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fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects

Jennifer Townsend^a, Susan Y. Bookheimer^a, Lara C. Foland^b, Catherine A. Sugar^{c,d}, and Lori L. Altshuler^{a,e}

^aDepartment of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, CA

^bLaboratory of Neuroimaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA

^cDepartment of Biostatistics, School of Public Health, University of California, Los Angeles, CA

^dJane and Terry Semel Institute of Neuroscience and Human Behavior, University of California, Los Angeles

^eDepartment of Psychiatry, VA Greater Los Angeles Healthcare System, West Los Angeles Healthcare Center

Abstract

Neuropsychological studies of subjects with bipolar disorder suggest impairment of working memory not only in acute mood states, but also while subjects are euthymic. Using fMRI to probe working memory regions in bipolar subjects in different mood states, we sought to determine the functional neural basis for these impairments. Typical working memory areas in normal populations include dorsolateral prefrontal cortex (BA9/46) and the posterior parietal cortex (BA40). We evaluated the activation in these regions using an n-back task in 42 bipolar subjects (13 manic, 15 euthymic and 14 depressed subjects) and 14 control subjects. While both control and bipolar subjects performed similarly on the task, bipolar subjects in all three mood states showed a significant reduction in activation in right BA9/46 and right BA40. Patients with bipolar disorder exhibit significantly attenuated neural activation in working memory circuits, independent of mood state. The reduction of neural activation may suggest a trait-related deficit. Subjects with bipolar disorder activated other additional frontal and temporal regions, perhaps as a compensatory mechanism, but this remains to be further explored.

Keywords

bipolar disorder; dorsolateral prefrontal cortex; parietal cortex; mania; depression; euthymia; working memory

Address correspondence to: Lori Altshuler, M.D., 300 UCLA Medical Plaza, Suite 1544, Box 957057, Los Angeles, CA 90095-7057, 310.794.9911 telephone, 310.794.9915 facsimile, laltshuler@mednet.ucla.edu.

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1. Introduction

Many studies have documented an alteration in neuropsychological function in patients with bipolar disorder during the manic and depressed mood states (Clark et al., 2001; Malhi et al., 2007; Martinez-Aran et al., 2004; Murphy et al., 1999; Rubinsztein et al., 2006). Several have additionally reported a persistence of neuropsychological dysfunction even after the acute mood state resolves. Relevant to the current study, euthymic bipolar subjects have been reported to perform significantly worse than normal control subjects on measures of executive functioning, including working memory (Altshuler et al., 2004; Depp et al., 2007; Ferrier et al., 1999; Goldberg et al., 1993; Malhi et al., 2007; Martinez-Aran et al., 2004; Rossi et al., 2000; Thompson et al., 2007; Trivedi et al., 2008; Trivedi et al., 2007; van Gorp et al., 1998). Persistent neurocognitive abnormalities in euthymic bipolar patients may provide clues to brain areas of underlying pathology in the illness. To date, however, the neurophysiological correlates for these cognitive impairments remain underexplored.

Two consistent functional neuroimaging findings of working memory in normal populations are activation of the dorsolateral prefrontal cortex (dlPFC) (BA9/46) and activation of the inferior, posterior parietal cortex (BA40) (Belger et al., 1998; Carlson et al., 1998; Cohen et al., 1997; Curtis 2006; Smith et al., 1998). fMRI studies probing these brain regions in the bipolar population have rarely been performed. It is possible that the working memory deficits observed during neurocognitive testing in euthymic bipolar subjects implicate dysfunction in the dlPFC and/or the posterior parietal cortices in these patients.

To our knowledge, only five fMRI studies have been reported using working memory tasks in subjects with bipolar disorder during euthymia. Lagopoulos et al. (2007) (Lagopoulos et al., 2007) demonstrated that euthymic bipolar subjects ($n = 10$) failed to engage dlPFC during a Sternberg working memory task compared to normal controls. Monks et al. (2004) (Monks et al., 2004) also found reduced activation in dlPFC in bipolar euthymic ($n = 12$) compared to control subjects using an n-back task. Drapier et al. (2008) (Drapier et al., 2008) found no differences in this region between euthymic and control subjects, but observed a trend toward increased left ventrolateral activation in euthymic compared with control subjects. However, Adler et al. (2004) (Adler et al., 2004) found no significant differences in dlPFC activation in euthymic bipolar subjects ($n = 15$) compared to a normal control group. Frangou et al. (2008) (Frangou et al., 2008) found no significant between-group differences in the working memory task using the n-back task with a small sample size ($n = 7$ bipolar subjects; $n = 7$ normal control subjects). Thus, the extant fMRI literature of working memory in bipolar disorder remains inconsistent.

While the above studies evaluated euthymic bipolar vs. normal control subjects, no studies to date have directly compared neural activation during a working memory task in bipolar subjects in a range of mood states. This would allow for an exploration of mood state-specific neurofunctional deficits. To our knowledge, only one fMRI study in the literature to date has reported on bipolar patients in different mood states while performing a neurocognitive task, and that study involved a set shifting/response inhibition task (Blumberg et al., 2003).

In the present study, we sought to evaluate the neurofunctional basis for the working memory deficits seen in bipolar patients using the n-back task. The n-back task is one of the most common fMRI paradigms used to observe working memory function in normal and patient populations (Wager et al., 2003) and it has been used successfully in the euthymic-bipolar population (Drapier et al., 2008; Frangou et al., 2008; Monks et al., 2004). We evaluated subjects across all three mood states to assess the extent to which the presence and severity of these deficits are mood-state specific or enduring despite remission of the acute

state. Based on the persistent working memory neurocognitive deficits reported in euthymic bipolar subjects and discussed above, we hypothesized there would be a reduced neural activation of the traditional working memory areas of BA 9/46 and BA40 in all bipolar patient groups irrespective of mood state.

2. Methods

2.1 Subjects

The Institutional Review Board at UCLA and the VA Greater Los Angeles Healthcare System approved the study protocol. Each subject provided written informed consent. Subjects with bipolar I disorder were recruited through the UCLA Mood Disorders Clinic, the Bipolar Disorders Clinic of the Veterans Affairs Greater Los Angeles Health Care System, and the inpatient units of both hospitals. Subjects enrolled in other research projects of the UCLA Mood Disorders Research Program were also invited to participate. Control subjects were recruited by advertisement in local newspapers and campus flyers. Both control and patient populations were evaluated using the Structured Clinical Interview for DSM-IV (SCID) to confirm an accurate diagnosis or the absence thereof. Illness duration and medication information for patients was obtained by patient self-report and by reference to medical records when available. Exclusion criteria for all subjects included left-handedness, hypertension, neurological illness, metal implants and a history of skull fracture or head trauma with loss of consciousness > 5 min. Bipolar subjects with other active Axis I comorbidities were also excluded. Exclusion criteria for healthy control subjects included current or past psychiatric diagnosis (including history of substance abuse) or current medication use.

In total, 17 euthymic, 21 manic, 15 depressed and 16 controls subjects were scanned. Excessive motion, as defined by motion greater than half a voxel (1.5mm), excluded 2 control, 8 manic, 1 depressed and 2 euthymic subjects from further analysis. Thus, the final analysis included scans from 14 control (8f, 30.8 ± 5.98 yrs), 13 bipolar manic (8f, 38.5 ± 9.05 yrs), 15 euthymic (8f, 37.0 ± 10.1 yrs) and 14 depressed (7f, 38.7 ± 9.72 yrs) subjects.

Table 1 shows the complete demographic, illness characteristics and medication information of the included sample. There were no significant differences in age or illness duration between groups. The control group showed a trend toward being younger than the bipolar groups, and this was taken into account in the analyses (see results below). Hypomania/mania, depression and euthymia were assessed and confirmed using the criteria on the SCID. Mood symptoms were rated on the day of the scan for the patient groups using the Young Mania Rating Scale (YMRS) (Young et al., 1978) to assess for current severity of mania, and the 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960) to assess for presence of depressive symptoms. Euthymic subjects were further required to lack manic, hypomanic or depressive symptoms operationalized by a YMRS < 8 and HAM-D < 7 on the day of the scan. None of the subjects had psychotic symptoms at the time of the scan.

2.2 Experimental Paradigm

The 2-back working memory paradigm of the n-back task consists of two conditions, presented in a block design, with a 20 sec. resting condition interleaved between conditions. Each block lasted 30 sec. with a 2.5 sec. instruction. In the experimental 2-back condition ("exp"), subjects tracked letter sequences and pressed a button when they detected a letter that appeared 2 positions back. In the control 0-back condition ("con"), subjects pressed the button every time the letter "X" appeared on-screen. This version of the n-back paradigm was used as it has been well-validated in the literature and in our laboratory. The "exp-con"

contrast specifically has been reported to activate working memory networks. Prior to scanning, all subjects were given training to ensure they understood the direction of the task and performed it well. Behavioral data were collected online to ensure subjects actively engaged in the task during scanning.

2.3 Image Acquisition

Functional neuroimaging data were collected using a 3.0 Tesla GE MRI scanner at the UCLA Brain Mapping Center. For all scans, subjects were positioned comfortably in a supine orientation with their head located in a head RF coil and stabilized with foam pads to minimize head motion. Blood oxygen level dependent (BOLD) functional images were acquired with a gradient echo-planar imaging (EPI) sequence, and covered 16 trans-axial slices (3 mm thick, 1 mm gap) encompassing the cerebrum (TR/TE = 2500/35 ms, FOV = 24 cm, matrix = 64×64). All scanning parameters were selected to optimize the quality of the BOLD signal, especially within the dlPFC and inferior parietal lobule, while maintaining a sufficient number of slices to acquire as much of the brain as possible within the technical confines of the scanner. Before the collection of fMRI data for each subject, we acquired a reference EPI scan to register each subject's data into standard space.

2.4 Behavioral Data Analysis

Behavioral data were collected during scanning, and accuracy of performance and reaction times were recorded for the experimental and control tasks. Due to technical difficulties with the button box and trigger system, not all subjects had usable behavioral data for later analysis. However, subjects with and without behavioral data were compared on fMRI regions of interest (ROI) activation to evaluate possible group differences and to ensure all subjects used in the final analyses performed the task (Carter et al., 2008). Differences between groups on each task for both accuracy and response time were assessed with a mixed-effects analysis of variance model in Excel.

2.5 fMRI Analysis

Functional images were examined closely for severe motion or spike artifacts. All subjects with more than half a voxel of motion ($>1.5\text{mm}$) were excluded. Data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.91, part of FSL 4.0 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain removal using BET (Smith 2002); spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 65.0\text{s}$).

Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Registration to high-resolution structural and standard space images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson et al., 2001), using 7 degrees of freedom to register functional images to subject's high-resolution structural images and 12 degrees of freedom to register those high-resolution images to standard space. All registrations were manually inspected to ensure proper registration. Statistical images were generated for the experimental vs. control ("exp-con") contrasts for each subject, and these were used in subsequent analyses. Higher-level statistical analyses for within and between group analyses were carried out using FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al., 2003; Woolrich et al., 2004). Within-group results were reported using a cluster-based model (Friston 1997; Hochberg et al., 1990; Worsley et al., 1997). Using this method, a threshold of $Z > 2.3$ is considered conservative and is standard with this software. The resulting clusters were then tested for significance

using random field theory with a final significance test of $P > .05$, corrected for multiple comparisons (Genovese et al., 2002).

Due to our *a priori* hypothesis and the as yet undeveloped methods for analyzing a between group whole brain differences in four groups with fMRI data, we used a region of interest analysis for the between-group results. This approach is more conservative than whole-brain approaches in which any activated cluster is accepted as relevant, a common error in the neuroimaging literature (Poldrack 2006). As the literature consistently shows bilateral dlPFC and bilateral parietal regions subserve working memory (Belger et al., 1998; Carlson et al., 1998; Cohen et al., 1997), regions of interest (ROI) were drawn in these areas of the brain to interrogate differences in the working memory network between groups. Rather than use an anatomically-drawn ROI, we used an ROI analysis approach using the maximally activated voxel in the left and right dlPFC (BA46/9 centered at $x = -42, y = 28, z = 22$ and $x = 42, y = 32, z = 30$) and in left and right posterior parietal cortex (BA 40 centered at $x = -56, y = -56, z = 28$ and $x = 56, y = -52, z = 28$) and dilating a 5 mm sphere around the voxel to define the ROI. These maximally activated voxels in our subjects are quite similar to those reported in the literature (Belger et al., 1998; Carlson et al., 1998; Cohen et al., 1997) and thus were used to create a ROI. For large regions with poorly defined anatomical boundaries and marked functional heterogeneity, the use of a functionally-defined ROI is more appropriate and has been used in other studies (Anand et al., 2007; Anand et al., 2005; Siegle et al., 2007). The time course of the voxels in the entire 5 mm sphere was used to calculate a mean percent signal change in that region for the exp-con contrast of each subject using FEATQuery. These mean percent signal change values for each subject were entered into a second-level analysis of variance (ANOVA) to determine brain activation differences as a function of group. Follow-up pairwise group comparison t-tests were performed.

3. Results

3.1 Behavioral Results

All groups performed the n-back task with high accuracy. There were no differences in accuracy (ANOVA: $F = 1.45, df = 3,34, p = 0.25$) or reaction times (ANOVA: $F = 0.99, df = 3,34, p = 0.41$) in behavioral performance between groups (Table 2). While the groups appear to have differences in spread for the accuracy measure, a test for inequality of variance was not significant. Additionally, pair-wise comparisons of the groups using (i) regular t-tests (assuming equal variances), (ii) Welch's t-tests (not assuming equal variances) and (iii) nonparametric Wilcoxon rank-sum tests all showed no significant behavioral differences after adjusting for multiple comparisons.

3.2 Within-Group Results

Table 3 and Figure 1 display the within-group regions of activation in each group.

Control subjects activated typical working memory regions (Figure 1a) including bilateral frontal lobe dlPFC (BA 9/46), bilateral parietal lobe supramarginal gyri (BA 39/40), as well as bilateral precuneous (BA 19) and bilateral inferior frontal gyrus (right BA 47 and left BA 44) (Table 3).

Manic subjects did not activate the working memory circuits activated in the control subjects. Instead they activated other frontal lobe regions including activated bilateral inferior frontal gyrus (BA 44/45 and BA 47) as well as other frontal regions in left precentral gyrus (BA44) and bilateral middle frontal gyri (BA 10 and BA 11). They also activated the left middle temporal gyrus (BA 21, 37 and 39), and left inferior parietal lobule (BA 40) (Figure 1b). The bilateral middle frontal gyri and temporal activations were not active in the control group, but were seen in depressed and euthymic groups.

Euthymic subjects activated predominately right hemisphere regions. They showed similar activation to both controls and bipolar depressed subjects in right dlPFC (BA9/46), again activating a more ventral portion of this region than the control subjects, and right inferior frontal gyrus (BA 47). Unlike the control subjects, the euthymic subjects additionally activated right superior frontal gyrus (BA 10) and right anterior cingulate (BA 24) (Figure 1c).

Bipolar depressed subjects activated bilateral dlPFC (BA9/46) but the activation occurred more ventrally and medially than in controls (Table 3). Bipolar depressed subjects also activated bilateral parietal regions (BA 39/40). Additional regions not activated in controls, including bilateral middle frontal gyri (BA 10), bilateral inferior frontal gyri (BA 47), and temporal limbic regions (BA 39/40 and the left insula) were also activated (Figure 1d).

Due to a trend in age differences between control and patient groups (ANOVA $F=2.44$, $df = 3,52$, $p=.0748$), and because we want to compare regional areas of activation across groups, additional analyses using age as a covariate were performed. The results of these analyses exhibited no substantive differences with those from the initial unadjusted within-group analyses.

3.3 Between-Group ROI Results

ROIs were drawn in left and right dlPFC centered and left and right supramarginal gyri (posterior parietal cortex BA40). fMRI ROI activation results did not differ significantly within bipolar or control subgroups between the subjects with and without behavioral data. It was therefore appropriate to assume that all subjects were actively engaged in the task, thus the entire group of subjects was included in the following analyses. A four group ANOVA revealed significant between group differences in the right dlPFC ($F = 3.33$, $df = 3,52$, $P = 0.026$); (Figure 2). Control subjects activated right dlPFC significantly more than bipolar subjects, irrespective of mood state (controls vs. manic subjects: $T = 2.49$, $df = 1,23$, $P = 0.01$; control vs. euthymic subjects: $T = 3.63$, $df = 1,26$, $P = 0.0006$; control vs. depressed subjects: $T = 1.75$, $df = 1,23$, $P = 0.04$). There were no differences between bipolar subjects across mood states (manic vs. euthymic subjects: $T = 0.50$, $df = 1,26$, $P = 0.62$; manic vs. depressed subjects: $T = -0.48$, $df = 1,25$, $P = 0.64$; euthymic vs. depressed: $T = -1.01$, $df = 1,27$, $P = 0.32$).

Similarly, a four group ANOVA showed that control subjects activated right BA 40 significantly more than any patient group (overall $F = 3.15$, $df = 3,52$, $P = 0.03$; controls vs. manic subjects: $T = 2.40$, $df = 1,25$, $P = 0.01$; control vs. euthymic subjects: $T = 2.81$, $df = 1,25$, $P = 0.005$; control vs. depressed subjects: $T = 1.66$, $df = 1,26$, $P = 0.05$) (Figure 3). Again, there were no differences in right BA40 across mood states among bipolar subjects (manic vs. euthymic subjects: $T = 0.97$, $df = 1,26$, $P = 0.34$; manic vs. depressed subjects: $T = -0.43$, $df = 1,25$, $P = 0.67$; euthymic vs. depressed subjects: $T = -1.25$, $df = 1,27$, $P = 0.22$).

There were no significant between group differences between control, depressed, euthymic or manic subjects in either of the *a priori* regions in the left hemisphere (dlPFC: ANOVA: $F = 0.61$, $df = 3,52$, $p = 0.61$; BA40: ANOVA: $F = 0.38$, $df = 3,52$, $p = 0.77$) (Figures 2 and 3).

Due to a trend in age differences between control and patient groups (ANOVA $F=2.44$, $df = 3,52$, $p=.0748$), we performed follow-up analyses of co-variance (ANCOVA) with age as a covariate. Adjustment for age did not affect the observed group differences in the right dlPFC or BA40 in either the overall models or the post hoc pairwise comparisons. This is not surprising given the fact that we did not find a significant relationship between age and activation in these regions either overall (right dlPFC: $F = 1.38$, $df=1,54$, $p = 0.25$; right BA40: $F = 0.33$, $df=1,54$, $p = 0.57$) or in any of the subgroups.

4. Discussion

Our study replicates prior studies demonstrating activation of bilateral dlPFC and parietal regions in normal control subjects (Adler et al., 2004; Belger et al., 1998; Carlson et al., 1998; Cohen et al., 1997; Frangou et al., 2008; Lagopoulos et al., 2007; Monks et al., 2004; Smith et al., 1998). Working memory task performance was associated with activation in dlPFC (BA46, BA9), inferior frontal gyrus (IFG) (BA47), left IFG (BA44), and parietal lobe (BA39/ BA40) in control subjects. These areas are part of the cognitive control network, defined by functional connectivity and described by Cole and Schneider (2007) (Cole et al., 2007). Supporting the goal of this study, all subjects demonstrated some activation of the working memory network. However, bipolar subjects failed to engage this cognitive control network to the same extent as the control subjects. While bipolar subjects activated dlPFC and parietal regions, they showed significantly less activation than the control subjects in both the right frontal and right parietal regions involved in working memory. Bipolar subjects across all mood states additionally activated temporal lobe and other frontal lobe structures (see Table 3).

Working memory tasks activate bilateral frontal and parietal regions. However, there is a laterality effect with the right hemisphere as predominant regardless of stimulus type (Nystrom et al., 2000). In this regard, it is interesting that the major differences between patients and controls were found in the right hemisphere. The abnormal neurophysiologic pattern in this region, specifically the less robust right-sided dorsal frontal activation in bipolar disorder, may relate to the clinical phenomenon of impairment in working memory previously reported (Altshuler et al., 2008; Altshuler et al., 2004; Clark et al., 2001; Coffman et al., 1990; Depp et al., 2007; Ferrier et al., 1999; Goldberg et al., 1993; Malhi et al., 2007; Martinez-Aran et al., 2004; Morice 1990; Murphy et al., 1999; Rossi et al., 2000; Rubinshtein et al., 2006; Senturk et al., 2007; Tam et al., 1998; Thompson et al., 2007; Trivedi et al., 2008; Trivedi et al., 2007; van Gorp et al., 1998).

Our study adds to the small literature using fMRI during working memory tasks in euthymic bipolar subjects and suggests network impairments even in the absence of an acute mood state. The lack of behavioral differences between groups is consistent with the majority of the literature (Frangou et al., 2008; Lagopoulos et al., 2007; Monks et al., 2004), but not all (Adler et al., 2004; Drapier et al., 2008). This study's fMRI results are consistent with two other working memory studies involving smaller numbers of euthymic subjects. Using the Sternberg task, Lagopoulos et al., (2007) (Lagopoulos et al., 2007) studied 10 bipolar women and 10 matched controls. Monks et al., (2004) (Monks et al., 2004) studied 12 bipolar men and 12 matched controls using the n-back task. Both studies, like ours, found a reduction in activation of right dlPFC and parietal regions in euthymic bipolar subjects compared to controls.

In contrast, Frangou et al., (2008) (Frangou et al., 2008) found no between group differences while subjects performed an n-back task. However, as there were only 7 subjects in each group for that study, the negative results may have been due to reduced power to detect group differences. Interesting, their data did suggest some dysfunction in the network in bipolar subjects, as differential activation patterns in these regions were observed when examining the effects of memory load. Specifically, controls were found to show an increased activation in dlPFC with increased memory load, as has been shown in a previous study of normal controls (Nystrom et al., 2000). Euthymic subjects showed no such pattern. Similar to Frangou, Adler et al. (2004) (Adler et al., 2004) did not find significant differences in activation in dlPFC or parietal cortex in 15 euthymic bipolar subjects and 15 matched controls using the n-back task. It is unclear why our study differs from this latter study despite a similar paradigm and sample size. As in our study, however, a heightened

activation in temporal lobe structures was observed in the bipolar subjects that was not observed in the normal control group while performing this task. Lagopoulos et al. (2007) (Lagopoulos et al., 2007) similarly found engagement of temporal lobe activation in the bipolar subjects when performing the working memory task. Thus, three of the five studies (including the current one) that used fMRI to assess frontal lobe neural activation during a working memory task have found that limbic/temporal lobe structures are activated in bipolar subjects during a task that does not normally activate these brain regions. Some imaging studies in patients with bipolar disorder have suggested limbic hyperactivity (Altshuler et al., 2005) even during euthymia (Hassel, S. et al., in press; Lawrence et al., 2004; Yurgelun-Todd et al., 2000). Whether this represents a compensatory mechanism or a chronically hyperactive brain region in bipolar illness remains to be further studied.

Increased activation in an orbitofrontal region (BA10) was also observed in the subjects with bipolar disorder, but not in the control subjects. Subjects in all three states showed significant activation in BA10, whereas the control subjects showed no such activation in this region. Tasks involving conflict resolution and decision making typically recruit this region (Cabeza et al., 2000; Zhang et al., 2003). Other studies have found activation of this brain region during semantic retrieval and making familiarity judgments (Buckner et al., 2000; Eldridge et al., 2000; MacLeod et al., 1998; Wagner et al., 1998). The exact reason for activation of this brain region in our patient population is not clear. Activation of this frontopolar region is not commonly reported in working memory studies among normal control subjects, suggesting that this region is not a part of the typically functioning working memory network. As the bipolar subjects performed as well as controls, it is possible that activation of BA10 in the bipolar group may represent a compensatory physiologic activation. We had no *a priori* hypothesis regarding this region in patients while performing a working memory task. However, this brain region has previously been reported as active in bipolar subjects across a variety of tasks in ours (Altshuler et al., 2008) and others' (Roth et al., 2006; Strakowski et al., 2004) studies. Interestingly, this frontal lobe brain region shows the greatest expansion in size across the primate species (Semendeferi et al., 2001). The role of BA10 in mood regulation is not known and requires further investigation.

There are several limitations of the present study. First, a number of bipolar subjects were excluded from participation. For example, the most severely manic patients were excluded due to their inability to remain still in the scanner. Additionally, patients with current comorbidities were excluded. Some patients who were screened for the study refused to participate (although the exact number was not tracked). Thus, how representative our bipolar sample is of the overall bipolar population is unclear. It is also possible that the use of medication could be a confound in our study. If medication were a primary factor, however, we might have expected to see a global dampening of activation across all brain regions rather than a selective decrease in activation in some specific regions (e.g. DIPFC, parietal) and increased activation in others (e.g. BA10, temporal lobe). In addition, the areas directly related to the network, there was a laterality difference between groups, that is, unlikely to be due to the effects of medication. Thus, medication use per se does not appear to be solely responsible for the findings. One published study has suggested that treatment at least with lithium, a common medication used by our bipolar subjects, does not alter brain activation while performing a memory task (Silverstone et al., 2005). Additionally, a current review of the bipolar disorder neuroimaging studies examining medication effects on brain activation suggest either no significant effect or ameliorative effects of psychotropic medications on abnormal functional measures (Phillips et al., 2008). Future studies with unmedicated subjects would help further refine the role medication may play in fMRI findings.

In a recent review, impaired verbal memory and executive function have been proposed as potential cognitive endophenotypes for bipolar disorder (Glahn et al., 2004), particularly since these deficits present early in the illness course and do not exclusively result from multiple or prolonged episodes or only subjective complaints (Gruber et al., 2008; Martinez-Aran et al., 2005; Nehra et al., 2006). These may not be an artifact of illness duration or episode frequency, but instead may relate more inherently to the biology of the disorder. A recent study found abnormal frontal activation in relatives of bipolar subjects, suggesting that a genetic liability for bipolar disorder may be characterized by more general frontal lobe abnormalities (Drapier et al., 2008).

Our study points to an underlying neurofunctional deficit that may be related to a cognitive deficit previously reported in subjects with bipolar disorder. While the relative ease of our task did not result in group differences in behavioral performance, it revealed differences in the regional brain function while performing this task. In bipolar subjects, deficits were revealed in activation of this network, regardless of mood state. While we had hypothesized that a decrease in neural activation would be present in euthymic subjects compared to control subjects, it was also found that the subjects in a mood state of mania or depression did not significantly differ in degree of neural activation from the euthymic subjects. A greater number of subjects in each group might have allowed for subtle differences across mood states to show significant differences. But our findings strongly suggest a more illness-related than mood state-related alteration in neural activation. Thus, the results of our study suggest an enduring neurophysiological abnormality in a specific cognitive network in bipolar illness. The underlying etiology of the functional deficit might be structural in nature, but this remains to be further explored and such studies are ongoing in our laboratory. Some unpublished data by our group suggests decreases in cortical thickness in these same regions where functional deficits have been observed in bipolar subjects compared to controls. Thus, there may be a structural abnormality that drives the functional deficits. If structural abnormalities are confirmed to be associated with the functional abnormalities, it would remain to be determined whether they occur early in the illness or occur as the result of mood episodes (Altshuler 1993). Future studies including patients in their first mood episode would help address this important issue.

In summary, consistent with previous reports, we found dlPFC and parietal activation in healthy subjects during a working memory task. This pattern in activation was significantly decreased in bipolar subjects, regardless of mood state at the time of scanning. Our study supports the presence of an enduring neurophysiological abnormality in a specific cognitive network in bipolar illness. This neurophysiological deficit may underlie the working memory neurocognitive deficit previously reported across mood states. How or if these deficits are involved with mood dysregulation, the defining feature of bipolar disorder, remains to be determined. Future studies that examine whether structural differences occur in overlapping regions as well as whether structural deficits exist in brain regions that project to this area would be of interest.

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Fig. 1.
Within-group results for NBACK task, EXP-CON condition ($z > 1.7$, $P = .05$ corrected).

Fig. 2.
Activation in DLPFC: ROI results.

Fig. 3.
Activation in parietal cortex: ROI results.

Table 1

Demographic and Medication Information

	Manic Group	Euthymic Group	Depressed Group	Control Group
N	13	15	14	14
Age (mean±SD) *	38.5 ± 9.1	37.0 ± 10.1	38.7 ± 9.7	30.8 ± 6.0
Weeks in Current Episode	6.2 ± 4.0	14.0 ± 20.5	15.8 ± 29.2	--
Gender (F/M)	8/5	8/7	7/7	8/6
Illness Duration (mean±SD) **	19.6 ± 12.4	12.5 ± 9.4	18.3 ± 13.3	--
HAM-D score (mean±SD)	5.3 ± 4.3	3.8 ± 3.7	21.0 ± 4.2	--
YMRS score (mean±SD)	15.9 ± 3.6	1.7 ± 2.3	3.1 ± 2.2	--
Medication				
lithium	8%	40%	7%	--
valproic acid	54%	60%	57%	--
gabapentin	15%	7%	7%	--
lamotrigine	8%	7%	21%	--
carbamazepine	0%	0%	7%	--
anti-psychotic	15%	13%	14%	--
antidepressant	23%	20%	50%	--

* F = 2.44, df = 55, p = 0.07

** F = 1.48, df = 40, p = 0.24

Table 2
Behavioral Data Analysis for Experimental and Control Conditions

	Control Group	Manic Group	Euthymic Group	Depressed Group
Total Accuracy (% correct $\pm$ SD)	87.4 $\pm$ 4.1	88.4 $\pm$ 2.6	84.3 $\pm$ 4.2	94.9 $\pm$ 2.4
Average Reaction Time (sec. $\pm$ SD)	0.49 $\pm$ 0.04	0.56 $\pm$ 0.03	0.55 $\pm$ 0.05	0.49 $\pm$ 0.03

Table 3
Within Group Results showing the Coordinates of Maximally Activated Voxels

	<i>Controls</i>				<i>Depressed</i>				<i>Euthymic</i>				<i>Manic</i>			
	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score
Frontal Lobe																
R MFG (BA 46/9)	42	32	30	3.84*	42	28	20	3.45*	42	38	24	3.28				
	48	12	32	3.30*												
L MFG (BA 46/9)	-42	28	22	3.28*	-34	32	16	2.84								
	-54	16	26	2.98												
R MFG (BA 10)					38	46	22	3.30	30	58	-6	3.14	30	50	-10	2.96*
L MFG (BA 10)					-28	50	2	2.80					-34	54	12	3.18*
R IFG (BA 47)	34	24	-4	3.71	36	14	-10	3.23	32	20	0	2.99*	36	42	-6	3.22
													44	18	-6	3.00
L IFG (BA 47)					-38	18	-14	2.86								
R IFG (BA 44)					48	12	26	3.18					56	12	10	2.74
L IFG (BA 44)	-48	10	22	3.37*	-56	12	28	2.87					-46	6	8	3.17
	-34	8	28	2.96									-42	2	28	3.15*
R IFG (BA 45)													50	12	20	2.96
L IFG (BA 45/46)					-50	22	18	3.54					-44	20	8	3.01
SFG (BA 9)					0	44	18	3.29								
Insula					-38	16	0	3.65								
Cingulate									12	32	10	3.05*				
Parietal Lobe																
R SMG (BA 40/39)	56	-52	28	3.65*	34	-54	30	3.13*								
	30	-58	40	2.91												
	38	-46	38	2.80												
L SMG (BA 40/39)	-56	-56	28	3.33	-46	-58	30	2.58								
R IPL (BA 39/40)	44	-50	38	3.00	50	-54	42	2.94*								
	-58	-58	22	3.29	-58	-60	38	2.73					-42	-56	42	3.08
L IPL (BA 39/40)					-44	-50	38	2.69*								

	<i>Controls</i>				<i>Depressed</i>				<i>Euthymic</i>				<i>Manic</i>			
	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score
R Precun. (BA19)	24	-74	38	2.85	-24	-56	40	2.55								
L Precun.(BA19)	-28	-74	24	3.90*	28	-74	36	2.90								
Temporal Lobe																
L MTG (BA 39)													-46	-66	24	3.26
L MTG (BA 37)													-48	-64	12	3.04
Occipital Lobe																
L MOG (BA19)					-34	-74	30	2.98					-52	-66	8	3.12

* Denotes additional regions within 10mm in any direction