Alterations in Functional Activation in Euthymic Bipolar Disorder and Schizophrenia During a Working Memory Task

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Abstract

Dysfunctions in prefrontal cortical networks are thought to underlie working memory (WM) impairments consistently observed in both subjects with bipolar disorder and schizophrenia. It remains unclear, however, whether patterns of WM-related hemodynamic responses are similar in bipolar and schizophrenia subjects compared to controls. We used fMRI to investigate differences in blood-oxygen-level-dependent (BOLD) activation during a WM task in 21 euthymic bipolar I patients, 20 schizophrenia patients, and 38 healthy controls. Subjects were presented with four stimuli (abstract designs) followed by a fifth stimulus, and required to recall whether the last stimulus was among the four presented previously. Task-related brain activity was compared within and across groups. All groups activated prefrontal cortex (PFC), primary and supplementary motor cortex, and visual cortex during the WM task. There were no significant differences in PFC activation between controls and euthymic bipolar subjects, but controls exhibited significantly increased activation (cluster-corrected P<0.05) compared to schizophrenia patients in prefrontal regions including dorso-lateral prefrontal cortex (DLPFC). While the bipolar group exhibited intermediate percent signal change in a functionally-defined DLPFC region of interest with respect to the schizophrenia and control groups, effects remained significant only between schizophrenia patients and controls. Schizophrenia and bipolar disorder may share some behavioral, diagnostic, and genetic features. Differences in the patterns of WM-related brain activity across groups, however, suggest some diagnostic specificity. Both patient groups showed some regional task-related hypoactivation compared to controls across the brain. Within DLPFC specifically, schizophrenia patients exhibited more severe WM-related dysfunction than bipolar subjects.
Keywords
bipolar; schizophrenia; working memory; executive function; fMRI; dorsolateral prefrontal cortex

Introduction
Working memory (WM) is the process whereby the brain stores, maintains, and manipulates information in the short term and is a critical component of general cognition and decision-making used in everyday planning and action (Baddeley 2003). WM deficits are a core feature of schizophrenia (Green 2006; Horan, et al. 2008) and persist throughout the course of illness (Manoach 2003). Patients with bipolar disorder exhibit deficits in WM that persist even during euthymia, when affective symptoms are not present (Altshuler, et al. 2004; Bearden, et al. 2001; Green 2006; Mur, et al. 2007; Robinson, et al. 2006). Thus, WM may be an important treatment target for improving functional outcomes in both bipolar disorder and schizophrenia (Green 2006; Mur, et al. 2007; Robbins 2005). Despite observations of WM deficits in patients with both schizophrenia and bipolar disorder, it remains unclear whether impairments involve similar or diagnosis-specific pathophysiological processes.

WM processes are traditionally split into encoding (taking in visual and spatial cues) and maintenance (holding information online for later retrieval). In the canonical Baddeley and Hitch three-component model of WM, WM is split into the central executive “control system”, and two storage systems, the phonological loop and the visuospatial sketchpad (Baddeley 2003). The phonological loop allows for rehearsal and thus maintenance of encoded information (particularly sound and language), while the visuospatial sketchpad is involved in holding visual and spatial representations online in WM. The central executive system is thought to regulate attention to stimuli and information flow in and out of these storage modules. Investigations on the neural basis of these WM components have suggested that the central executive is located in the prefrontal cortex (D'Esposito, et al. 1995). More recent research further suggests that the DLPFC is specifically involved in directing attention to internal representations of information in more posterior cortices (Curtis and D'Esposito 2003). Studies employing dynamic causal modeling in fMRI have found that the prefrontal cortex mediates activity in more posterior areas via top-down feedback, for example, fusiform face area (FFA) and parahippocampal place area (PPA) while viewing faces and houses (Ranganath 2006). Lesion studies (reviewed in Jonides, et al. 2008) have also shown that damage to prefrontal cortex impairs executive function during WM tasks, but does not affect memory storage. Other investigators have shown that DLPFC is active when participants are simply asked to refresh an active representation in WM (Johnson, et al. 2005). This evidence suggests that the DLPFC is recruited during tasks requiring executive control. It is this sub-process of WM that is posited to be disturbed in both euthymic bipolar patients (Monks, et al. 2004) and in schizophrenia patients (Kim, et al. 2004), thus we have chosen to examine prefrontal networks serving the central executive control system in our study.

Schizophrenia is characterized by varying but widespread impairment in multiple cognitive domains, where deficits in memory, attention, and executive function appear most pronounced (Heinrichs and Zakzanis 1998). Neuropsychological research has shown that WM deficits are pervasive and encompass spatial, verbal, and visual WM (Altshuler, et al. 2004; Green 2006). First-degree relatives of schizophrenia patients also show WM deficits, though to a lesser degree than patient groups, suggesting that impairments may serve as an endophenotype for disease-related genetic predisposition (Glahn, et al. 2003; Karlsgodt, et al. 2007). Imaging studies in schizophrenia implicate prefrontal regions, in particular the dorsolateral prefrontal cortex (DLPFC), as being associated with WM deficits (Manoach
2003; Ragland, et al. 2007; Seidman, et al. 1994), although the regional specificity, magnitude, and direction of differences depend on task demands and performance (Fletcher and Henson 2001). While studies more typically report hypoactivation (where activation is defined as a measurement of the relative differences in cerebral perfusion between behavioral states) in prefrontal regions during WM tasks in patients, hyperactivations have also been reported (Callicott, et al. 1999; Koch, et al. 2008; Manoach 2003). Observations of DLPFC hypoactivation in both medicated (Koch, et al. 2008) and medication-free (Scheuerecker, et al. 2008) schizophrenia patients suggest that WM impairments are not necessarily attributable to antipsychotics.

Much evidence now supports that patients with bipolar disorder exhibit marked deficits in cognition that were initially considered more characteristic of schizophrenia. Bipolar subjects show impairments in executive function, WM, verbal memory, and sustained attention, and these deficits persist even when no major mood symptoms are present (Altshuler, et al. 2007; Altshuler, et al. 2008; Altshuler, et al. 2004; Bearden, et al. 2001; Mur, et al. 2007; Robinson, et al. 2006). As in studies on schizophrenia, WM dysfunction may serve as an endophenotype for bipolar disorder, as unaffected first-degree relatives of bipolar patients show similar WM deficits (Arts, et al. 2007). Furthermore, functional imaging studies on bipolar euthymia have implicated hypoactivation, primarily of the DLPFC, as being associated with WM impairment (Lagopoulos, et al. 2007; Savitz, et al. 2005), though hyperactivation has also been reported (Adler, et al. 2004; Chang, et al. 2004). Despite similar findings in imaging experiments, behavioral studies consistently show greater WM and cognitive impairment in schizophrenia patients compared to bipolar patients (Altshuler, et al. 2004; Glahn, et al. 2006; Green 2006). Recent studies have suggested that research on aspects of WM, particularly maintenance and updating, are promising targets for attempts to improve cognition in patients with schizophrenia (Barch and Smith 2008). Still, if WM impairments were found in similar networks in bipolar disorder and schizophrenia, it might be possible to extend work initiated by the NIMH funded Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (http://cntrics.ucdavis.edu/) to bipolar disorder to further examine WM similarities and differences in these disorders. We thus seek to determine whether WM impairments in bipolar disorder and in schizophrenia are the result of similar pathophysiological processes, but with more pronounced disturbances of WM in schizophrenia, or whether different components of WM are affected in bipolar versus schizophrenia patients.

While several studies have investigated behavioral indices of WM function in both bipolar disorder and schizophrenia, to our knowledge, no prior studies have directly examined differences in brain activity between these two groups as they are engaged in a WM task. We used fMRI to investigate changes in blood-oxygen-level-dependent (BOLD) activity in a large (N=78) adult sample of healthy control, euthymic bipolar and schizophrenia subjects during a WM task. Based on prior imaging (Koch, et al. 2008; Scheuerecker, et al. 2008) and neurocognitive findings in these groups (Altshuler, et al. 2004), we predicted that reduced activation would be present in prefrontal regions in both euthymic bipolar and schizophrenia subjects compared to controls, but that effects would be greater in schizophrenia than in bipolar patients. By investigating WM in both psychiatric groups simultaneously, we hope to clarify how behavioral similarities and differences in WM performance are reflected in the regional specificity of functional alterations.
Materials and Methods

Subjects

We analyzed data from 21 subjects with bipolar disorder, 20 subjects with schizophrenia, and 38 healthy controls. Groups did not differ significantly in age or in sex distribution (Table I). All subjects were right-handed, as assessed by a score ≥ 70 on a modified version of the Edinburgh Handedness Inventory (Oldfield 1971). Schizophrenia patients were recruited through admissions to the UCLA Aftercare Research Program from local public and private psychiatric hospitals and clinics in the Los Angeles area. Bipolar subjects were outpatients at the West Los Angeles VA Medical Center or the UCLA Mood Disorders Clinic, or had responded to advertisements placed in local newspapers. Informed written consent was obtained from all subjects, and all experimental procedures were approved by the Institutional Review Board (IRB) at the VA Greater Los Angeles Healthcare System, West Los Angeles Medical Center and by the UCLA IRB.

Diagnosis for schizophrenia and bipolar I disorder was determined using DSM-IV criteria, as documented through the Structured Clinical Interview for DSM-IV (SCID) (First, et al. 1997) and informant information. Symptom assessments for the bipolar subjects included the Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960) and the Young Mania Rating Scale (YMRS) (Young, et al. 1978). Patients with schizophrenia were assessed using the Brief Psychiatric Rating Scale (BPRS; see Ventura, et al. 2000). Bipolar subjects were required to be euthymic at testing, which was defined as meeting criteria on the SCID (Spitzer, et al. 1992) for no manic or depressive episodes and for having a YMRS < 7 and HAM-D < 7 on the day of fMRI acquisition. Schizophrenia subjects were similarly stable, with average BPRS scores < 2 for both negative and positive symptom ratings (Table I).

Community control subjects were screened to exclude any current DSM-IV diagnosis. Furthermore, control subjects with a first-degree relative diagnosed with any schizophrenia spectrum disorder or bipolar disorder were excluded. Other exclusion criteria for all participants included mental retardation, neurological disorder (e.g., temporal lobe epilepsy), or significant and habitual drug abuse or alcoholism. Furthermore, schizophrenia patients were excluded if there was any evidence that a history of substance abuse accounted for their psychotic symptoms or was a dominant factor in the course of illness. All patients with schizophrenia were receiving standard antipsychotic medications, with some patients receiving combinations of treatments (Table II). Four bipolar subjects were not taking any psychotropic medications, while the remaining eighteen were receiving medications listed in Table II.

Functional image acquisition

We acquired functional imaging data on a Siemens 3T Allegra scanner (Erlangen, Germany) using an echo planar T2*-weighted gradient echo sequence (TR=4000 ms, TE=30 ms, flip angle=90°, 64 × 64 matrix, 45 brain slices, 3.125 mm in-plane resolution, 2.19 mm slice thickness, 1 mm gap). To minimize head movement for all subjects in the scanner, foam padding and padded plastic restraints were used in conjunction with the head coil.

Stimulus presentation

While in the scanner, subjects participated in a WM fMRI paradigm from the Functional Reference Battery developed by the International Consortium for Human Brain Mapping (ICBM) (Mazzotta, et al. 2001) (see http://www.loni.ucla.edu/ICBM/Downloads/Downloads_FRB.shtml). This WM task used a block design with six “off” blocks and six “on” blocks. The first “off” block lasted 40 seconds, followed by 28 second “on” and “off” blocks, for a total running time of 5 minutes.
and 48 seconds. For the “off” (baseline) condition, an arrow facing up, down, left, or right appeared for 200 ms every 1800 ms, and subjects were asked to respond with a left button press whenever the left arrow appeared.

“On” blocks (Figure 1) consisted of five consecutive WM trials in which subjects were required to remember a set of sequentially presented abstract designs. The same five abstract designs, made familiar to each subject through training prior to the fMRI data acquisition, were used for each trial. In each trial, the start cue (green disc) was presented for 400 ms, followed by a 50 ms blank screen. Then, four of the five stimuli were presented for 450 ms each, with 50 ms blank screens between each. The stop cue (red disc, 400 ms) signified the end of the set to keep in memory. This was followed by a 50 ms blank screen, then a fifth stimulus presented for 2200 ms. Subjects responded with a button press to indicate whether or not the fifth stimulus was among the four presented previously, and reaction time was recorded for each response. Thus, to assure perfect performance a subject would have to retain the first stimulus in memory for a minimum of 1950 ms, the second stimulus for 1450 ms, and the third and fourth stimuli in memory for at least 950 and 450 ms respectively. The presentation order of stimuli and the order of baseline and abstract design stimulus presentations were in a fixed random order. The fifth stimulus was included in the set of four 50% of the time. Before fMRI scanning, subjects engaged in a practice block of 5 minutes and 48 seconds (as described above), which was repeated until 4 out of 5 correct responses in a row were achieved.

Functional Image Analysis

Functional MRI data was analyzed using the fMRI Expert Analysis Tool (FEAT) Version 5.63 from FSL3.3 (Smith, et al. 2004). High-resolution structural images were skull stripped using BET (Smith 2002) and used for intra-subject registration. Motion correction was performed using MCFLIRT (Jenkinson, et al. 2002) followed by slice-timing correction using Fourier-space time-series phase-shifting. Subjects with motion artifacts >1mm in any direction were removed from the analysis (maximum absolute head movement<0.78mm). Images were smoothed with an 8mm FWHM Gaussian filter, and all volumes underwent mean-based intensity normalization by the same factor and high-pass temporal filtering using a Gaussian-weighted least-squares straight line fitting, with sigma=28.0s. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, et al. 2001). Functional images were registered to high-resolution structural images using FLIRT (Jenkinson, et al. 2002; Jenkinson and Smith 2001), then aligned to the MNI-152 atlas (Montreal Neurological Institute, Montreal, QC, Canada) using a 12-parameter affine registration. Task-related patterns of brain activity were compared between schizophrenia patients, bipolar patients, and controls after covarying for sex and age (orthogonalized with respect to diagnosis) using FSL’s FLAME 1+2 (FMRIB’s Local Analysis of Mixed Effects) (Beckmann, et al. 2003; Woolrich, et al. 2004). To confirm that observed effects were disorder specific and not related to duration of illness differences between patient groups, we performed a post hoc analysis including this factor as an additional covariate. Gaussianized T/F statistic images were thresholded using clusters determined by Z>2.3 and a cluster-corrected P<0.05 (Worsley, et al. 1992). Locations of local maxima were determined using the Talairach Daemon Database and refined by visual inspection (Lancaster, et al. 2000).

In addition, we investigated group-related DLPFC effects specifically using an ROI mask created by computing the average task-associated activation in the DLPFC across all groups, thresholding at Z>2.3 and P<0.05. This ROI was then registered to single subject data with a 12-parameter registration in FLIRT. Finally, Featquery was used to extract mean percent signal change values in each subject’s DLPFC ROI, which were compared using a univariate ANOVA with age as a covariate and diagnosis as the fixed factor.
Results

Behavioral task performance

Accuracy on the WM task did not differ significantly according to independent samples t-tests between bipolar subjects and schizophrenia subjects (P=0.678), bipolar subjects and controls (P=0.693), and schizophrenia subjects and controls (P=0.454; mean percent correct ± standard deviation for all groups: controls=64.47±17.96; bipolar euthymic=62.69±13.23; schizophrenia=61.05±11.50). Most errors were due to incorrect responses rather than the omission of a response, with the mean percentage of errors of omission as follows: controls: 2.5±6.9%; bipolar euthymic: 5.5±13.1%; schizophrenia: 2.6±6.9%. The percentage of errors of omission did not differ across groups (independent samples t-test, bipolar euthymic group and controls: P=0.994, schizophrenia group and controls: P=0.269, bipolar euthymic group and schizophrenia group: P=0.39). We also analyzed reaction times for correct WM trials in each group using independent sample t-tests, and found no significant differences between the bipolar group and controls (P=0.373), schizophrenia patients and controls (P=0.081), or bipolar subjects and schizophrenia subjects (P=0.424). Mean correct reaction times for each group were: controls: 1239.24 ± 217.85 ms; bipolar euthymic: 1185.46 ± 211.31 ms; schizophrenia: 1129.52 ± 232.01 ms. Though it was not possible to collect eye-tracker data while subjects were in the scanner, button-press data for both the control and experimental blocks (not shown) also indicated that subjects were attending adequately to the visual stimuli.

Within-group fMRI activation during WM task versus rest

Control subjects exhibited significant (P<0.05 cluster-corrected) task-related activation in bilateral occipital cortex, DLPFC, primary motor cortex, and secondary motor cortex. Bipolar euthymic and schizophrenia subjects activated similar regions (Figure 2), but to a lesser degree, particularly in frontal regions. Coordinate locations of local maxima (cluster-corrected at P<0.05) for each group are provided in supplementary Table I.

Between-group contrasts

Controls vs. schizophrenia subjects—Control subjects exhibited significantly greater (cluster-corrected P<0.05) activation than schizophrenia patients in unilateral prefrontal areas including the left inferior frontal gyrus and left DLPFC (Figure 3; Table III). Increased activation in controls extended across left perisylvian areas and into the superior temporal gyrus. No brain regions showed significantly greater activation in schizophrenia patients compared to controls.

Controls vs. euthymic bipolar subjects—Controls showed significantly increased activation compared to bipolar euthymic patients in occipital regions including right primary visual cortex (P<0.05, cluster-corrected; Figure 3; Table III). While controls activated DLPFC to a greater extent than the bipolar subjects, the between group difference was not significant. There were no regions where activation in bipolar subjects was significantly greater than in controls.

Euthymic bipolar vs. schizophrenia subjects—Activation during the external order WM task was significantly greater in the schizophrenia group compared to the bipolar euthymic group in left hemisphere motor regions including precentral and postcentral gyrus, medial frontal gyrus, and some parietal regions (Figure 3; Table III). A post hoc analysis with duration of illness included as an additional covariate produced almost identical results (Figure not shown). While bipolar subjects appeared to show more widespread within-group DLPFC activation than the schizophrenic group in the average activation maps for the WM task (Figure 2), these differences were not statistically significant (Figure 3).
Group-related DLPFC activation—When prefrontal activation was investigated specifically using a functionally-defined DLPFC ROI, percent BOLD signal change was highest in the control group and lowest in the schizophrenia group (Figure 4). A univariate ANOVA with age as a covariate showed that percent signal change in DLPFC differed significantly between the control group and the schizophrenia group ($P=0.011$), but not between the control and bipolar groups ($P=0.46$) or the bipolar and schizophrenia groups ($P=0.73$).

Discussion

Behavioral deficits in WM have been observed in both schizophrenia and bipolar disorder, though the disorders maintain distinct profiles with regard to other cognitive and clinical symptoms (Green 2006). To our knowledge, no prior imaging studies have examined both populations simultaneously to determine whether there are neurophysiological differences in brain activation between groups while performing a WM task. We found that despite similar WM task performance, controls showed increased BOLD activation in DLPFC compared to both schizophrenia patients and euthymic bipolar patients. The difference in activation was significant between the controls and schizophrenic subjects. Bipolar subjects fell intermediate to both groups in level of DLPFC activation, and were not significantly different from either.

In accordance with our hypothesis, we found increased activation in the DLPFC and proximal frontal regions in controls compared to schizophrenia patients. The DLPFC is an integral part of the frontostriatal circuitry thought to participate in WM (Manoach, et al. 2000), and is involved in prefrontal networks thought to be the basis of the “central executive” component of WM. Researchers report both hyperactivation (Callicott, et al. 2000; Manoach, et al. 2000) and hypoactivation (Ragland, et al. 2007; Scheuerecker, et al. 2008) of this region in schizophrenia patients during WM tasks. Though visual WM is generally associated with activation in the right DLPFC, our findings of overall bilateral DLPFC activation, with left hemisphere lateralization in the group contrast, may be related to symbolic or linguistic rather than image-based encoding of stimuli in this task (Ungerleider, et al. 1998).

In both the within and between group analyses, bipolar subjects had an average activation pattern of DLPFC in between the schizophrenic and control groups (Figure 2 and Figure 4). In contrast to the schizophrenia group, the bipolar group did not differ significantly from controls with regard to activation in DLPFC or other prefrontal regions, but showed hypoactivation of some spatially-diffuse areas of visual cortex compared to controls. This could indicate differences between the groups in the encoding and maintenance strategies used in the “visuospatial sketchpad” component of WM, which is consistent with reports of bipolar-related behavioral impairments in visuospatial WM tasks (Bearden, et al. 2001). Reductions in BOLD activation in the visual cortices of bipolar patients have also been seen in non-WM related studies (Pavuluri, et al. 2007), though differences in stimulus conditions and subject populations make it difficult to compare results. We predicted less pronounced prefrontal hypoactivation in the bipolar group, and thus may have been underpowered to detect more subtle effects in PFC. Sub-threshold reductions in prefrontal activation were observed in the bipolar group average activation, and overall magnitude and pattern of activation was more similar to the schizophrenia group than to the control group (Figure 2). Importantly, another (unpublished) study investigating working memory using an n-back task in a sample of bipolar patients overlapping with those in the current study found decreased activation in bipolar patients compared to controls in right DLPFC specifically, regardless of mood state (Townsend, et al. 2008), which suggests that differences may be both subtle and task-specific.
We observed unexpected increases of brain activation in left motor regions in schizophrenia compared to bipolar subjects. This finding, however, does not appear suggestive of group differences in WM, since effects appeared restricted to primary motor areas. Instead, this effect could reflect group differences related to other task demands. For example, regional changes identified in motor cortices may reflect differences in information processes associated with the motor responses for memory or baseline condition stimuli, or could relate to degree of dextrality—though the latter explanation may be unlikely given handedness scores were similar across groups. Finally, manipulation of the button box may have influenced results, despite the inclusion only of right-handed subjects and attempts by the researchers to control for the hand/fingers used to operate the button box.

Discrepancies in the directionality of DLPFC findings might result from differences in performance and/or training on the task, the type of WM task, and whether visual or spatial WM is being tested. For example, schizophrenia and bipolar patients perform significantly worse than controls on the Wisconsin Card Sort Test (WCST) (Altshuler, et al. 2004; Heinrichs and Zakzanis 1998), but because this test incorporates task switching and requires sustained attention from the participant, discrepancies in performance or functional activation cannot be attributed to impairments in WM alone (Manoach 2003). Interpretations must account for the type of task used and additional requirements for task execution including attention, manipulation, and maintenance. Manoach et al. (2003) also suggested that greater spatial heterogeneity of DLPFC activation in schizophrenia may contribute to increased findings of hypoactivation in this region, especially in studies averaging across subjects. This hypothesis was corroborated by Anticevic and colleagues (2008), who showed greater WM-related signal preservation in schizophrenia patients relative to controls after employing surface-based registrations of structural and functional data that control for heterogeneity in cortical folding, which is predicted to be greater in patients. Thus, it is possible that individual differences in brain structure may manifest as functional variation and reduce statistical power, especially in diseased populations known to possess alterations in brain structure. Larger structural variation in schizophrenia, which may be less pronounced in bipolar disorder, could similarly have influenced the patterns of group-related DLPFC activation observed in this study.

In general, DLPFC hypoactivation appears most prevalent in fMRI studies, but it is also suggested that fMRI signal in the DLPFC relates to WM load in an inverted-U shaped curve, with hypoactivation occurring when WM load has exceeded capacity (Callicott, et al. 1999). Models of WM deficits in schizophrenia in nonhuman primates have shown similar inverted-U shaped functions relating performance to dopamine D1 receptor stimulation, where dysregulation of dopamine in the PFC may relate to observed symptoms (Robbins 2005). Schizophrenia-related differences of DLPFC activation in either direction may also be explained by an inefficient recruitment of this cortical network. Potkin et al. (2009) suggest that hypofrontality may reflect poorer performance in schizophrenic subjects, or could reflect that WM capacity has been exceeded for high load tasks. This hypothesis is supported by observations of schizophrenia-related DLPFC hyperactivation during a Sternberg Item Recognition WM task, although schizophrenia patients also exhibit peak DLPFC activation at a lower WM load than controls. A meta-analysis by Van Snellenberg, et al. (2006) further supports the notion that WM capacity may be reached earlier in schizophrenia. Specifically, investigators showed that there was a shift in the inverted-U relationship between WM performance and DLPFC activation in schizophrenia (as suggested by Callicott et al. 1999), where schizophrenia patients reached peak activation at lower task difficulties compared to controls. They do note, however, that in cases of comparable performance in schizophrenia patients and controls, it is difficult to interpret differences in DLPFC activation. Consequently, they suggest that hypofrontality in patients may be related to the use of non-DLPFC cortical networks to perform WM tasks. Since task
load was not manipulated in the current investigation, we were unable to address whether WM capacity may differ in bipolar and schizophrenia patient groups, although this may be a focus of future studies. Still, it is clear that dysfunctions in either direction (hypo- and hyperfrontality) are detrimental to performance.

Despite significant alterations in BOLD activation during the WM task, accuracy was comparable between groups. This was expected, given the practice requirements. Furthermore, the difficulty load allowed more unambiguous interpretation group differences, as there was no “ceiling effect” to suppress observable differences in accuracy. Alterations in BOLD activation were seen irrespective of performance, though variations in accuracy within groups could mask subtle differences across individuals.

Potential Limitations

Imaging studies in psychiatric populations are sensitive to several unique confounds, including global deficits in attention or IQ, the modulating factors of antipsychotic drugs, and potential increases of head motion. We excluded subjects with head movement artifacts (>1mm), and carefully registered each brain to a standard template. Prior behavioral and imaging research (Manoach 2003; Phillips, et al. 2008; Scheuerecker, et al. 2008) suggests antipsychotic medication has little measurable effect on WM in bipolar disorder and schizophrenia. It remains possible, however, that medications could have contributed to increased variance in our sample. It is clear that active psychosis is not required for the manifestation of cognitive deficits in bipolar disorder (Robinson, et al. 2006). We cannot rule out the contribution of other agents not included in our screening (e.g. nicotine, caffeine, or alcohol) to observed changes in the BOLD signal. In addition, although we expect that the within-group activations observed in visual cortices are attributable to the use of less visually complex stimuli for the control task, we cannot rule out that this aspect of the study design might also affect brain activation outside of visual cortices.

Although our sample sizes were larger than those typically included in other schizophrenia/bipolar functional imaging studies (Abler, et al. 2004; Lagopoulos, et al. 2007; Manoach, et al. 2000), it is possible we may have been underpowered to detect subtle prefrontal deficits in the bipolar group. Though the percent signal change in the DLPFC in the bipolar group appeared to be intermediate to the control and schizophrenia groups (Figure 4), it was not significantly different from either of the other two groups. Thus, our study does not provide direct support for prefrontal dysfunction in the role of WM impairments in bipolar disorder, although clearly indicates that schizophrenia patients exhibit more severe dysfunction with respect to controls in cortical networks serving WM. Finally, discrepancies in our findings and the findings of others may be due in part to testing different WM sensory modalities, testing manipulation versus retention, and other variables regarding the behavioral testing itself. The ICBM WM task shows robust and reliable activation in areas related to visual WM, making this paradigm well suited to study differences in WM function between diagnostic groups.

Conclusion

WM dysfunction is a proposed endophenotype for both schizophrenia and bipolar disorder (Glahn, et al. 2003; Savitz, et al. 2005). Both disorders appear to share some common genetic susceptibility factors (Badner and Gershon 2002), so examining the neural bases of WM function in both may clarify how mechanisms of dysfunction in the disorders overlap. We observed significant task-related hypofrontality in schizophrenia patients compared to controls, but not in bipolar patients, suggesting that the observed behavioral deficits in WM may be attributable to some distinct aspects of information processing in the two disorders. Given that bipolar patients showed lower (though not significant) percent signal change in

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the DLFPC compared to controls, but showed significant hypoactivation across other areas of the cortex, it is possible that hypoactivation in prefrontal cortices in bipolar disorder is less pronounced than in schizophrenia, and that additional impairments in lower level processing may contribute to the deficits in WM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


Townsend J, Bookheimer S, Foland L, Altshuler L. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic or depressed bipolar subjects. 2008 (under review).


“On” block schematic. In each 5.6 second trial, subjects were presented with four random stimuli, followed by a fifth (after the red disc) that was either in previous set of four 50% of the time. During the last 500 ms interval, subjects were asked to make a button press response to indicate whether the fifth design was contained in the set of four prior designs. “On” blocks were made up of 5 of these 5.6 second working memory trials, so each block lasts 28 seconds.
Figure 2.
Overlays of within-group activation for the working memory task. The overlays of average activation within groups show the similarities and differences in activation between control subjects (blue) and schizophrenia patients (green) in the top panel, between control subjects (blue) and euthymic bipolar subjects (red) in the middle panel, and schizophrenia patients (green) and euthymic bipolar subjects (red) in the bottom panel. Average maps were thresholded at Z=2.3 with a cluster corrected significance threshold of P=0.05. L=left, R=right, A=anterior, P=posterior. The same within-group activation maps are provided for each diagnostic group separately as Supplementary Figure 1.
Figure 3. Contrasts showing significantly greater (FWE cluster-corrected $P<0.05$, $Z>2.3$) activation in (1) controls compared to schizophrenia patients, (2) controls compared to bipolar patients, and (3) schizophrenia patients compared to bipolar patients during the working memory task. Color indicates Z statistic values. L=left, R=right, S=superior, I=inferior, P=posterior, A=anterior.
Figure 4.
Mean percent change of the BOLD signal in the dorsolateral prefrontal cortex (DLPFC) of each subject group. Raw mean values are displayed next to each data point. Error bars represent 95% confidence intervals for the mean.
Table I

Subject demographic information. Standard deviations (where applicable) are in parentheses.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenia</th>
<th>Bipolar</th>
<th>Controls</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.40(9.45), range 19–50</td>
<td>36.38(10.70), range 19–57</td>
<td>32.50(11.68), range 18–64</td>
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<td>23/15</td>
<td>$\chi^2 = 0.530$, p=0.767, df=2</td>
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<td>Handedness</td>
<td>All right-handed</td>
<td>All right-handed</td>
<td>All right-handed</td>
<td>–</td>
</tr>
</tbody>
</table>
### Table II

Information on age of onset, illness duration, symptom scores, severity, and antipsychotic medication for psychiatric groups (bipolar I subjects and schizophrenia subjects).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenia</th>
<th>Bipolar</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years)</td>
<td>22.07(4.65)</td>
<td>18.29(7.30)</td>
<td>p=0.095, F=2.293, df=33</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>8.79(7.75)</td>
<td>18.57(9.96)</td>
<td>p=0.004, F=1.1815, df=33</td>
</tr>
<tr>
<td>BPRS Thought Disturbance* (Positive Symptoms Factor)</td>
<td>1.65(0.63)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BPRS Anergia** (Negative Symptoms Factor)</td>
<td>1.88(0.63)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hamilton Depression Score</td>
<td>–</td>
<td>4.6(2.3)</td>
<td>–</td>
</tr>
<tr>
<td>Young Mania Score</td>
<td>–</td>
<td>2.0(2.4)</td>
<td>–</td>
</tr>
<tr>
<td>Antipsychotic medications</td>
<td>aripiprazole (n=5), clozapine (n=2), fluphenazine (n=2), olanzapine (n=2), quetiapine (n=3), risperidone (n=9)</td>
<td>None (n=4), aripiprazole (n=6), bupropion (n=1), citalopram (n=1), clonazepam (n=1), fluoxetine (n=2), gabapentin (n=1), lamotrigine (n=5), modafinil (n=1), olanzapine (n=3), oxcarbazepine (n=1), quetiapine (n=4), trazodone (n=1), valproate (n=5), ziprasidone (n=1)</td>
<td>–</td>
</tr>
</tbody>
</table>

* Mean of scores for conceptual disorganization, grandiosity, hallucinatory behavior, unusual thought content, and bizarre behavior.

** Mean of scores for emotional withdrawal, motor retardation, blunted affect, disorientation, and self-neglect.
Table III

Brain regions and coordinates of clusters and local maxima for each group contrast. (C=controls, BD=euthymic bipolar I patients, SZ=schizophrenia patients).

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Region</th>
<th>Talairach Coordinates</th>
<th>Brodmann Area</th>
<th>Z max</th>
</tr>
</thead>
<tbody>
<tr>
<td>C &gt; SZ</td>
<td>Left insula</td>
<td>−30 18 −4</td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Left inferior frontal gyrus (VLPFC)</td>
<td>−42 16 −8</td>
<td>BA47</td>
<td>3.49</td>
</tr>
<tr>
<td></td>
<td>Left superior temporal gyrus/Left inferior frontal</td>
<td>−48 18 −16</td>
<td>BA38</td>
<td>3.34</td>
</tr>
<tr>
<td></td>
<td>Left middle frontal gyrus</td>
<td>−46 20 28</td>
<td>BA46</td>
<td>3.22</td>
</tr>
<tr>
<td></td>
<td>Left inferior frontal gyrus</td>
<td>−58 14 12</td>
<td>BA44</td>
<td>3.11</td>
</tr>
<tr>
<td>C &gt; BD</td>
<td>Left cuneus (occipital lobe)</td>
<td>−8 −70 32</td>
<td>BA18</td>
<td>3.08</td>
</tr>
<tr>
<td></td>
<td>Right cuneus</td>
<td>10 −76 10</td>
<td>BA18</td>
<td>3.05</td>
</tr>
<tr>
<td></td>
<td>Right lingual gyrus</td>
<td>8 −82 2</td>
<td>BA18</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Right posterior lobe (declive)</td>
<td>10 −72 −12</td>
<td>BA17</td>
<td>2.96</td>
</tr>
<tr>
<td></td>
<td>Right inferior occipital gyrus</td>
<td>28 −86 −6</td>
<td>BA17</td>
<td>2.96</td>
</tr>
<tr>
<td>SZ &gt; BD</td>
<td>Postcentral gyrus</td>
<td>−50 −22 52</td>
<td></td>
<td>4.19</td>
</tr>
<tr>
<td></td>
<td>Left medial frontal gyrus</td>
<td>−6 −10 52</td>
<td>BA6</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td>Left precentral gyrus</td>
<td>−42 −18 62</td>
<td>BA4</td>
<td>3.89</td>
</tr>
<tr>
<td></td>
<td>Right medial frontal gyrus</td>
<td>6 −12 52</td>
<td>BA6</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Left precentral gyrus</td>
<td>−16 −14 70</td>
<td>BA4</td>
<td>3.43</td>
</tr>
</tbody>
</table>