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Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder

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Abstract

Objectives—Individuals with bipolar disorder (BD) have trait-like deficits in attention and working memory (WM). A fundamental dissociation for most verbal WM theories involves the separation of sensory-perceptual encoding, reliant upon attention, from the maintenance of this information in WM proper. The present paper examined if patients with BD demonstrate differential neural changes in encoding and maintenance WM processes that underlie cognitive impairment.

Methods—Event-related functional magnetic resonance imaging during a delayed match-to-sample WM paradigm was employed with 23 inter-episode medicated patients with BD and 23 demographically similar healthy comparison participants. We examined brain regions during encoding and maintenance task intervals to identify regions that demonstrated differential effects between groups. Medication effects and functional connectivity between prefrontal cortex and basal ganglia/thalamus were examined during the encoding interval due to the importance of these regions and the connection among them for encoding into WM.

Results—Patients with BD exhibited deficits in task accuracy and attenuated brain response during the encoding interval in areas of the prefrontal cortex, caudate, thalamus, and posterior visual regions. In contrast, patients with BD exhibited hyperactivation in posterior sensory regions during the maintenance interval. Among the BD group, those with greater medication load exhibited the greatest brain response within the prefrontal cortex.

Conclusions—Reduction in activation during the encoding interval suggests that attentional deficits underlie WM deficits in patients with BD. These deficits appear to be trait-like in so far as they were observed during periods of euthymia in patients with BD. Medication effects remain to be further explored as there was evidence of prefrontal changes dependent on medication load.

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Keywords

bipolar disorder; encoding; euthymia; functional magnetic resonance imaging; maintenance; verbal working memory

Bipolar disorder (BD) is a complex mental illness characterized by vacillations in mood from the lows of depression to the highs of mania with relatively normal mood in between (1). Disruptions in brain function and cognition play a prominent role in BD and cognitive deficits have been widely reported among patients experiencing manic and depressive episodes (2, 3). However, there is growing evidence that cognitive impairment persists during periods of remission or euthymia suggesting that cognitive dysfunction may be a trait-like feature of the disorder (4, 5). Two prominent domains of impairment are attention and working memory (WM), both of which are critical for adequate functioning in many other cognitive domains. Studies measuring attention and WM deficits in inter-episode patients with BD have yielded medium-to-large effect sizes (6). Further, BD impairs social and occupational functioning, with cognitive processing deficits playing a particularly important role (7-9).

WM refers to a form of ongoing memory involving the active maintenance and/or updating of information (10, 11). WM is believed by many theorists to have limited capacity and composed of dissociable subcomponents (12, 13). Thus, a fundamental dissociation for most WM theories involves the separation of early sensory-perceptual encoding of stimuli (driven by attentional processes) from WM maintenance/updating processes (reliant upon WM proper). A multitude of studies with healthy individuals have identified a neural network underlying WM component processes, though the theoretical accounts of the functions of these regions are debated (14). Studies utilizing functional magnetic resonance imaging (fMRI) have demonstrated that sensory regions (e.g., visual or acoustic depending on the modality) along with prefrontal cortex (PFC) regions and subcortical regions in the basal ganglia and thalamus play a critical role in encoding information into WM (15). This is, in part, due to the role these regions play in selectively attending to stimuli in the environment and encoding the relevant information into temporary storage, processes dependent upon adequate attention. Once information is encoded, the dorsolateral PFC and supramarginal gyrus maintain and/or update the store (16, 17). However, variations in these regional activation patterns and additional sensory regional activation are involved depending on the presentation modality, such as visual or acoustic presentation (18-20). Regardless of modality, the PFC is thought to play a critical role in both the top-down attentional processes required for encoding and the maintenance processes required to keep information within WM, possibly due to reciprocal connections with subcortical and posterior cortical structures. Patients with BD are known to have both structural and functional abnormalities within the PFC (21, 22). This has led to neurobiological theories that attribute cognitive deficits and emotional changes to a disconnect between cognitive top-down centers in the ventrolateral and dorsolateral PFC with emotional bottom-up centers in medial and orbitofrontal PFC and limbic regions (23, 24). Supporting these theories, fMRI studies of WM in inter-episode patients with BD have primarily found attenuated activation patterns in dorsolateral and ventrolateral PFC compared to healthy participants (21), though this is not

always the case (25, 26). Additionally, studies demonstrate decreased activation in other brain regions underlying WM including the supramarginal gyrus (5). However, these studies have primarily focused on WM as a whole using block designs to compare brain systems involved in overall WM performance. These task designs are not able to examine WM component processes such as attentional processes required for encoding and processes required for maintenance and/or updating information. As such, while emerging findings suggest inter-episode patients with BD have WM deficits and abnormal neuronal activation, the specific WM component process or processes leading to overall deficits are largely unknown. One study of inter-episode patients with BD employed a fast event-related fMRI design to examine encode, updating, and response intervals in a Sternberg-like task (27). The authors found attenuated patterns of activity, primarily in the frontal lobes, across all task intervals supporting fronto-cortico-limbic dysfunction in BD. However, there were no dissociations between verbal encoding, updating of information, and response component processes reflected in the task intervals. The task complexity, WM updating requirements, fast timing of events, and/or sample size may have limited their ability to discover a clear distinction between perceptual encoding processes and maintenance or updating/manipulation processes. The present study employed a slow event-related fMRI design during a simple delayed match-to-sample WM task to examine if inter-episode patients with BD exhibit WM perceptual verbal encoding and/or maintenance component processing deficits in brain function as measured with the blood oxygen level dependent (BOLD) signal. This task has been used previously in healthy participants to link brain activation patterns in WM brain regions during task encode and maintenance intervals with the respective parameter estimates from a computational model of WM reflecting encoding and maintenance processes (28).

Neurobiological models of cognitive dysfunction in BD would predict attenuated response in specific PFC regions underlying deficits in WM behavioral performance. Further, given the broad attentional deficits (i.e., in attentional systems not confined to WM operations) observed in inter-episode patients with BD, we predict that PFC and subcortical regions underlying the selective attention processing responsible for encoding into WM will show the greatest neuronal abnormalities compared to healthy participants. Specifically, these include bilateral dorsolateral PFC, middle frontal gyrus, and inferior frontal gyrus (IFG); and subcortical regions including the thalamus and basal ganglia. To fully explore the pattern of activation within these regions, we also hypothesize that functional connectivity among PFC and basal ganglia/thalamus will vary between patients with BD and healthy participants and differentially relate to behavioral performance. Given that recent research suggests that deficits in attention, but not working WM, meet criteria for an endophenotype of BD (6) we do not predict WM maintenance processes will show the same magnitude of deficit compared to encoding processes.

Materials and methods

Participants

Following procedures approved by the University of California, San Diego (UCSD) and San Diego Veterans Affairs Healthcare System, written informed consent was obtained from 23

patients with BD and 23 age- and gender-comparable healthy participants. All participants were deemed eligible if they were: (i) between the ages of 30 and 79 years, (ii) right-handed, (iii) free of diagnoses of substance abuse for six months and dependence for 12 months, (iv) free of any serious neurological or medical condition, (v) suitable for magnetic resonance imaging, (vi) native English speakers, and (vii) not currently under conservatorship. Patients met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (29) criteria for the diagnosis of bipolar I disorder with first mood episode occurring between ages 13 and 30 years as determined by an expanded version of the Structured Clinical Interview for DSM-IV (SCID-IV) (30), and on stable doses of psychotropic medication for at least six weeks. Potential patients with BD were excluded from the study if they were currently experiencing a mood episode as determined by the SCID-IV, or significant residual symptoms as determined by assessment for depression [Hamilton Rating Scale for Depression (31)], mania [Young Mania Rating Scale (32)], or psychotic symptoms [Positive and Negative Syndrome Scale (33)] symptoms, or had a history of any other Axis I DSM-IV diagnosis. Healthy participants were eligible if they (i) had no Axis I DSM-IV diagnosis as determined by the Mini International Neuropsychiatric Interview (34), (ii) were not taking medication known to interfere with cognitive functioning, and (iii) had no first-degree relatives with a diagnosis of major depressive disorder, BD, or schizophrenia. All patients with BD were taking medications at the time of the study. Demographic information and clinical rating scores are presented in Table 1.

Delayed match-to-sample task

Participants were administered the task while undergoing fMRI, which has been previously validated (28). Stimuli consisted of multi-syllabic pronounceable pseudowords, with each constituent syllable consisting of a consonant–vowel–consonant letter string (e.g., MUV). The number of syllabi was parametrically manipulated such that participants were presented with two-, three-, and four-syllable pseudowords with seven stimuli presented in each condition. Figure 1 presents an example trial from the task with the timing of each event. Briefly, pseudowords were visually presented followed by a maintenance interval and then a forced choice recognition trial. The forced choice involved two choices where the target pseudoword differed from the foil by one letter. Participants used their dominant right-hand to respond by using a response box (*Current Designs*). Each trial condition (e.g., two-, three-, or four-syllable pseudoword) was pseudo-randomly presented with an inter-trial interval (ITI) between trials. The ITI served as the baseline condition, which was designed to keep mental set fixed on anticipating the next trial, similar to visual detection paradigms used to study attention and was composed of two phases. The first involved the fading out of an orientation cross, where the cross becomes progressively less visible over a four-second interval. The second involved a blank screen where the next trial could start at any moment over the next 20 secs. The median length was six secs and no longer than 20 secs as governed by the hazard function of a percentile distribution derived from a geometric distribution. The total time for each task depended on which maintenance interval and ITI was chosen for each task trial with an expected average time of 9 min 52 secs. The instructions were to memorize the visually-presented pseudowords, mentally rehearse pseudowords by repeating them continuously (akin to subvocalization), and choose the

correct pseudoword on a recognition test. Once tested, participants were further instructed to no longer rehearse pseudowords.

Data acquisition

Participants were scanned at the UCSD Keck Center for fMRI using a GE Signa EXCITE 3.0 Tesla whole-body imaging system. Anatomical scans utilized a T1-weighted fast spoiled gradient echo pulse sequence [echo time (TE) = 4 msec, flip angle = 90°, 1 mm³ resolution]. The functional scans were sensitive to the T2*-weighted BOLD signal. A total of 32 echoplanar 4-mm axial slices covering the whole brain [repetition time (TR) = 2000 msec, TE = 30 msec, image matrix = 64 × 64, 4 mm × 4 mm resolution] were acquired parallel to the intercommissural plane in an interleaved manner using a gradient echo pulse sequence. The number of repetitions acquired varied over the task, as described above. To correct for warping in the echo-planar images due to inhomogeneities in the magnetic field, scans with opposite phase encoding polarities resulting in opposite spatial distortion patterns were acquired. The resulting images were aligned using a fast nonlinear registration procedure (35).

Image processing

We used local software, FSL (36), and the Analysis of Functional NeuroImages (37) for analyses. To improve structural to functional image correspondence we used a cost function optimized for T2*- to T1-weighted image alignment (38). Echo planar slices were aligned to have the same temporal origin and then corrected for motion artifact by co-registering to a base image. A general linear model was applied to each participant's time series yielding brain response estimates during encode, maintenance, and recognition intervals using the ITI as the common baseline. For this study, we focused only on encode and maintenance intervals as these were the component processes of interest. Figure 1 presents the timing of the intervals of interest within the task paradigm. Raw BOLD signal data was transformed into a percent signal change from baseline, spatially smoothed using a Gaussian filter (full-width at half-maximum = 6 mm), and normalized into standard Talairach atlas space (39).

Data analyses

Group analyses of behavioral and BOLD data followed standard statistical procedures. For both behavioral and BOLD data, we examine between group differences (BD versus healthy comparison), within-subject differences across working memory load (two-, three-, and four-syllables), and their interaction by conducting a 2 (*Group*) × 3 (*Load*) mixed-effects analysis of variance (ANOVA). For BOLD data we conducted our analyses within encode and maintenance intervals separately and across the whole brain. We considered utilizing a strict region-of-interest (ROI) approach to fMRI analyses since our previous work with this task resulted in modulation of specific WM regions (28). However, we chose a whole brain approach to allow for regions outside of typical WM regions to show group differences (e.g., limbic structures involved in emotional processing). We controlled type I error using a cluster threshold method (40). This method utilizes Monte Carlo simulations to determine the probability that a single significantly activated voxel is also part of a contiguous cluster of N-voxels that are all individually significantly activated at $p = 0.01$. That is, we only

considered an area of activation as reliable if it contained a threshold of 22 contiguous voxels (1408 μL , $p = 0.01$), each of which were individually activated at the $p = 0.01$ level providing a corrected p -value of 0.01.

Functional connectivity analyses were conducted in functionally-defined ROIs within the basal ganglia/thalamus and PFC from analyses during the encoding interval to examine connectivity in regions implicated in WM encoding processes (15). For these analyses, we raised the statistical threshold to $p = 0.0025$ in order to concentrate only on those voxels that showed the greatest effect size. From these highly task-responsive subregions, we extracted each participant's task time series from each of the ROIs and created cross-correlation Fisher Z-transformed matrices from the time series in each brain region for each participant. Analyses focused on group differences among the pair-wise correlations between brain regions using t -tests with Tukey's method to control for multiple comparisons and the association of behavioral performance with the correlations between brain regions.

To explore the medication effects on performance and brain activation, a psychotropic medication load variable was calculated for each patient with BD as previously developed by Hassel and colleagues (41). Current doses of antipsychotics, mood-stabilizers, antidepressants, and anxiolytics were assigned a value and grouped into low or high dosages based on dosage and duration of use, and then summed across medication type for each patient, resulting in a unique medication load variable. Multiple linear regression analyses were conducted with the behavioral data and within the task encoding and maintenance intervals to examine the association between medication load and behavioral and brain response using standard statistical methodology.

Results

Behavioral data

Figure 2 presents the behavioral data. There was no significant interaction between group and WM load. However, there was a large main effect of load such that all participants were less accurate as syllable length increased ($F_{2,42} = 24.68$, $p < 0.001$, $\eta^2 = 0.37$). Follow up contrasts revealed three-syllable pseudowords were recalled less accurately than two-syllable pseudowords ($F_{1,43} = 14.32$, $p < 0.001$, $\eta^2 = 0.25$) and four-syllable pseudowords were recalled less accurately than the average of two- and three-syllable pseudowords ($F_{1,43} = 42.54$, $p < 0.001$, $\eta^2 = 0.50$). There was also a medium-to-large main effect of group such that patients with BD were less accurate than healthy participants averaging across syllable length ($F_{1,43} = 5.60$, $p = 0.023$, $\eta^2 = 0.12$). Independent sample t -tests comparing groups at each syllable length revealed the only significant group difference was for four-syllable pseudowords ($t_{43} = 2.17$, $p = 0.036$, $\eta^2 = 0.10$). For response latency, the only significant effect was a large main effect of load such that all participants were slower at responding as syllable length increased ($F_{2,42} = 55.38$, $p < 0.001$, $\eta^2 = 0.57$). Follow up contrasts revealed three-syllable pseudowords were responded to slower than two-syllable pseudowords ($F_{1,43} = 96.61$, $p < 0.001$, $\eta^2 = 0.69$) and four-syllable pseudowords were responded to slower than the average of two- and three-syllable pseudowords ($F_{1,43} = 36.49$, $p < 0.001$, $\eta^2 = 0.46$).

BOLD data

During the encoding interval, no regions showed an interaction between group and WM load. However, a number of brain regions were found in which the response differed between the BD and healthy groups in a load-independent manner. Table 2 presents the clusters of activation demonstrating a main effect of group averaging across syllable length (all $p < 0.01$). In all clusters, patients with BD exhibited significantly less activation than healthy participants in regions implicated in WM (see Fig. 3). Examination of each group's BOLD signal within significant clusters revealed that healthy participants exhibited increased BOLD signal relative to baseline in all clusters including regions within the PFC, basal ganglia, thalamus, premotor cortex, precuneus, and regions within the ventral visual stream. In contrast, patients with BD only exhibited significant increased activation relative to baseline in the right putamen, right premotor cortex, and bilateral precuneus. Further, patients with BD demonstrated decreased activation relative to baseline in bilateral insula, anterior PFC, and posterior cingulate cortex.

Similar to the encoding interval, during the maintenance interval no interactions between group and WM load were observed. Main effects of group averaging over syllable length during the maintenance interval revealed an opposite pattern compared to the encode period, such that patients with BD exhibited significantly greater BOLD signal compared to healthy participants in all clusters (all $p < 0.01$) (see Table 2). Examination of each group's BOLD signal within significant clusters revealed deactivations relative to baseline in the right associative visual cortex and middle temporal gyrus for healthy participants. For patients with BD, increased BOLD signal relative to baseline was observed in bilateral post-central gyri and bilateral secondary visual cortices (see Fig. 4).

Functional connectivity

We identified six regions within the PFC and basal ganglia/thalamus using a more stringent threshold for between group differences ($p = 0.0025$) during the encoding interval of the task. These included regions encompassing right and left caudate/thalamus, left medial PFC, bilateral medial PFC, right middle PFC, and right IFG. Table 3 presents the matrix of Fisher Z-transformed correlational values among all pairwise functional connections within each group. Among all significant pairs of regions correlational values were positive indicating similar directional changes in the time series between two regions. Independent sample t -tests, using Tukey's method to control for multiple pair-wise comparisons, revealed only a trend for one functional connection that differed between groups, between the bilateral medial PFC and right IFG ($t_{43} = 1.99$, $p = 0.061$, $\eta^2 = 0.08$). However, there was a medium effect size with patients with BD having a stronger connection than healthy participants. Correlating the significant pairwise connections with behavioral performance within each group revealed that better average accuracy was associated with higher connectivity values between bilateral medial PFC and right middle PFC ($r = 0.458$, $p = 0.032$) for healthy participants. There were no significant correlations between accuracy or response latency and functional connections among patients with BD.

Medication

For behavioral data, linear regression analyses revealed a significant association between medication load and average response latency for patients with BD such that higher medication load was associated with faster response latency ($F_{1,20} = 5.04$, $p = 0.036$, $\eta^2 = 0.20$). For BOLD data, linear regression analyses during the encoding interval revealed associations in bilateral medial PFC, right IFG, and left thalamus. Within all clusters, higher medication load was related to linear increase in the BOLD signal in response to increasing syllables (all corrected $p < 0.01$). There were no significant associations during the maintenance interval. In light of the observed medication effects during the encoding interval, we examined the association of medication load among patients with BD with the caudate/thalamus–PFC correlations and with the BOLD signal in clusters that demonstrated significant group differences. There were no associations between medication load and functional connectivity values among patients with BD. However, higher medication load in patients with BD was associated with greater linear increases in the BOLD signal in two clusters encompassing the bilateral precuneus, cingulate gyrus, caudate, putamen, thalamus, and insula ($r = 0.424$, $p = 0.044$) and encompassing the right dorsolateral PFC and inferior and middle frontal gyrus ($r = 0.460$, $p = 0.027$).

Discussion

The present study examined two component processes of verbal WM in inter-episode patients with BD: (i) an encoding component that required selective attentional processes to attend to and encode visually presented verbal information within WM and (ii) a maintenance component that required rehearsal to maintain this information for later recognition. Overall, the behavioral results support the general findings in the literature that inter-episode patients with BD have WM impairment, especially when WM is taxed with increased demands. The fMRI data suggest that the WM deficit observed in patients with BD may primarily be due to an inability to adequately engage the attentional neural systems required to encode visually presented verbal information into the WM system rather than maintaining this material. During the encoding interval of the task we observed an attenuated BOLD signal in patients with BD across all syllable lengths in a range of brain regions responsible for attending to visually present verbal stimuli including bilateral medial PFC, right middle frontal gyrus, IFG, dorsolateral PFC, and bilateral putamen, caudate, and thalamus. These findings suggest that patients with BD exhibit general perceptual encoding deficits regardless of the load placed upon WM. Further, these findings support current neurobiological theories that posit a trait-like hypoactivation of cognitive control regions in the frontal lobes (24). We also observed an attenuated BOLD signal in bilateral insula for patients with BD, a region implicated not only in cognitive processes but also in processing emotional material and integrating cortical and subcortical regions (42). In terms of PFC–subcortical functional connections specifically important for WM encoding processes (c.f., emotional processes) we did not observe a significant group difference in functional connectivity between PFC regions and caudate/thalamic regions. However, we did observe a medium effect size between groups in the magnitude of medial PFC–IFG connection with patients with BD exhibiting a stronger connection than healthy participants. Further, greater strength of the functional connectivity between medial and middle PFC was associated with

higher accuracy in the healthy sample while there were no correlations within the BD sample. Therefore, it may be the case that the observed attentional impairment is largely due to both cortical and subcortical regional impairment along with subtle changes to intra-PFC connections which impact behavioral performance. However, our limited sample size may not be sufficient to detect smaller effects in functional connections. These data cannot speak to the functional connectivity with emotional limbic regions, though it is likely that these connections are disrupted in BD.

A different picture emerged during the maintenance interval of the task. While during the encoding interval patients with BD exhibited attenuated BOLD responses in attention networks, during maintenance, patients with BD did not show deficits in regions that are known to subserve maintenance. Instead, they exhibited increased BOLD response compared to healthy participants in only a few regions and only outside those implicated in verbal WM maintenance processes. Regions in the bilateral postcentral gyri, bilateral cuneus, and middle temporal/occipital cortex showed a positive BOLD response in patients with BD while healthy comparison participants did not activate these regions.

Higher activation in patients with BD in these regions may reflect abnormal processing in these sensory regions during maintenance processing or it may reflect less activation during the baseline condition. The latter is consistent with attentional deficits possibly resulting in attentional fluctuations during the baseline fixation when participants have no task objective. It is important to note that the lack of findings in WM-related brain regions during the maintenance interval does not necessarily mean that there are no abnormalities of processing during WM proper in BD. Rather, we can only conclude that within our slow event-related design utilizing a task which does not require manipulation processing patients with BD do not exhibit maintenance-specific deficits.

A limitation of many fMRI studies of inter-episode patients with BD is a failure to examine or account for potential medication effects. Use of psychotropic medication, in particular, has been shown to influence brain response in patients with BD. While medication effects on BD performance and brain response are not fully understood, studies that have examined the effect have found an increased neuronal response in PFC regions with activity patterns similar to non-medicated healthy participants (43). A similar pattern was observed in the present study such that increased medication load was associated with increased BOLD signal in frontal regions including bilateral medial and middle PFC during the encoding interval. This may be one reason why more interaction effects were not significant, as all patients were on medication, bolstering the BOLD signal to levels more similar to those seen in healthy comparison participants in response to increasing task demands. Nonetheless, even within a BD-patient sample in which all were stable on psychotropic medication, we observed large main effects of group during the encoding interval suggesting that attentional deficits with the WM domain persist in the face of psychopharmacologic treatment. However, our study used a cross-sectional design, and other factors associated with medication load may contribute to the observed attentional deficits such as severity of illness and history of psychosis. Future longitudinal studies are needed to parse out the effects of psychotropic medication on brain-behavior relationships among patients with BD. Interpretation of neuroimaging studies in BD is complicated by a myriad of factors that are

involved in the disorder and difficult to address in a single study. Our sample was homogeneous in regards to mood state (all euthymic) and diagnosis (all bipolar I disorder), and we directly examined the effect of current medication load. However, we did not analyze other factors that may affect cognitive and brain function in BD such as genotype, sleep/circadian rhythms, or endocrine and neurotransmitter differences. Further, we did not assess vocational or social functioning, which is an important outcome related to cognition. Future studies will need to integrate across multiple domains and biological systems to better understand the complex changes in brain and body underling BD. Nonetheless, the present findings suggest that patients with BD have verbal WM impairment, even during inter-episode periods. This impairment is likely driven primarily by a difficulty in WM encoding processes reliant upon selective attention required to perceptually attend to and encode verbal information into WM.

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Fig. 1.

An example of a single trial from the delayed match-to-sample paradigm. Stimuli below the horizontal line represent what participants viewed while the time of each interval is presented above the horizontal line. Intervals of interest were encode and maintenance intervals.

Fig. 2.

Behavioral results. Mean accuracy is presented on the left graph and response latency on the right graph. The lines around each mean represent the standard error. BD = bipolar disorder group; HC = healthy comparison group.

Fig. 3.

Clusters of significant blood oxygen level dependent (BOLD) response during the encoding interval. **(A)** Main effect of group from a group-by-syllable-length ANOVA, **(B)** within healthy comparison participants, and **(C)** within patients with bipolar disorder. Statistical parametric maps reflect the effects size η^2 . Warm colors indicate a greater effect in the BOLD signal during the encoding interval relative to baseline whereas cool colors indicate greater effect in the BOLD response in baseline relative to the encoding interval. A negative sign was applied to η^2 values that demonstrated less activation relative to baseline. All MRI images are in the axial plane and in neurological orientation. Numbers correspond to Talairach coordinates in the Z-direction.

Fig. 4.

Clusters of significant blood oxygen level dependent (BOLD) response during the maintenance interval. **(A)** Main effect of group from a group-by-syllable-length ANOVA, **(B)** within healthy comparison participants, and **(C)** within patients with bipolar disorder. Statistical parametric maps reflect the effects size η^2 . Warm colors indicate a greater effect in the BOLD signal during the maintenance interval relative to baseline whereas cool colors indicate greater effect in the BOLD response in baseline relative to the maintenance interval. A negative sign was applied to η^2 values that demonstrated less activation relative to baseline. All MRI images are in the axial plane and in neurological orientation. Numbers correspond to Talairach coordinates in the Z-direction.

Table 1
Clinical characteristics of sample

	Bipolar disorder (n = 23; 8 males)	Healthy comparison (n = 23; 8 males)
Age, years	45.31 (9.45)	44.78 (10.59)
Education, years	15.96 (2.12)	14.74 (2.24)
Illness duration, years	26.53 (9.12)	
No. depressive episodes	10.68 (12.24)	
No. manic episodes	5.36 (6.53)	
No. mixed episodes	8.67 (10.87)	
YMRS score	1.22 (1.40)	
HAMD-17score	3.22 (2.28)	
PANSS		
Positive	10.35 (2.62)	
Negative	9.78 (1.70)	
General	23.30 (4.22)	

Values presented as mean (standard deviation). All patients were medicated with 48% taking antidepressants, 52% taking antipsychotics, 74% taking mood stabilizers, and 43% taking anxiolytics or benzodiazepines. Also, 74% were on polytherapy involving two or more classes of these psychotropic medications. YMRS = Young Mania Rating Scale; HAMD-17 = Hamilton Rating Scale for Depression; PANSS = Positive and Negative Syndrome Scale.

Table 2
Brain regions demonstrating a significant group difference during task intervals

Encode interval				Maintenance interval							
Brain region	Peak intensity Talairach coordinates			BA	Peak intensity Talarach coordinates			BA			
	Volume (μL)	X	y		z	Volume (μL)	X		y	z	
Bipolar disorder < Healthy comparison participants											
B medial PFC	2,496	2	-59	0	10	R postcentral gyrus	1,536	-50	25	36	2
R dorsolateral PFC/IFG/middle frontal gyrus	4,160	-50	-47	16	10, 45, 46	R middle occipital cortex/middle temporal cortex	1,984	-54	65	8	19, 37
B postcentral gyrus/premotor cortex	3,392	-2	45	68	3, 4, 6	B cuneus	2,432	-6	85	16	18
B precuneus/cingulate gyrus/caudate/putamen/thalamus/insula	44,608	-2	77	44	7, 13, 23						
L middle temporal gyrus/posterior cingulate gyrus	7,744	50	57	0	21, 30						

Each entry represents a significant cluster of activation. Clusters represent group main effects from a group-by-syllable-length ANOVA. The magnitude of the blood oxygen level dependent (BOLD) response from each cluster was significant at a minimum F -value of ± 7.248 (two-tailed $\alpha = 0.01$, $df = 1, 44$) and of sufficient volume (1408 μL ; $\alpha = 0.01$). BA = Brodmann's area; B = bilateral; R = right; L = left; PFC = prefrontal cortex; IFG = inferior frontal gyrus.

Table 3

Fisher Z-transformed correlational matrices for each group

Healthy comparisons							
	R caudate/thalamus	L caudate/thalamus	L medial PFC	B medial PFC	R middle PFC	R IFG	
R caudate/thalamus	–	1.257^b	0.109	-0.112	0.043	0.380^b	
L caudate/thalamus		–	0.157	-0.097	0.019	0.361^b	
L medial PFC			–	0.772^b	0.575^b	0.166	
B medial PFC				–	0.532^b	-0.011	
R middle PFC					–	0.246^b	
R IFG						–	
Bipolar disorder							
	R caudate/thalamus	L caudate/thalamus	L medial PFC	B medial PFC	R middle PFC	R IFG	
R caudate/thalamus	–	1.217^b	0.185	0.003	0.124	0.414^b	
L caudate/thalamus		–	0.196	-0.036	0.139	0.327^b	
L medial PFC			–	0.492^b	0.560^b	0.286^b	
B medial PFC				–	0.491^b	0.194^a	
R middle PFC					–	0.204^a	
R IFG						–	

Correlational values in **bold** are significantly different from zero based upon a single-sample *t*-test (*df* = 22) within each group. Center mass RAI coordinates for each region were: right caudate/thalamus (13.3, 21.5, 23.1), left caudate/thalamus (-14.3, 11.0, 19.3), left medial PFC (16.6, -53.9, 3.3), bilateral medial PFC (2.4, -57.9, 0.0), and right inferior frontal gyrus (-44.4, -24.8, 15.3). R = right; L = left; B = bilateral; PFC = prefrontal cortex; IFG = inferior frontal gyrus.

^a *p* < 0.05.

^b *p* < 0.01.