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A Preliminary fMRI Study of Sustained Attention in Euthymic, Unmedicated Bipolar Disorder

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The symptoms of bipolar disorder suggest dysfunction of anterior limbic networks that modulate emotional behavior and that reciprocally interact with dorsal attentional systems. Bipolar patients maintain a constant vulnerability to mood episodes even during euthymia, when symptoms are minimal. Consequently, we predicted that, compared with healthy subjects, bipolar patients would exhibit abnormal activation of regions of the anterior limbic network with corresponding abnormal activation of other cortical areas involved in attentional processing. In all, 10 unmedicated euthymic bipolar patients and 10 group-matched healthy subjects were studied with fMRI while performing the Continuous Performance Task-Identical Pairs version (CPT-IP). fMRI scans were obtained on a 3.0 T Bruker system using an echo planar imaging (EPI) pulse sequence, while subjects performed the CPT-IP and a control condition to contrast group differences in regional brain activation. The euthymic bipolar and healthy subjects performed similarly on the CPT-IP, yet showed significantly different patterns of brain activation. Specifically, bipolar patients exhibited increased activation of limbic, paralimbic, and ventrolateral prefrontal areas, as well as visual associational cortices. Healthy subjects exhibited relatively increased activation in fusiform gyrus and medial prefrontal cortex. In conclusion, these differences suggest that bipolar patients exhibit overactivation of anterior limbic areas with corresponding abnormal activation in visual associational cortical areas, permitting successful performance of an attentional task. Since the differences occurred in euthymia, they may represent trait, rather than state, abnormalities of brain function in bipolar disorder.

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INTRODUCTION

Bipolar disorder is a dynamic illness characterized by fluctuations among emotional extremes (ie mania and depression), and even within extremes (ie mixed states), that are accompanied by similarly extreme oscillations in psychomotor and neurovegetative behaviors. The dynamic expression of bipolar disorder suggests that its neuropathophysiology involves dysfunction of brain networks that maintain emotional homeostasis. The orbitofrontal division of the limbic forebrain provides these networks (Mega *et al*, 1997). This 'anterior limbic network' consists of linked cortical and subcortical areas with common phylogenetic and cytoarchitectural features that modulate complex emotional and social behaviors (Mega *et al*, 1997; Ongür and Price, 2000). Specifically, medial orbitofrontal and ventrolateral prefrontal areas receive processed sensory information through extensive reciprocal connections with basal amygdala, anterior temporal regions, rostral insula, and subgenual and anterior cingulate (Mega *et al*, 1997; Ongür and Price, 2000). These prefrontal areas form feedback loops with the ventromedial striatum and thalamus that provide effector mechanisms for psychomotor responses. Projections from this network to hypothalamus and autonomic nervous system produce visceromotor outputs to create bodily sensations (ie 'feelings') (Mega *et al*, 1997; Ongür and Price, 2000). Several investigators have suggested that the symptoms of bipolar disorder arise from dysfunction within this anterior limbic network (Blumberg *et al*, 2003; Ketter *et al*, 2001; Phillips *et al*, 2003; Strakowski, 2002; Strakowski *et al*, 2002).

In addition to mood and neurovegetative disturbances, impaired attention is a defining symptom of both mania and depression. Neuropsychological studies of bipolar patients consistently report decrements in sustained attention during affective episodes (reviewed in Bearden *et al*, 2001). These observations are not particularly surprising since both experiential and experimental evidence support the notion that strong emotional states interfere with attention (Mayberg *et al*, 1999; Yamasaki *et al*, 2002). Therefore, activation of emotional (anterior limbic) networks may disrupt function of attentional brain regions.

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Indeed, attentional and emotional networks intersect within the anterior cingulate, providing a neuroanatomic basis for interactions between these circuits (Mega *et al*, 1997; Mayberg *et al*, 1999; Yamasaki *et al*, 2002). Consequently during mood episodes, dysregulation of the anterior limbic network may inhibit cognitive brain regions, thereby producing both the affective and attentional impairments of bipolar disorder. Moreover, because of these reciprocal interactions, studying attentional function in bipolar disorder provides one approach towards identifying inappropriately activated anterior limbic areas that might not be possible to identify by direct emotional probes; that is, this approach may identify inappropriate activation of emotional areas during a nonemotional task.

During euthymia, bipolar patients exhibit minimal symptoms by definition, although a persistent vulnerability for mood dysregulation is always present. This persistent vulnerability has been hypothesized to result from overreactive emotional (ie anterior limbic) brain networks (Ketter *et al*, 2001; Phillips *et al*, 2003; Strakowski, 2002; Strakowski *et al*, 2002). If correct, this hypothesis suggests that, even during euthymia, dysfunction within the anterior limbic network persists, leaving patients at risk for mood and cognitive disturbances. The goal of this study was to determine whether abnormal anterior limbic activation during an attentional task was present during euthymia, to specifically identify this persistent dysfunction.

Several challenges face imaging studies that compare healthy and bipolar subjects, which have limited previous investigations (Strakowski, 2002). First, bipolar patients are typically taking psychotropic medications, which may alter patterns of brain activation in unpredictable ways. Second, if patients perform a cognitive task significantly worse than comparison subjects, interpreting differences in brain activation is confounded. Specifically, if task performance differs, then differences in brain activation may simply reflect the inability of the patients to complete the task, rather than differences in how they process information. Finally, if bipolar patients are studied while in a mood episode, then differences in brain activation from healthy subjects might simply represent epiphenomena of that mood state, rather than representing a trait of bipolar disorder *per se*. To address these limitations, we studied brain activation using functional magnetic resonance imaging (fMRI) in unmedicated, euthymic bipolar and healthy subjects while they performed the Continuous Performance Task-Identical Pairs version (CPT-IP), an established measure of sustained attention (Adler *et al*, 2001a; Cornblatt *et al*, 1988; Häger *et al*, 1998). From these and previous considerations (Ketter *et al*, 2001; Phillips *et al*, 2003; Strakowski, 2002; Strakowski *et al*, 2002; Mayberg *et al*, 1999; Yamasaki *et al*, 2002), we hypothesized that, compared with healthy subjects, bipolar patients would exhibit abnormal activation of regions of the anterior limbic network during a nonemotional attentional task.

METHODS

Subjects

Patients with DSM-IV type I bipolar disorder were recruited from the University of Cincinnati First-Episode Mania Study (Strakowski *et al*, 2000a, b, c). From ongoing ratings obtained for this study, patients ($N = 10$) were identified who had discontinued medication for at least 1 month and were euthymic. Euthymia was defined as at least 4 weeks of Young Mania Rating Scale (YMRS; Young *et al*, 1978) total scores $\leqslant 5$ and Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) total scores $\leqslant 7$. Since this study is naturalistic, the study investigators do not control treatment prescription. Therefore, a number of patients had discontinued medications in conjunction with their personal psychiatrist or on their own (despite encouragement by investigators not to do so). Subjects were subsequently followed to ensure that they remained euthymic for at least 1 month after the MRI exam as well.

In all, 10 healthy comparison subjects were recruited from the same communities as the patients and were individually matched to the patients by age, sex, and ethnicity. Healthy subjects had no history of any major psychiatric disorder in themselves or first-degree family members. All bipolar and healthy subjects met the following inclusion criteria: (1) age 18–45 years; (2) no history of alcohol or drug dependence; (3) no alcohol or drug abuse for at least 3 months prior to the scan; (4) no history of mental retardation or documented IQ < 70; (5) right-handed; (6) no history of major medical or neurological disorders that were felt by the investigators to influence fMRI results; (7) no contraindication for an MRI study; (8) ability to communicate in English; and (9) a negative pregnancy test in women. All subjects provided written informed consent for this study after the procedures and risks were explained in full. Both the University of Cincinnati and Children's Hospital Medical Center Institutional Review Boards approved this study.

Clinical Assessments

A diagnosis of bipolar disorder (patients) or the absence of a psychiatric condition (healthy subjects) was established using the Structured Clinical Interview for DSM-IV (SCID-I/P; First *et al*, 1997) administered by trained, experienced clinicians (inter-rater kappa > 0.90; Strakowski *et al*, 2000a). Assessment of euthymia during the previous 4 weeks was obtained from the bipolar subjects' participation in the outcome study (Strakowski *et al*, 2000a, b, c). Additionally, all subjects were administered the YMRS and HDRS at the time of the MRI study. Treatment contacts and medications prescribed and taken were also recorded. The patients were relatively young (Table 1) with an average illness age at onset of 23 (SD 9) years and average illness duration of 2.2 (SD 1.9) years.

The presence of substance use disorders was assessed using the SCID-I/P and the Addiction Severity Index (ASI; McClellan *et al*, 1992). Additionally, subjects provided a sample for a urine toxicology screen at the time of the MRI study (which had to be negative for participation). A medical review of systems performed by a licensed physician (CMA) identified any potentially exclusionary medical problems. All of the subjects were medically healthy and none had any history of significant medical or neurological disorders. Demographic information was obtained by direct interview. Finally, right-handedness was verified using the Crovitz Handedness Scale (Crovitz

Table 1 Clinical and Demographic Characteristics of 10 Unmedicated, Euthymic Patients with Bipolar Disorder, and 10 Healthy Subjects Studied Using fMRI

Characteristic	Bipolar patients ($N = 10$)	Healthy subjects ($N = 10$)	*p*-value
Age, years	25.5 (8.1)	25.3 (7.3)	>0.9
Sex, *N* (%) women	6 (60)	6 (60)	1.0
Ethnicity, *N* (%) white	8 (80)	8 (80)	1.0
HDRS	3.1 (2.5)	1.6 (1.8)	>0.1
YMRS	1.6 (1.8)	0.4 (0.8)	>0.07
CPT performance[a]			
Discriminability	5.9 (2.2)	6.9 (2.5)	>0.4
Percent correct	94.3 (6.5)	95.6 (5.8)	>0.7
Percent false positives	4.0 (3.2)	2.0 (2.8)	>0.2

Variables are listed as mean (SD) unless otherwise noted. HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale. Two-tailed *p*-values calculated by Wilcoxon rank-sum test for continuous variables and χ^2-test for dichotomous variables.
[a]Three patients' CPT performance measures that were obtained in the scanner were lost after the session due to a computer failure. These three patients appeared to perform the task without difficulty, however.

Table 2 Medication Histories of 10 Euthymic Bipolar Patients prior to MRI Scan Acquisition, Including Time since Last Medication Exposure

Medication	Number receiving	Weeks of treatment, mean (range)	Months since last use, mean (range)
Divalproex	8	26 (2–83)	14 (3–39)
Risperidone	3	27 (3–59)	9 (8–11)
Olanzapine	3	4 (2–6)	21 (7–43)
Quetiapine	2	14 (10–18)	9 (7–11)
Sertraline	2	34 (2–66)	10 (7–12)
Lithium	1	1	9
Haloperidol	1	44	30
Perphenazine	1	50	39
Clonazepam	1	18	5
Gabapentin	1	4	8
Fluoxetine	1	1	8
Mirtazapine	1	13	4

and Zener, 1962). Demographic and clinical variables are listed in Table 1.

Although unmedicated at the time of the study, all patients had previously received psychotropic medications. Prior medication use is listed in Table 2. As can be seen, most patients had discontinued medications for a number of months prior to this fMRI study.

Cognitive Tasks

As noted, the CPT-IP version was the experimental cognitive task of interest. Pilot data suggested that euthymic bipolar and healthy subjects would perform this task similarly (SM Strakowski *et al*, unpublished data), which was one reason it was chosen. Subjects were presented with a series of four-digit numbers and were asked to respond with a button press when the same number occurred twice sequentially. The control task consisted of the number '1234' presented at the same rate and intervals as the CPT-IP to the subjects. The subjects were asked to watch the control presentation, but not to respond. This task was designed to control for being in the MRI scanner and the simple visual components of watching flashing numbers; therefore, a response was not required, since to do so would have made the control task a form of continuous performance task, thereby potentially limiting ability to detect activations associated with attention.

In the MRI scanner, subjects were presented stimuli using nonferromagnetic goggles (Resonance Technologies Inc.) that provided a 30″ field-of-view (FOV) visual presentation that mimics the presentation of a computer monitor and obscures the peripheral FOV. The experimental and control tasks were given in alternating blocks of 30 s each with numbers being presented for 700 ms at 750 ms intervals (ie there was a 50 ms gap between presentations, for a total of 40 numbers/block). Five blocks of each task were obtained for analysis during each scan session. Subjects responded to targets (ie two identical numbers presented sequentially) in the CPT-IP task using a button box. The responses were electronically recorded on a computer to permit calculation of response parameters (ie discriminability and percent correct and percent false-positive responses).

Image Acquisition

All images were obtained using a 3.0 T, Bruker Biospec 30/60 MRI scanner (Bruker Medizintechnik, Karlsruhe, Germany), specifications and procedures for which have been previously described (Adler *et al*, 2001a, b, 2004). Following a three-plane gradient echo scan for alignment and brain localization, a shim procedure was performed to generate a homogeneous magnetic field. To provide anatomical localization for activation maps, a high-resolution, T1-weighted, 3-D brain scan was obtained using a modified driven equilibrium Fourier transform (MDEFT) sequence (TI = 550 ms, TR = 16.5 ms, TE = 4.3 ms, FOV = 25.6 × 19.2 × 14.4 cm, matrix 256 × 128 × 96 pixels, flip angle = 20°). After the anatomic scan was obtained, subjects participated in an fMRI session in which scans were acquired using a T2*-weighted gradient-echo echo planar imaging (EPI) pulse sequence (TR/TE = 3000/38 ms, FOV = 25.6 × 25.6 cm, matrix 64 × 64 pixels, slice-thickness = 5 mm, flip angle = 90°). Contiguous 5 mm axial slices, 24 in number, which extended from the inferior cerebellum to encompass most of the brain were selected from a sagittal localizer scan.

During the fMRI sessions, subjects performed the CPT-IP and control tasks in an alternating boxcar design. A boxcar design was chosen to maximize signal-to-noise in this relatively small sample. In all, 24 image slices were acquired at each time point. Data from the first (control task) interval were discarded during postprocessing to avoid any nonequilibrium intensity modulation effects. Following that first interval, five alternating blocks of each

task were obtained. High-frequency noise was removed in preprocessing using a Hamming filter applied to the *k*-space data prior to image reconstruction. Binary masking was applied to each image to remove pixels outside the brain. Linear and quadratic drift components in the temporal baseline of each pixel were removed using a quadratic drift correction algorithm (Adler *et al*, 2001a, b, 2000, 2004). Subjects' head movements were minimized by instructing them to remain still and by packing foam padding around their heads. Images were corrected for motion using a pyramid coregistration technique without landmarks that measures mean square differences in intensity between a reference image and succeeding time point images (Thévenaz and Unser, 1998). After realignment, all data sets were reviewed as a cine loop for uncorrected movement and were to be removed from the study if motion was detected. All images had less than 2 mm of movement.

Analysis

Comparisons in demographic variables were made using Wilcoxon rank-sum tests for continuous variables and χ^2-tests for dichotomous variables. Discriminability (d') was calculated to assess CPT-IP task performance in the scanner. Discriminability is a well-recognized signal-detection measure that incorporates both false-positive and true positive responses in its calculation (Coren and Ward, 1989). For completeness, we also report the more familiar percent of true and false-positive responses in Table 1. Comparisons between groups for these measures were made using Wilcoxon rank-sum tests.

Image data were processed using the Children's Hospital Imaging Processing Software (CHIPS®) (Adler *et al*, 2000, 2001a, b, 2004; Holland *et al*, 1998a, b). Images were analyzed as composites to determine activation differences between groups. Smoothing was applied (6 mm. FWHM) and *t*-statistics calculated, contrasting voxels across the experimental (CPT-IP) and control (repeating numbers) tasks. The *t*-maps were transformed to Talairach space. Then a *t*-statistic was determined for each voxel across subjects to create group-specific composite images (Figures 1 and 2), using a significance threshold of $p<0.05$ based on a combination of voxel cluster size and activation threshold to control for multiple comparisons following the recommendations of Xiong *et al* (1995). Voxel-by-voxel comparisons were then made between subject groups. Only differences in which positive activation relative to the control task was observed in at least one group were included (ie none of the differences in activation analyzed involve differences in relative deactivation). In order to control for multiple comparisons and protect against type I error a clustering technique was employed. Specifically, a minimum cluster size of 15 with a significance threshold of $p<0.05$ was used to identify activation, as previously suggested (Adler *et al*, 2001a, 2004). Functional maps were coregistered to a structural template of averaged T1-weighted MDEFT structural images to aid interpretation.

In order to help interpret activation differences, we examined correlations among brain regions of activation that significantly differed between groups and CPT-IP performance (using the signal detection measure d'). Specifically, regions of interest were defined as those areas showing significant group differences in activation, as identified using the methods described in the previous paragraph. We then identified correlations between d' and activation at each voxel within those identified regions of interest only, in order to increase power. We defined significant correlations as $r>0.75$ which corresponded to a $p<0.05$. For simplicity, the maximal *r*-value (for those voxels with $r>0.75$) for each region is reported.

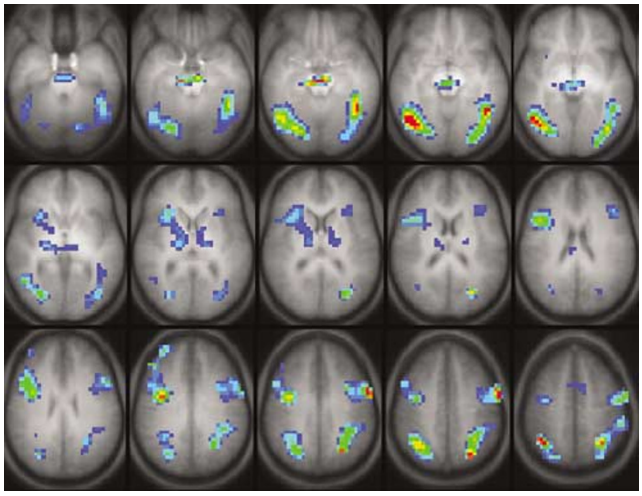

Figure 1 Functional brain activation map overlaid on T1-weighted anatomic images in 10 healthy subjects performing the CPT-IP. Statistically significant activation was defined as $p<0.05$ using a combination of voxel cluster size and activation threshold to control for multiple comparisons following the recommendations of Xiong *et al* (1995).

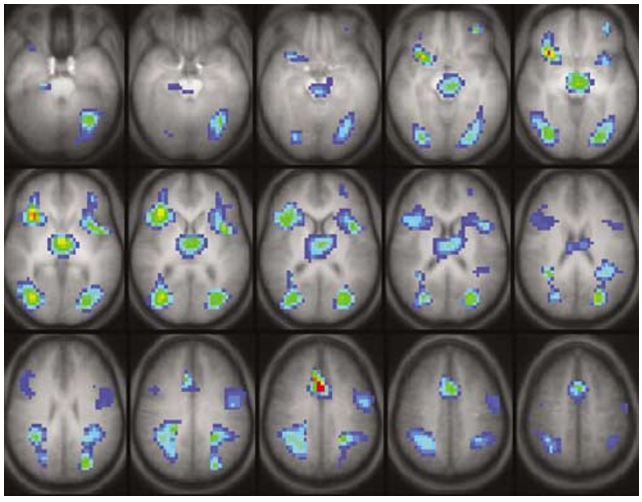

Figure 2 Functional brain activation map overlaid on T1-weighted anatomic images in 10 euthymic, unmedicated bipolar subjects performing the CPT-IP. Statistically significant activation was defined as $p<0.05$ using a combination of voxel cluster size and activation threshold to control for multiple comparisons following the recommendations of Xiong *et al* (1995).

RESULTS

Demographics and Task Performance

The patient and healthy subject groups were closely matched on demographic and clinical variables (Table 1).

Although differences in YMRS ratings approached significance, the mean and range of values of this mania rating is so low that this difference is clinically meaningless. The groups also performed the CPT-IP similarly (Table 1). Individual group activation maps are illustrated in Figures 1 and 2.

fMRI Group Comparisons in Activation

Figure 3 illustrates areas of significant regional brain activation differences in healthy *vs* bipolar subjects while performing the CPT-IP as contrasted with the control task. These regional differences are listed in Table 3, with corresponding Brodmann areas and Talairach coordinates. As illustrated, healthy subjects showed relative greater activation in the fusiform gyrus and medial frontal cortex. Bipolar patients showed relative greater activation in limbic (hypothalamus, parahippocampus/amygdala), paralimbic (insula) and prefrontal and visual associational regions. Activation in other brain areas commonly associated with attentional tasks, such as the anterior cingulate (see Figures 1 and 2) did not significantly differ between groups (Figure 3).

Correlations in fMRI Activation and Task Performance

For the bipolar patients, significant positive correlations were observed between task performance (d') in the right inferior frontal ($r = 0.93$, $p < 0.003$) and bilaterally in the ventrolateral frontal (specifically BA 10; $r = 0.85$, $p < 0.02$ and $r = 0.78$, $p < 0.04$ on the left and right, respectively) regions. In the healthy subjects, d' was significantly negatively correlated with activation in the left mid-occipital/temporal region ($r = -0.90$, $p < 0.0004$).

DISCUSSION

The results of this preliminary study support the hypothesis that dysfunctional anterior limbic networks are present in

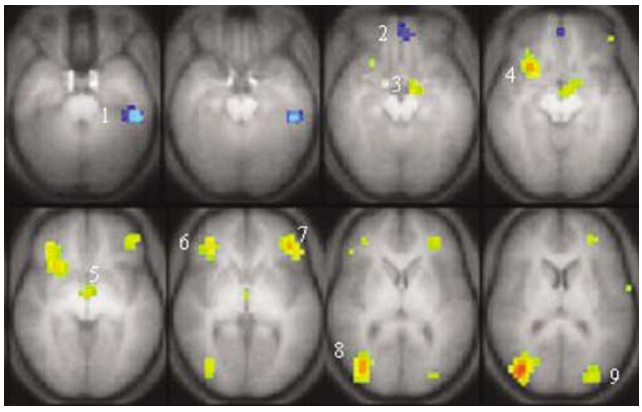

Figure 3 Difference images displaying differences in brain activation between healthy subjects and euthymic bipolar patients while performing an attentional task (CPT-IP). Areas in which healthy subjects exhibited greater activation are in blue tones and include: (1) left fusiform gyrus (BA 20) and (2) left medial frontal cortex (BA 11). Areas in which bipolar patients exhibited greater activation are in yellow/green/red hues and include: (3) left parahippocampus/amygdala (BA 34), (4) right inferior frontal cortex/insula (BA 13, 47), (5) hypothalamus, (6 and 7) bilateral ventral prefrontal cortex (BA 10, 47), and (8 and 9) bilateral mid-occipital/mid-temporal cortex (BA 18, 19, 39). Images are in radiological convention.

Table 3 Brain Regions Exhibiting Significant Differences in Activation between Healthy and Unmedicated, Euthymic Bipolar Subjects While Performing the CPT-IP (See Also Figure 1). Brodmann Areas Derived from Talairach Daemon are Provided Unless Otherwise Noted

Regions	Brodmann area	Hemi-sphere	Talairach coordinates[a]	Cluster size	Z-score[c]
Increased in healthy subjects					
Fusiform gyrus	20	L	−50, −29, −25	27	−0.66
Medial frontal cortex	11	L	−6, 47, −15	15	−0.52
Increased in bipolar subjects					
Inferior frontal cortex/insula	13, 47	R	26, 15, −10	35	0.73
Ventral prefrontal cortex	10, 47	L	−38, 39, 0	39	0.75
		R	34, 35, −5	36	0.66
Parahippocampus/amygdala	34	L	−10, −1, −15	8	0.64
Hypothalamus	—	—	2, −5, −5	12	0.65
Mid-occipital/mid-temporal cortex	18, 19, 39	R	38, −77, 10	75	0.81
		L	−30, −85, 15	15	0.61
Inferior parietal cortex[b]	40	R	34, −41, 45	57	0.57
Superior parietal cortex[b]	7, 40	R	26, −53, 50	39	0.60
Postcentral gyrus[b]	43	L	−62, −5, 15	27	0.79

[a]Talairach coordinates of pixel within structure with maximal activation difference.
[b]This region not shown in Figure 1.
[c]Z-score is for the point indicated by the Talairach coordinates.

euthymic bipolar patients. Specifically, compared with the healthy subjects, patients showed increased activation in limbic and paralimbic areas (parahippocampus/amygdala and insula, BA 13) as well as ventrolateral prefrontal regions (BA 10/47) that are components of this network (Mega *et al*, 1997; Ongür and Price, 2000; Yamasaki *et al*, 2002). The bipolar patients in this study, then, activated these brain regions, which are typically involved in emotional arousal, yet they were performing a nonemotional attentional task. This activation therefore suggests that the bipolar subjects attached emotional valence to this task differently than healthy subjects. This suggestion is supported by the significant correlation between task performance (d') and ventrolateral prefrontal cortical activation in the bipolar patients, which was not observed in healthy subjects. In the absence of specific measures of emotional responses to this task, these suggestions remain speculative, however. Moreover, alternatively, these differences may represent differences in levels of performance anxiety, concerns about the MRI scanner experience, or simply differences in how bipolar and healthy subjects process attentional information. These alternatives require additional study to extend the present preliminary work.

Healthy subjects demonstrated greater activation than bipolar patients in left medial orbitofrontal (BA 11) and fusiform areas. Previously, we demonstrated that fusiform activation (bilaterally) was associated with CPT-IP performance in healthy human subjects (Adler *et al*, 2001a). Yamasaki *et al* (2002) also observed fusiform activation during a CPT task with emotional and neutral distracters. In their analysis, fusiform was more strongly activated in response to distracters than targets and was greatest with emotional distracters. Since the subjects in the Yamasaki *et al* (2002) study performed the task despite the distracters, the fusiform activation may have signaled inhibition of emotional networks to permit attention to the task. Similarly, the medial prefrontal area (BA 11) is a component of the anterior limbic network that modulates emotional and social behavior (Mega *et al*, 1997). The increased activation in the healthy *vs* bipolar subjects in these brain areas may represent a failure in bipolar disorder to activate regions that would inhibit other components of emotional networks in order to focus brain resources on cognitive activities, namely sustained attention. The activation pattern observed in these healthy subjects was similar to that we reported previously from a completely independent set of healthy subjects (Adler *et al*, 2001a).

Importantly, despite different patterns of brain activation, bipolar and healthy subjects exhibited similar performance on the CPT-IP. This suggests that the patients used an alternative neural 'strategy' to process attentional information or that, despite potential interference from inappropriate emotional network activation, they were able to compensate for the overactivation of emotional brain areas in order to do the attentional task. In the healthy subjects, discriminability was significantly inversely correlated with activation in visual association areas (eg BA 18, 19, 39, 40, and 43). The inverse correlation suggests that these areas were recruited when subjects were having difficulty with the task. These same areas exhibited increased activation in the bipolar patients, perhaps as a means to maintain attention despite disruption from overactivated anterior limbic (emotional) brain networks. Alternatively, bipolar patients may have a dysfunction of inhibitory cognitive networks that leads to overactivated emotional circuits (Mayberg *et al*, 1999). Activation in these visual association areas is a recognized part of the healthy response pattern during the CPT-IP (Adler *et al*, 2001a).

Several limitations should be considered when interpreting these results. Although the CPT-IP is a widely used measure of sustained attention, it is not a pure attentional task as it incorporates elements of working memory. This confounds interpretation of the data somewhat as attentional and memory neural systems, though sharing components, are separate. In this study, differential activation in areas commonly associated with working memory (eg dorsolateral prefrontal cortex) were not observed. Although this could be a result of no differences in working memory function, the CPT-IP has only a modest working memory component, so may simply not be able to differentiate these subject groups. Future studies that examine the specific separate aspects of this task would clarify the contributions of each. However, as the aim of this preliminary study was to identify whether anterior limbic networks inappropriately activated during a cognitive task, this limitation is secondary. Studying unmedicated patients eliminates the uncertain effects of psychotropic medication on brain activation. However, patients who are able to discontinue medication and still remain well for extended periods of time may not be representative of all bipolar patients. Additionally, all patients had received psychotropic medications at some point in their course of illness. It is possible that residual effects from these medications contributed to the differences observed. The comparison task used did not have a response parameter, as we were concerned that most responses require an attentional component, which would defeat the role of a comparison task. Therefore, differences in motor activation were expected and observed in left postcentral gyrus in these right-handed subjects (Table 2). However, the primary regions of interest were not motor brain regions, suggesting this task limitation is not likely to explain the other activation differences reported. Finally, the number of subjects in each group in this study is relatively small, thereby increasing the risk of type II statistical error. Therefore, these results should be viewed as preliminary and interpreted cautiously. Nonetheless, we believe that these limitations are obviated by the strengths and uniqueness of our study design, which removed confounds of medications, mood state, and poor task performance.

By studying unmedicated, euthymic patients, group differences could not be attributed to the effects of affective symptoms or medications. Additionally, since both groups exhibited similar performance measures on the CPT-IP, activation differences could not be attributed to bipolar patients failing to perform the task. Therefore, the findings may reflect core abnormalities in brain function present in bipolar disorder even during periods of clinical stability. Coupled with other studies that have reported structural and functional brain abnormalities in bipolar disorder (reviewed by Strakowski, 2002), these results help to define specific regional brain abnormalities within the anterior limbic network that may underlie the loss of emotional homeostasis that defines this common mental illness.

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