical system (Figure 4). These findings implicate that the higher cortical centers of cognitive and affective circuitry are not efficiently recruited under the stress of being exposed to negative emotions in PBD patients, unlike the healthy adults (Fossati et al., 2003; Ochner et al., 2004) or healthy children in our study (Figure 4). These results indicate a need to modify use of “negative consequences” in behavioral modification strategies in psychosocial treatments.

There is intricate connectivity between VLPFC, DLPFC and limbic system, thought to be responsible for the top down regulation. Direct feedforward excitatory afferents from PFC and thalamus to pyramidal cells in amygdala have been described (Lane et al., 1998; Szinyei et al., 2000). These fibers interact with GABAergic interneurons in amygdala to reduce pyramidal cell activity, and via this mechanism are believed to modulate affective responses that are contextually inappropriate or exaggerated in magnitude or persistence. VLPFC (BA 12, 45, 47) has strong intrinsic connections to DLPFC, DMPFC, OFC and anterior cingulate (Owen et al., 1996), and is believed to play a critical role in affect regulation through top-down biasing (Desimone and Duncan, 1995; Petrides and Pandya, 2002).

Adult bipolar studies have demonstrated decreased activation in the rostral region of VLPFC during both cognitive and emotional Stroop tasks (Blumberg et al., 1999; Blumberg et al., 2003b; Malhi et al., 2005). Notably, in acutely ill adult patients performing tasks requiring attention and response inhibition during fMRI paradigms, underactivation in the right VLPFC (Robinson et al., 1988; Blumberg et al., 2003b; Altshuler et al., 2005) was noted. While our task does not involve response inhibition like a Stroop task, similar findings are seen in our unmedicated and euthymic PBD patients. Therefore, pathophysiology of narrow phenotype of PBD (bipolar disorder Type I and II, that does not include broadly defined categories) may be very similar to adult bipolar disorder. Lesions resulting from brain injury to the right VLPFC have resulted in secondary mania (Robinson et al., 1988; Starkstein et al., 1988) consistent with the role of this brain region in affect modulation. Further, this pattern of reduced activity in an area that integrates and provides top down cortical modulation of the amygdala, present while viewing negative but not positive stimuli, suggests a selective impact on the regulation of adverse emotions by this frontoamygdala circuitry in PBD.

4.3. Impaired cognitive function: Interface between affective and cognitive areas

One aspect of our color word matching paradigm was it introduced emotional interference during a cognitive response-choice task. This feature provides insights into affective neural system dysfunction in PBD and its impact on DLPFC regions supporting higher cognition. Reduced activation of DLPFC in PBD patients in response to negative but not positive word matching suggests possible vulnerability of this region to perturbation by aversive emotional stimuli in PBD. This finding supports our third hypothesis of an increased impact in PBD of affective stimuli on the functioning of cognitive systems in DLPFC. It is well established that DLPFC is central to diverse cognitive functions pertinent to cognitive tasks involving response selection, executive control and problem solving (Duncan and Owen, 2000). There are strong reciprocal connections between VLPFC and DLPFC that work together to support the integration of higher emotional and cognitive processes (Bush et al., 2000; Petrides and Pandya, 2002). Dysfunctional operation of the higher neurocognitive systems in the presence of aversive stimuli may be an important aspect of the pathophysiology of PBD. In a developmental context, this may compromise the maturation of cognitive abilities and contribute to established persistent neuropsychological deficits in PBD.

The pregenual anterior cingulate was also more active in patients when negative words were presented. This region is an intermediate structure between isocortex and allocortex in lamination and connectivity and receives extensive modulatory input from DLPFC. The increased activation of the pregenual anterior cingulate region and amygdala, along with decreased activation in DLPFC and VLPFC in response to negative stimuli, suggest that the top-down regulation of limbic emotional systems may be dysfunctional in PBD.

These results must be interpreted in the light of some limitations. The small numbers make it difficult to offer definitive conclusions, or further examination of laterality effects and comment on the effect of comorbid ADHD. Additionally, it remains uncertain if inattention seen in these children is a residual symptom of bipolar diathesis or due to independent ADHD,

given the persistence of related cognitive symptoms in euthymic PBD patients (Pavuluri et al., 2006b). However, one of the strengths in our study is the inclusion of well characterized homogenous sample of unmedicated euthymic Type I bipolar youth, and the exclusion of comorbid disorders other than ADHD. Another potential limitation is that the PBD patients were exposed to medications even though they were off the psychotropics for several days. Also, an event related design would have offered further precision in isolating the effects of emotional interference on cognitive function compared to the block design, although the power is enhanced with multiple trials in a block.

4.4 Conclusion

Findings from the present study with unmedicated euthymic PBD patients provide new insights into the affect dysregulation that characterizes the disorder and its potential impact on cognitive function. Our results demonstrate overactivity of the pregenual anterior cingulate and amygdala as well as reduced activation at the dorsal convexity of the PFC in the VLPFC and DLPFC areas during processing of words with negative emotional associations. This limbic overactivity could be due to reduced top-down control from VLPFC and/or to intrinsic limbic abnormalities. Dysfunction in interfacing affective and cognitive brain areas was seen during challenge with negative but not positive affect. While the underlying causes of this pattern of dysfunction remain to be further explored and clarified, our results demonstrate disturbances in both the cognitive and affective brain systems in PBD, and suggest mechanisms through which these disturbances could interact in problematic ways in a developmental context.

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Figure 1.
Pediatric Affective Stroop Paradigm

Figure 2. Negative and Positive Condition Effect Size Maps

PANEL A: Negative emotion task PANEL B: Positive emotion task; PICTURES A show Effect size maps of pediatric bipolar disorder (PBD) patients' activation while responding to emotion words relative to neutral words. PICTURES B show Effect size maps of healthy controls' (HC) activation while responding to emotion words relative to neutral words. In both columns A and B, red indicates either increased activation with emotion words or decreased activation with neutral words while blue indicates either increased activation with matching neutral words or decreased activation matching emotion words. PICTURES C show Effect size maps of PBD patients (red) and HC (blue) activation patterns while responding to emotion words. All images show right sagittal slice -41.

Figure 3. Negative vs. Neutral Condition Effect Size Map
comparing healthy controls' activation (blue) and pediatric bipolar patients' activation (red)
in response to negative emotion words, (right sagittal slice -7)

Figure 4. Positive vs. Negative Condition Effect Size Maps

Pictures A shows an Effect size map of pediatric bipolar patients' activation in response to positive emotion words (red indicating activation) compared to negative emotion words (blue indicating activation, but absent). Picture B shows healthy control activation in the same comparison, (coronal slice -48)

Table 1

Demographic and Clinical Characteristics for Healthy Individuals (HC) and Subjects with Pediatric Bipolar Disorder (PBD)

Variables	HC Mean (SD)	PBD Mean (SD)	Analysis <i>t</i> ; (<i>P</i>)
Age (years)	16.2 (1.32)	15.0 (2.36)	0.406; (0.177)
Est. FSIQ [*]	110.7 (10.68)	110.7 (9.43)	0.000; (0.99)
WRAT-3, Reading (SS) [†]	105.6 (9.56)	107.4 (11.35)	0.385; (0.706)
YMRS	0.40 (1.26)	6.10 (3.7)	4.582; (0.001)
CDRS-R	18 (0.00)	21.7 (6.8)	1.729; (0.101)
	<i>N</i> (%)	<i>N</i> (%)	Fisher's <i>P</i>
Sex			0.370 (ns)
Male	3 (30%)	6 (60%)	
Female	7 (70%)	4 (40%)	
Race			0.070 (ns)
Caucasian	3 (30%)	8 (80%)	
Other	7 (70%)	2 (20%)	

* Estimated with Wechsler Abbreviated Scale of Intelligence (WASI; Matrix Reasoning and Vocabulary Subtests);

[†] Wide Range Achievement Test – Third Edition (WRAT; Reading Subtest); KYMRS = Kiddie Young Mania Rating Scale; CDRS-R=Child Depression Rating Scale-Revised; PBD=Pediatric Bipolar Disorder; HC = Healthy Control

Table 2

Response Time and Accuracy Measures for Healthy Individuals (HC) and Subjects with Pediatric Bipolar Disorder (PBD) Color Matching Task

Response Time (msec)	HC Median (SD)	PBD Median (SD)
Positive Words	743 (134)	835 (171)
Negative Words	753 (153)	872 (214)
Neutral Words	742 (162)	859 (183)
Accurate Responses	%	%
Positive Words	96	83
Negative Words	95	83
Neutral Words	96	80

Table 3

Counts of Active Voxels in the Amygdala, Hippocampus, Parahippocampal Gyrus, and Caudate in Healthy Individuals (HC) and Subjects with Pediatric Bipolar Disorder (PBD) During a Color Matching Task

Negative compared to Neutral Words				
Hemi	Region	HC Mean (SD)	PBD Mean (SD)	U value (P value)
R	Amygdala	0.60 (0.84)	4.8 (5.67)	28 (0.08)
L	Amygdala *	0.20 (0.63)	3.5 (5.54)	24.5 (0.02)
R	Hippocampus	3.00 (3.19)	11.2 (11.49)	35.0 (0.24)
L	Hippocampus	3.6 (6.29)	12.3 (13.86)	27 (0.08)
R	Parahippocampal Gyrus	6.8 (8.80)	19.8 (19.99)	29.5 (0.12)
L	Parahippocampal Gyrus	10.3 (12.17)	20.2 (21.26)	35.0 (0.26)
Positive compared to Neutral Words				
Hemi	Region	HC Mean (SD)	PBD Mean (SD)	U value (P value)
R	Amygdala	3.80 (9.94)	6.90 (9.02)	32.5 (0.17)
L	Amygdala	2.20 (4.29)	6.80 (6.73)	26.5 (0.07)
R	Hippocampus	3.70 (6.34)	13.30 (17.63)	26.0 (0.07)
L	Hippocampus	8.90 (11.73)	15.70 (21.16)	36.0 (0.29)
R	Parahippocampal Gyrus	15.40 (24.14)	29.90 (39.37)	33.5 (0.21)
L	Parahippocampal Gyrus	16.90 (18.56)	32.40 (31.79)	26.5 (0.08)

* Significant between group difference at $P < 0.05$.

Hemi = Hemisphere; R = Right; L = Left; HC = Healthy Controls; PBD = Pediatric Bipolar Disorder