Published in final edited form as:

Psychol Med. 2015 June ; 45(8): 1731–1740. doi:10.1017/S0033291714002852.

Prefrontal hypoactivation during working memory in bipolar II depression

J. O. Brooks III^{*,†}, N. Vizueta[†], C. Penfold, J. D. Townsend, S. Y. Bookheimer, and L. L. Altshuler

Department of Psychiatry & Biobehavioral Sciences, UCLA Semel Institute for Neuroscience & Human Behavior, Los Angeles, CA, USA

Abstract

Background—Patterns of abnormal neural activation have been observed during working memory tasks in bipolar I depression, yet the neural changes associated with bipolar II depression have yet to be explored.

Method—An n-back working memory task was administered during a 3T functional magnetic resonance imaging scan in age- and gender-matched groups of 19 unmedicated, bipolar II depressed subjects and 19 healthy comparison subjects. Whole-brain and region-of-interest analyses were performed to determine regions of differential activation across memory-load conditions (0-, 1- and 2-back).

Results—Accuracy for all subjects decreased with higher memory load, but there was no significant group $\times$ memory load interaction. Random-effects analyses of memory load indicated that subjects with bipolar II depression exhibited significantly less activation than healthy subjects in left hemispheric regions of the middle frontal gyrus [Brodmann area (BA) 11], superior frontal gyrus (BA 10), inferior parietal lobule (BA 40), middle temporal gyrus (BA 39) and bilateral occipital regions. There was no evidence of differential activation related to increasing memory load in the dorsolateral prefrontal or anterior cingulate cortex.

Conclusions—Bipolar II depression is associated with hypoactivation of the left medio-frontal and parietal cortex during working memory performance. Our findings suggest that bipolar II depression is associated with disruption of the fronto-parietal circuit that is engaged in working memory tasks, which is a finding reported across bipolar subtypes and mood states.

Keywords

Bipolar disorder; depression; functional MRI; n-back task; neuroimaging; prefrontal cortex; working memory

* Address for correspondence: J. O. Brooks, Ph.D., M.D., Department of Psychiatry & Biobehavioral Sciences, UCLA Semel Institute for Neuroscience & Human Behavior, 300 Medical Plaza, Suite 2229, Los Angeles, CA 90024, USA., (john.brooks@ucla.edu).

[†]Equal contributions from authors.

Declaration of Interest

J.O.B. is on the speakers' bureau for Sunovion and has received research funding from Pfizer. L.L.A. has received past funding from Takeda Pharmaceuticals North America, Inc., and H. Lundbeck A/S (advisory board honoraria, October 2012), and past and potential future funding from Sunovion Pharmaceuticals Inc. (advisory board honoraria, January 2013). The remaining authors report no financial relationships with commercial interests.

Introduction

Working memory impairments have been documented in subjects with bipolar I disorder during euthymic and depressed phases (Murphy *et al.* 1999; Malhi *et al.* 2007; Godard *et al.* 2011; Yates *et al.* 2011; Xu *et al.* 2012; Volkert *et al.* 2014). Impairment of working memory in this population has been associated with occupational deficits (Bearden *et al.* 2011) and suicidal behavior (Keilp *et al.* 2013). Though there are two primary subtypes of bipolar disorder, investigations of the neuropathology of working memory impairments have focused on bipolar I disorder. For example, a recent meta-analysis (Cremaschi *et al.* 2013) of functional magnetic resonance (fMRI) studies assessing working memory in euthymic bipolar I patients points to abnormal activation patterns in the dorsolateral pre-frontal cortex (DLPFC), ventrolateral prefrontal cortex, other prefrontal regions, as well as the parietal and temporal cortices.

Bipolar II disorder is also associated with neurocognitive impairments, including working memory (Torrent *et al.* 2006; Dittmann *et al.* 2008; Hsiao *et al.* 2009; Sole *et al.* 2011, 2012; Pålsson *et al.* 2013), but the functional correlates of the deficits in bipolar II disorder remain largely unexplored. Recent evidence further suggests that a major part of the cognitive impairment observed in euthymic bipolar I and II disorder may be due to subthreshold depressive symptoms rather than disease severity (Volkert *et al.* 2014), highlighting a need for bipolar studies during the depressed phase of the illness. Even so, the underlying neural correlates of working memory performance in bipolar II depression have yet to be identified.

With respect to bipolar I disorder, previous research has suggested, though with some disparate findings, that DLPFC dysregulation is a core feature associated with working memory performance. An fMRI study of bipolar I depression explored blood oxygenation level-dependent (BOLD) response during a 2-back working memory task and found that medicated depressed subjects with bipolar I disorder exhibited increased left DLPFC activation compared with healthy subjects (Deckersbach *et al.* 2008). An increased activation pattern has also been found in studies in predominantly medicated unipolar depressed subjects (Fitzgerald *et al.* 2008; Bertocci *et al.* 2012) in which performance on n-back tasks is associated with increased anterior cingulate response, which could represent compensatory activation. However, Townsend *et al.* (2010), found that, relative to healthy comparison subjects, medicated subjects with bipolar I depression exhibited decreased activation in the right DLPFC and the posterior parietal cortex [Brodmann area (BA) 40] during a working memory task. These findings also parallel those reported in other work in bipolar depression of unspecified subtype (Fernandez-Corcuera *et al.* 2013) where an inverse relationship between left DLPFC activation and depression severity scores in medicated subjects was found.

The demonstrated, though somewhat unclear, differences in neural activation in bipolar I depression raise the question of whether bipolar II depression is associated with similar or different patterns of neural activity. To our knowledge, there have been no functional neuroimaging studies of working memory in bipolar II depression. Additionally, in many fMRI studies of bipolar disorder, subjects are taking various medications that have unclear effects on fMRI activation. However, one recent working memory study in euthymic

subjects with bipolar I disorder demonstrated that those with greater medication load exhibited the greatest brain response within the prefrontal cortex, including in the DLPFC (McKenna *et al.* 2014).

Here we report an initial study of neurobiological changes associated with bipolar II depression in the absence of potentially confounding medication effects. Our primary hypothesis was that unmedicated depressed subjects with bipolar II disorder would exhibit hypoactivation of the DLPFC compared with healthy controls. We also predicted that, given our prior results in depressed subjects with bipolar I disorder (Townsend *et al.* 2010), there would be additional areas of hypoactivation in bipolar II subjects including in the inferior frontal cortex and parietal cortex during working memory tasks.

Method

Participants

Twenty-four depressed subjects with bipolar II disorder and 21 healthy comparison subjects were enrolled and scanned. Subjects with bipolar disorder were recruited through the UCLA Mood Disorders Clinic and through local advertising. Comparison subjects were recruited by advertisement in local newspapers and campus flyers. Participants provided written informed consent in accordance with the Institutional Review Boards at the University of California, Los Angeles.

All participants completed the Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version (SCID; First *et al.* 2002). Subjects who met DSM-IV criteria for bipolar II disorder in a current major depressive episode, and scored ≥ 22 on the 30-item Inventory of Depressive Symptomatology–Clinician Rated (Rush *et al.* 1996), were eligible to participate. Bipolar subjects with a history of an alcohol or drug use disorder could participate if they had been sober for at least 3 months, as confirmed by self-report and a urine toxicology screen before scanning. Course of illness information (i.e. bipolar illness duration, prior number of hypomanic and depressive episodes) was obtained by self-report and confirmed by reference to psychiatric care records when available. Comparison participants were required to have no current or past psychiatric diagnosis (including substance abuse) as assessed by the SCID.

Exclusion criteria for all subjects included current use of psychotropic medications, left-handedness, head injury with loss of consciousness >5 min, unstable medical illness, ferrous metal implants, neurologic illness, pregnancy, and a diagnosis of borderline personality disorder assessed using the Personality Diagnostic Questionnaire (Hyler *et al.* 1990) and confirmed with a clinical interview.

On the day of the scan, severity of hypomania and depression in bipolar II subjects was assessed using the Young Mania Rating Scale (Young *et al.* 1978) and the 21-item Hamilton Rating Scale for Depression (HAM-D-21; Hamilton, 1960). A seven-item extension of the HAMD was used to assess atypical depressive symptoms common in bipolar depression (Rosenthal & Heffernan, 1987).

Four bipolar II depressed participants and three control participants were excluded from the analyses because of excessive movement in the scanner (movement beyond 3 mm translation peak-to-peak over 117 functional images) or excessive magnetic susceptibility dropout. An additional bipolar subject was excluded because of poor behavioral performance. The final MRI analysis was conducted on 19 bipolar II depressed subjects and 19 comparison subjects.

Of the bipolar II depressed subjects, seven had never received psychotropic medication and the remaining 12 had been unmedicated for an average of 3.5 years (S.D. = 5.5 years, range 22 days to 20 years) at the time of the study. Two bipolar II depressed subjects had current co-morbid post-traumatic stress disorder, one had panic disorder with agoraphobia, and another had social phobia. Four bipolar subjects had past substance/alcohol use disorders.

Ethics

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Imaging task

The n-back paradigm included three memory-load conditions (0-back, 1-back and 2-back). For the 0-back condition, participants pressed a button whenever the letter 'X' appeared. For the 1-back condition, participants were instructed to press the button whenever a letter flashed upon the screen that was identical to the letter presented one position back. For the 2-back condition, participants pressed the button when the current letter appeared two letters back. The task included eight blocks [four blocks of the 0-back (control) condition, two blocks of each experimental condition] with 12 trials in each 30-s block. Instructions were presented on the computer screen for 6 s at the beginning of every block and subjects were asked to respond as accurately and rapidly as possible. Stimulus presentation time was 500 ms with an inter-trial interval of 1500 ms. The order of the experimental blocks was counterbalanced and interleaved with blocks of the 0-back condition. A rest period was presented at the beginning and end of the task (total duration 4 min 58 s). Before scanning, subjects completed a practice session outside the scanner to familiarize themselves with the task and to confirm performance accuracy.

Image acquisition

Functional imaging data were acquired on a Siemens 3T Magnetom Allegra scanner (Germany). T2*-weighted images were acquired with a gradient echo planar imaging (EPI) sequence as follows: repetition time (TR) = 2500 ms, echo time (TE) = 35 ms, field of view (FOV) = 200 × 200 mm, matrix size = 64 × 64 mm, voxel size = 3.1 × 3.1 × 3 mm, slice thickness = 3 mm with a 1-mm slice gap, number of interleaved acquired slices = 28, flip angle = 90°. High-resolution structural images aligned to the anterior and posterior commissure were acquired with the following parameters: TR = 5000 ms, TE = 33 ms, FOV = 200 × 200 mm, matrix = 128 × 128 mm, in-plane resolution = 1.56, slice thickness = 3 mm, gap = 1 mm, number of slices = 28, flip angle = 90°.

Data analysis

Demographic variables—Group differences in categorical and continuous demographic variables were computed using two-tailed Fisher's exact and independent-sample *t* tests, respectively. Statistical significance was defined as $\alpha = 0.05$.

Behavioral data—Mean accuracy and mean correct response times were computed for each participant for all three memory-load conditions. Data were analysed using a repeated-measures analysis of variance (ANOVA) with group as a between-subjects factor, and memory load (i.e. 0-back, 1-back or 2-back) as the within-subject factor. Accuracy and reaction times were analysed separately. Behavioral data were missing for one healthy control participant.

Image preprocessing—fMRI data were analysed using the fMRI Expert Analysis Tool (FEAT) version 5.98, part of FSL [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library, www.fmrib.ox.ac.uk/fsl]. Structural images were skull stripped using the Brain Extraction Tool (Smith, 2002) and used for intra-subject registration. The first two volumes of each subject's functional scans were discarded to allow for T1 equilibrium effects. Motion correction was performed using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool) (Jenkinson *et al.* 2002). Images were smoothed using a Gaussian kernel of 5 mm full width between half maximum values of a function. All volumes underwent grand-mean intensity normalization by a single multiplicative factor and high-pass temporal filtering using a Gaussian-weighted least-squares straight line fitting, with $\sigma = 60.0$ s. A high-pass filter of 120 s was used to remove low-frequency artifact signals. Time-series statistical analysis was performed using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (Woolrich *et al.* 2001). Using a seven-parameter affine registration, functional images were registered to high-resolution structural images using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson & Smith, 2001; Jenkinson *et al.* 2002) then aligned to the MNI-152 atlas (Montreal Neurological Institute, Canada) using a 12-parameter affine registration.

Image analysis—For first-, or subject-level, analysis, each of the three memory-load conditions, and the instructional cue at the beginning of each block condition, were modeled separately for each subject. Functional imaging data were analysed using a general linear model, and six motion-correction parameter estimates were incorporated as covariates of no interest to control motion-related signal change. Prior research using the n-back working memory task has shown that increasing working memory load produces increased prefrontal cortex activation (Braver *et al.* 1997; Cohen *et al.* 1997; Kammer *et al.* 1997). Therefore, to model our parametric design and further reduce the likelihood of a type I error, we conducted a single analysis that considered all memory-load conditions (0-back, 1-back and 2-back) simultaneously. To do so, we assigned weights (−0.5, 0.7, 1.2) to each condition (0-back, 1-back and 2-back), respectively, and obtained a statistical map for each subject.

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). For the whole-brain analysis of within-group and between-group effects on activation during

these contrasts, we report brain regions with a height threshold of $Z > 2.0$ and a cluster probability of $p < 0.05$, corrected for whole-brain multiple comparisons using Gaussian random field theory (Worsley, 2001). For reporting purposes, Montreal Neurological Institute (MNI) coordinates were transformed to Talairach space using the MNI to Talairach Conversion Applet (www.bioimagesuite.org). Anatomical localization was performed using stereotaxic atlases (Talairach & Tournoux, 1988; Oishi *et al.* 2011).

Region-of-interest (ROI) analysis in the DLPFC—Given our *a priori* hypothesis of differential DLPFC activation, we supplemented our whole-brain analysis with a ROI analysis. To avoid bias in ROI selection (Kriegeskorte *et al.* 2009), we functionally defined the left and right DLPFC using coordinates derived from a meta-analysis of normative n-back working memory fMRI studies (Owen *et al.* 2005). Specifically, a 10-mm sphere was placed at the peak voxel corresponding to activation in the left and right DLPFC centered at MNI coordinate (−41, 31, 31) and (41, 31, 31), respectively. The time course from these DLPFC ROI masks during the parametric analysis of 0-back > 1-back > 2-back trials was extracted separately for each subject and used for the calculation of mean percentage signal change using FEATQuery. Correlational analyses were performed to determine if mean activity in these regions was related to illness characteristics ($p < 0.05$), which included: current depression severity (using the HAMD); age at onset of bipolar illness; duration of bipolar illness; and number of weeks in current major depressive episode.

Results

Participant characteristics

Demographic data are provided in Table 1. There was no significant difference in age between patient and comparison groups. The comparison group included more female participants, but not significantly so ($\chi^2 = 0.42$, $p = 0.51$). Among patients diagnosed with bipolar II disorder, there were no significant correlations between medication-free period and age at illness onset, duration of illness, current episode duration, current depression severity or lifetime number of mood episodes (all p 's > 0.11).

Behavioral data

Behavioral data collected from the n-back task are shown for each group in Table 2. A repeated-measures ANOVA of accuracy data did not reveal a significant main effect of group ($F_{1,35} = 1.58$, $p = 0.22$), but there was a significant main effect of memory load ($F_{2,70} = 13.49$, $p < 0.001$), indicating that both bipolar II depressed and healthy comparison participants were more accurate on both the 0-back and 1-back conditions than on the 2-back memory-load condition. However, the group $\times$ memory load interaction was not statistically significant ($F_{2,70} = 1.32$, $p = 0.27$).

For reaction time, the group $\times$ memory load interaction was not statistically significant ($F_{2,70} = 1.20$, $p = 0.31$). There was no significant main effect of group ($F_{1,35} = 0.14$, $p = 0.71$), but there was a main effect of memory load ($F_{2,70} = 7.19$, $p = 0.001$), indicating that reaction times varied across the three memory-load conditions.

fMRI results

Analysis of motion artifacts—Analysis of the three rotational (roll, pitch, yaw) and three translational (anterior to posterior, superior to inferior, left to right) parameters yielded no significant differences in motion correction between subjects with bipolar II depression and healthy comparison subjects (all p 's > 0.25). Additionally, the relative and absolute motion values for each participant were examined to confirm that our patient and comparison groups did not differ significantly, which they did not ($t_{36} = 0.22$, $p = 0.82$ and $t_{36} = 0.45$, $p = 0.66$, respectively).

Whole-brain results: within-group findings for parametric analysis of memory load—The contrast across the three memory-load conditions for whole-brain analyses of each subject group is illustrated in Fig. 1. Control subjects demonstrated significant activation in the bilateral inferior frontal gyrus (BA 44 extending to BA 9), right medial frontal gyrus (BA 8), bilateral inferior parietal lobule (BA 40), bilateral thalamus and right temporal cortices (BA 22, 37) ($Z > 2.0$, $p < 0.05$, corrected). Bipolar subjects significantly activated similar regions including the bilateral middle frontal gyrus (BA 8), bilateral superior frontal gyrus (BA 8 and BA 6), left precentral gyrus (BA 6), bilateral inferior parietal lobule (BA 40) and bilateral striatal regions ($Z > 2.0$, $p < 0.05$, corrected).

Whole-brain results: between-group findings for parametric analysis of memory load—Table 3 provides the local peak maxima of the activation differences for the random-effects analysis (bipolar < control). There were no significant group differences observed in the DLPFC. In the parametric analysis of memory load, bipolar depressed subjects showed significantly reduced activity in the left middle frontal gyrus (BA 11) and left superior frontal gyrus (BA 10) relative to healthy comparison subjects ($Z > 2.0$, $p < 0.05$, corrected). Bipolar depressed subjects showed hypoactivation in additional regions including the left inferior parietal lobule (BA 40), left middle temporal gyrus and angular gyrus (both corresponding to BA 39), and occipital regions. The bipolar II depressed group did not exhibit significantly greater activation in any brain regions relative to comparison subjects across memory-load conditions. A graphic illustration of activation differences is provided in Fig. 2.

ROI results: DLPFC BOLD response in bipolar II depressed versus comparison subjects—Both groups demonstrated significant bilateral DLPFC activation. Our *a priori* ROI analysis did not reveal statistically significant differences in BOLD response across memory-load conditions between the bipolar and comparison groups in either the left or right DLPFC, nor did we find evidence of statistically significant correlations with HAMD score, illness duration, age at illness onset, or number of weeks in current depression (for all, $p > 0.05$).

Discussion

Our study is an initial report of differences in neural activation across memory-load conditions in an n-back working memory task involving unmedicated, acutely depressed subjects with bipolar II disorder. Accuracy and reaction time were matched in both bipolar

disorder and healthy comparison groups, and, relative to healthy subjects, we observed significantly decreased activation in the medial orbital, temporal, parietal, and occipital cortices in the bipolar group.

Our within-group findings in subjects with bipolar II depression demonstrated that our task activated regions as expected during a working memory task. Studies of healthy subjects have revealed that, across memory-load conditions, working memory tasks activate DLPFC as well as the posterior parietal cortex (Smith & Jonides, 1998; Curtis, 2006). We found similar activation patterns in both bipolar II depressed and healthy subjects.

We did not find significant differences in DLPFC activation in unmedicated subjects with bipolar II depression *versus* control subjects during a working memory task. A prior study by our group in medicated subjects with bipolar I disorder found reduced activation in the DLPFC and parietal cortex across mood states (Townsend *et al.* 2010) during a 2-back *versus* 0-back memory condition. Whereas some regions of hypoactivation may represent shared features of both bipolar I and II depression, DLPFC hypoactivation may be more specific to bipolar I depression. Neurobiological differences in brain activation during working memory tasks in bipolar I disorder may be trait characteristics and are thus present outside of depressive episodes. A recent review (Cremaschi *et al.* 2013) of n-back fMRI studies of medicated euthymic subjects diagnosed with bipolar I disorder revealed altered activation and connectivity within the ventrolateral circuit and parieto-temporal circuit dysfunction rather than dorsolateral. Although we did not include euthymic subjects with bipolar II disorder in this study, it may be that bipolar II disorder is associated more with ventrolateral circuit rather than dorsolateral circuit dysfunction. To the extent that this observation is true, it could account for the lack of differences in DLPFC activation in our study. Thus, our study of unmedicated depressed subjects with only the bipolar II subtype suggests that differential neural activation during working memory tasks in bipolar II depression shares some, but not all, the characteristics of activation patterns seen in subjects with bipolar I depression.

As in our previous work with subjects with bipolar I depression, we observed significant differences in BA 10 activation in bipolar II subjects compared with healthy controls. However, unlike medicated subjects with bipolar I disorder, who exhibited hyperactivation of BA 10 (Altshuler *et al.* 2008), the present study of unmedicated depressed subjects with the bipolar II subtype found hypoactivation of BA 10. Although BA 10 is generally considered with respect to its roles in coordinating tasks (Cabeza & Nyberg, 2000) or regulating emotion (Ochsner *et al.* 2002), it may also be involved in circuits activated by working memory tasks (Thermenos *et al.* 2010). Previously, researchers have suggested that BA 10 aberrations could be a trait marker for bipolar disorders (Drevets, 1999). Thus, the region may be involved in several critical circuits that could be differentially activated across bipolar subtypes.

In the current study, depressed subjects with bipolar II disorder also exhibited significantly decreased activation relative to healthy subjects in the inferior parietal cortex (BA 40). The posterior parietal cortex (encompassing BA 40) is a component of the working memory circuit, which probably plays a role in short-term storage of verbal information (Smith &

Jonides, 1998; Naghavi & Nyberg, 2005; Owen *et al.* 2005). Decreased parietal activation may represent a more general trait of bipolar disorders, as medicated euthymic patients with bipolar I disorder also exhibit parietal hypoactivation when performing a working memory task (Monks *et al.* 2004; Townsend *et al.* 2010). Though we found decreased parietal activation among patients with bipolar II depression, performance levels did not significantly differ from comparison subjects. Our analyses did not detect the nature of a compensatory mechanism, but such a mechanism may become evident with increased levels of task difficulty.

Some researchers have suggested that differential brain activation during working memory tasks may be a distinguishing characteristic between subjects with bipolar and unipolar depression (Schöning *et al.* 2009; Bertocci *et al.* 2012). Specifically, in a study of predominantly medicated female patients diagnosed with either bipolar I disorder or unipolar depression, Bertocci *et al.* (2012) reported that patients with unipolar depression exhibited greater anterior cingulate activation during an emotional working memory task than did either patients with bipolar I depression or healthy comparison subjects. However, the emotion-regulation component of the task may have played a substantial role in this finding.

As with studies in bipolar disorder, the fMRI activation findings in subjects with unipolar depression during working memory tasks are not consistent. One study found that medicated patients with non-psychotic unipolar depression exhibit significantly less right DLPFC activation during a working memory task than do healthy subjects (Garrett *et al.* 2011). Other work, however, suggests that medicated patients with unipolar depression exhibit increased left dorsolateral prefrontal activation during a verbal working memory task relative to healthy subjects (Fitzgerald *et al.* 2008), and this pattern of results is also observed in unmedicated unipolar depressed subjects (Harvey *et al.* 2005; Matsuo *et al.* 2007; Fitzgerald *et al.* 2008).

There are several limitations in the present study. While all of the bipolar subjects were unmedicated at the time of the scan, we were not able to control for effects of past medication. The 2-back condition may not have been sufficient memory load to demonstrate DLPFC differences between bipolar II disorder subjects and healthy ones. Thus, had we used a 3-back condition we may have observed even greater activation differences along with performance deficits as well. However, in their review of n-back fMRI studies in bipolar disorder, Cremaschi *et al.* (2013) noted the importance of having similar task performance between groups to reduce the confounds of performance-related differences on fMRI activation. Lastly, additional work with euthymic, as well as depressed, bipolar II subjects would be necessary to determine whether it is current mood or trait-like features of bipolar II that are most responsible for the effects observed.

Conclusions

Our study provides the first evidence of neural deficits associated with working memory performance in unmedicated depressed subjects with bipolar II disorder. These findings highlight the need for further study of the neural abnormalities associated with bipolar II

disorder and their interactions across mood states. Such studies could provide valuable insight into the underlying neural mechanisms of bipolar disorders.

Acknowledgments

Support for this research was provided by: the National Institute of Mental Health (NIMH) (to L.L.A., K24MH01848; and to N.V., T32MH17140); a fellowship from the UCLA Integrative Study Center in Mood Disorders; the National Center for Research Resources (NCRR) (RR12169, RR13642 and RR00865); the Brain Mapping Medical Research Organization; Brain Mapping Support Foundation; Pierson-Lovelace Foundation; The Ahmanson Foundation; William M. and Linda R. Dietel Philanthropic Fund at the Northern Piedmont Community Foundation; Tamkin Foundation; Jennifer Jones-Simon Foundation; Capital Group Companies Charitable Foundation; Robson Family and Northstar Fund. The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of NIMH, NCRR or the National Institutes of Health.

The authors thank: Ana R. Aquino, Jeffrey Fischer and the UCLA Deutsch Mood Disorders Fellows for diagnostic interviewing and assessment; Jacquelyn Dang for assistance with data entry; and the research subjects for their participation.

References

- Altshuler L, Bookheimer S, Townsend J, Proenza MA, Sabb F, Mintz J, Cohen MS. Regional brain changes in bipolar I depression: a functional magnetic resonance imaging study. *Bipolar Disorders*. 2008; 10:708–717. [PubMed: 18837865]
- Bearden CE, Shih VH, Green MF, Gitlin M, Sokolski KN, Levander E, Marusak S, Hammen C, Sugar CA, Altshuler LL. The impact of neurocognitive impairment on occupational recovery of clinically stable patients with bipolar disorder: a prospective study. *Bipolar Disorders*. 2011; 13:323–333. [PubMed: 21843272]
- Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in fMRI. *NeuroImage*. 2003; 20:1052–1063. [PubMed: 14568475]
- Bertocci MA, Bebko GM, Mullin BC, Langenecker SA, Ladouceur CD, Almeida JRC, Phillips ML. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychological Medicine*. 2012; 42:1417–1428. [PubMed: 22099606]
- Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage*. 1997; 5:49–62. [PubMed: 9038284]
- Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. *Current Opinion in Neurology*. 2000; 13:415–421. [PubMed: 10970058]
- Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. Temporal dynamics of brain activation during a working memory task. *Nature*. 1997; 386:604–608. [PubMed: 9121583]
- Cremaschi L, Penzo B, Palazzo M, Dobrea C, Cristoffanini M, Dell'Osso B, Altamura AC. Assessing working memory via n-back task in euthymic bipolar I disorder patients: a review of functional magnetic resonance imaging studies. *Neuropsychobiology*. 2013; 68:63–70. [PubMed: 23881005]
- Curtis CE. Prefrontal and parietal contributions to spatial working memory. *Neuroscience*. 2006; 139:173–180. [PubMed: 16326021]
- Deckersbach T, Rauch SL, Buhlmann U, Ostacher MJ, Beucke J-C, Nierenberg AA, Sachs G, Dougherty DD. An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. *Bipolar Disorders*. 2008; 10:928–942. [PubMed: 19594508]
- Dittmann S, Hennig-Fast K, Gerber S, Seemuller F, Riedel M, Emanuel Severus W, Langosch J, Engel RR, Moller HJ, Grunze HC. Cognitive functioning in euthymic bipolar I and bipolar II patients. *Bipolar Disorders*. 2008; 10:877–887. [PubMed: 19594503]
- Drevets WC. Prefrontal cortical–amygdalar metabolism in major depression. *Annals of the New York Academy of Sciences*. 1999; 877:614–637. [PubMed: 10415674]
- Fernandez-Corcuera P, Salvador R, Monte GC, Salvador Sarro S, Goikolea JM, Amann B, Moro N, Sans-Sansa B, Ortiz-Gil J, Vieta E, Maristany T, McKenna PJ, Pomarol-Clotet E. Bipolar

- depressed patients show both failure to activate and failure to de-activate during performance of a working memory task. *Journal of Affective Disorders*. 2013; 148:170–178. [PubMed: 22854099]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV TR Axis I Disorders Research Version, Patient Edition (SCID-I/P). Biometrics Research, New York State Psychiatric Institute; New York: 2002.
- Fitzgerald PB, Srithiran A, Benitez J, Daskalakis ZZ, Oxley TJ, Kulkarni J, Egan GF. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Human Brain Mapping*. 2008; 29:490–501. [PubMed: 17525987]
- Garrett A, Kelly R, Gomez R, Keller J, Schatzberg AF, Reiss AL. Aberrant brain activation during a working memory task in psychotic major depression. *American Journal of Psychiatry*. 2011; 168:173–182. [PubMed: 21078708]
- Godard J, Grondin S, Baruch P, Lafleur MF. Psychosocial and neurocognitive profiles in depressed patients with major depressive disorder and bipolar disorder. *Psychiatry Research*. 2011; 190:244–252. [PubMed: 21764461]
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1960; 23:56–62.
- Harvey P-O, Fossati P, Pochon J-B, Levy R, Lebastard G, Lehericy S, Allilaire J-F, Dubois B. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *NeuroImage*. 2005; 26:860–869. [PubMed: 15955496]
- Hsiao YL, Wu YS, Wu JY, Hsu MH, Chen HC, Lee SY, Lee IH, Yeh TL, Yang YK, Ko HC, Lu RB. Neuropsychological functions in patients with bipolar I and bipolar II disorder. *Bipolar Disorders*. 2009; 11:547–554. [PubMed: 19624394]
- Hyler SE, Skodol AE, Kellman HD, Oldham JM, Rosnick L. Validity of the Personality Diagnostic Questionnaire – revised: comparison with two structured interviews. *American Journal of Psychiatry*. 1990; 147:1043–1048. [PubMed: 2197883]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002; 17:825–841. [PubMed: 12377157]
- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*. 2001; 5:143–156. [PubMed: 11516708]
- Kammer T, Belleman ME, Guckel F, Brix G, Gass A, Schlemmer H, Spitzer M. Functional MR imaging of the prefrontal cortex: specific activation in a working memory task. *Magnetic Resonance Imaging*. 1997; 15:879–889. [PubMed: 9322207]
- Keilp JG, Gorlyn M, Russell M, Oquendo MA, Burke AK, Harkavy-Friedman J, Mann JJ. Neuropsychological function and suicidal behavior: attention control, memory and executive dysfunction in suicide attempt. *Psychological Medicine*. 2013; 43:539–551. [PubMed: 22781400]
- Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience*. 2009; 12:535–540. [PubMed: 19396166]
- Malhi GS, Ivanovski B, Hadzi-Pavlovic D, Mitchell PB, Vieta E, Sachdev P. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disorders*. 2007; 9:114–125. [PubMed: 17391355]
- Matsuo K, Glahn DC, Peluso MAM, Hatch JP, Monkul ES, Najt P, Sanches M, Zamarripa F, Li J, Lancaster JL, Fox PT, Gao J-H, Soares JC. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Molecular Psychiatry*. 2007; 12:158–166. [PubMed: 16983390]
- McKenna BS, Sutherland AN, Legenkaya AP, Eyler LT. Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder. *Bipolar Disorders*. 2014; 16:289–299. [PubMed: 24119150]
- Monks PJ, Thompson JM, Bullmore ET, Suckling J, Brammer MJ, Williams SC, Simmons A, Giles N, Lloyd AJ, Harrison CL, Seal M, Murray RM, Ferrier IN, Young AH, Curtis VA. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. *Bipolar Disorders*. 2004; 6:550–564. [PubMed: 15541071]

- Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, Paykel ES. Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine*. 1999; 29:1307–1321. [PubMed: 10616937]
- Naghavi HR, Nyberg L. Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? *Consciousness and Cognition*. 2005; 14:390–425. [PubMed: 15950889]
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*. 2002; 14:1215–1229. [PubMed: 12495527]
- Oishi, K.; Faria, AV.; van Zijl, P.; Mori, S. *MRI Atlas of Human White Matter*. 2nd. Academic Press; Amsterdam: The Netherlands: 2011.
- Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*. 2005; 25:46–59. [PubMed: 15846822]
- Pålsson E, Figueras C, Johansson AGM, Ekman C-J, Hultman B, Östlind J, Landén M. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. *BMC Psychiatry*. 2013; 13:165. [PubMed: 23758923]
- Rosenthal, NE.; Hefferman, ME., editors. *Bulimia, Carbohydrate Craving and Depression: a Central Connection?*. Raven Press; New York: 1987.
- Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine*. 1996; 26:477–486. [PubMed: 8733206]
- Schöning S, Zwitterlood P, Engelien A, Behnken A, Kugel H, Schiffbauer H, Lipina K, Pachur C, Kersting A, Dannlowski U, Baune BT, Zwanzger P, Reker T, Heindel W, Arolt V, Konrad C. Working-memory fMRI reveals cingulate hyperactivation in euthymic major depression. *Human Brain Mapping*. 2009; 30:2746–2756. [PubMed: 19086021]
- Smith EE, Jonides J. Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95:12061–12068. [PubMed: 9751790]
- Smith SM. Fast robust automated brain extraction. *Human Brain Mapping*. 2002; 17:143–155. [PubMed: 12391568]
- Sole B, Bonnin CM, Torrent C, Balanza-Martinez V, Tabares-Seisdedos R, Popovic D, Martinez-Aran A, Vieta E. Neurocognitive impairment and psychosocial functioning in bipolar II disorder. *Acta Psychiatrica Scandinavica*. 2012; 125:309–317. [PubMed: 21848702]
- Sole B, Martinez-Aran A, Torrent C, Bonnin CM, Reinares M, Popovic D, Sanchez-Moreno J, Vieta E. Are bipolar II patients cognitively impaired? A systematic review. *Psychological Medicine*. 2011; 41:1791–1803. [PubMed: 21275085]
- Talairach, J.; Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain: 3-D Proportional System: an Approach to Cerebral Imaging*. Thieme Medical Publishers, Inc; New York: 1988.
- Thermenos HW, Goldstein JM, Milanovic SM, Whitfield-Gabrieli S, Makris N, Laviolette P, Koch JK, Faraone SV, Tsuang MT, Buka SL, Seidman LJ. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2010; 153B:120–131.
- Torrent C, Martinez-Aran A, Daban C, Sanchez-Moreno J, Comes M, Goikolea JM, Salamero M, Vieta E. Cognitive impairment in bipolar II disorder. *British Journal of Psychiatry*. 2006; 189:254–259. [PubMed: 16946361]
- Townsend J, Bookheimer SY, Foland-Ross LC, Sugar CA, Altshuler LL. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Research: Neuroimaging*. 2010; 182:22–29. [PubMed: 20227857]
- Volkert J, Kopf J, Kazmaier J, Glaser F, Zierhut KC, Schiele MA, Kittel-Schneider S, Reif A. Evidence for cognitive subgroups in bipolar disorder and the influence of subclinical depression and sleep disturbances. *European Neuropsychopharmacology*. 2014; Published online 15 August 2014. doi: 10.1016/j.euroneuro.2014.07.017

- Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of fMRI data. *NeuroImage*. 2001; 14:1370–1386. [PubMed: 11707093]
- Worsley, KJ. Statistical analysis of activation images. In: Jezzard, P.; Matthews, PM.; Smith, SM., editors. *Functional MRI: An Introduction to Methods*. Oxford University Press; New York: 2001. p. 251-270.
- Xu G, Lin K, Rao D, Dang Y, Ouyang H, Guo Y, Ma J, Chen J. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. *Journal of Affective Disorders*. 2012; 136:328–339. [PubMed: 22169253]
- Yates DB, Dittmann S, Kapczinski F, Trentini CM. Cognitive abilities and clinical variables in bipolar I depressed and euthymic patients and controls. *Journal of Psychiatric Research*. 2011; 45:495–504. [PubMed: 20951385]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry*. 1978; 133:429–435. [PubMed: 728692]

Fig. 1.

Regions of significant within-group activation in healthy comparison subjects and depressed subjects with bipolar II disorder across 0-, 1- and 2-back conditions. Maps are thresholded at $Z > 2.0$, $p < 0.05$ with correction for multiple comparisons.

Fig. 2. Regions of significantly decreased activation in bipolar II disorder patients relative to healthy comparison subjects across 0-, 1- and 2-back conditions. Maps are thresholded at $Z > 2.0$, $p < 0.05$ with correction for multiple comparisons.

Table 1

Demographic and clinical characteristics of bipolar II depressed and healthy comparison subjects

Characteristic	Bipolar II depressed (<i>n</i> = 19)	Healthy comparison (<i>n</i> = 19)	<i>P</i>
Female, <i>n</i> (%)	8 (42.1)	10 (52.6)	0.52
Race, <i>n</i> (%)			
Caucasian	12 (63.2)	11 (57.9)	0.08
African-American	6 (31.6)	2 (10.5)	–
Asian	1 (5.3)	6 (31.6)	–
Age, years	36.7 (11.4)	42.6 (12.0)	0.13
HAMD (21-item) score	18.6 (3.3)	–	–
HAMD (28-item) score	25.8 (5.4)	–	–
YMRS score	2.7 (1.9)	–	–
Age at illness onset, years	17.3 (7.4)	–	–
Duration of current depressive episode, weeks	16.2 (23.2)	–	–
Lifetime depressive episodes ^a	7.7 (4.9)	–	–
Lifetime hypomanic episodes ^b	5.9 (5.8)	–	–
Depressive episodes in past year ^c	2.5 (1.3)	–	–
Hypomanic episodes in past year ^d	2.9 (3.4)	–	–
Lifetime hospitalizations for depression	0.4 (0.8)	–	–

Data are given as mean (standard deviation) unless otherwise indicated.

HAMD, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

^aBipolar subjects had a range of lifetime depressive episodes from 2 to 15; patients who had a number marked as too many to count were not included in the mean calculation.

^bBipolar subjects had a range of lifetime hypomanic episodes from 1 to 20; eight patients who had a number of lifetime episodes that were marked as too many to count were not included in the mean calculation.

^cBipolar subjects had a range of depressive episodes in the past 12 months from 1 to 6.

^dBipolar subjects had a range of hypomanic episodes in the past 12 months from 0 to 12.

Table 2

Accuracy and reaction time by group

Memory-load condition	Bipolar II depressed	Healthy comparison
Accuracy, % correct ^a		
0-Back	98.9 (2.0)	98.8 (2.5)
1-Back	95.6 (9.0)	97.5 (5.5)
2-Back	90.5 (8.8)	94.4 (6.1)
Reaction time, s ^b		
0-Back	0.47 (0.10)	0.49 (0.10)
1-Back	0.58 (0.20)	0.54 (0.10)
2-Back	0.57 (0.21)	0.62 (0.17)

Data are given as mean (standard deviation).

^aAccuracy data represent percentage of correct trials.^bReaction time data represent correct response reaction times.

Table 3

Significant between-group differences (bipolar II depressed<comparison) in regional functional activation for the parametric analysis of memory load^a

Regions	BA	Talairach peak coordinates, mm			Z
		x	y	z	
Frontal lobe					
Left middle frontal gyrus	11	-33	51	-14	3.21
Left superior frontal gyrus ^b	10 ^b	-30	62	-4	3.10
Parietal lobe					
Left inferior parietal lobule ^b	40 ^b	-38	-57	43	3.29
Temporal lobe					
Left middle temporal gyrus	39	-48	-75	25	2.96
Left angular gyrus	39	-44	-73	31	2.94
Occipital lobe					
Left precuneus	19	-28	-66	42	3.50
Left precuneus	7	-18	-68	45	3.91
Right precuneus	7	14	-51	39	2.96

BA, Brodmann area.

^aAnatomical labels and BAs were assigned according to Talairach & Tournoux (1988) after non-linear coordinate conversion x, y and z are Talairach peak coordinates of local maxima significant at $Z > 2.0$, $p < 0.05$, corrected for multiple comparisons.

^bMore than one local maxima within 10 mm corresponds to this anatomical label and BA region.