Published in final edited form as:

Bipolar Disord. 2009 June ; 11(4): 351–360. doi:10.1111/j.1399-5618.2009.00703.x.

Fronto-temporal dysregulation in remitted bipolar patients: an fMRI delayed-non-match-to-sample (DNMS) study

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Abstract

Objectives—Bipolar disorder is associated with working memory (WM) impairments that persist during periods of symptomatic remission. However, the neural underpinnings of these deficits are not well understood.

Methods—Fifteen clinically remitted bipolar patients and 15 demographically matched healthy controls underwent functional magnetic resonance imaging while performing a novel delayed-non-match-to-sample (DNMS) task. This nonverbal DNMS task involves two conditions, one requiring the organization of existing memory traces ('familiarity'), and one involving the formation of new memory traces ('novelty'). These processes are thought to differentially engage the prefrontal cortex and medial temporal lobe, respectively.

Results—Although behavioral performance did not differ between groups, bipolar patients and controls exhibited significantly different patterns of neural activity during task performance. Patients showed relative hyperactivation in the right prefrontal gyrus and relative hypoactivation in visual processing regions compared to healthy subjects across both task conditions. During the novelty condition, patients showed a pattern of hypoactivation relative to controls in medial temporal regions, with relative hyperactivation in the anterior cingulate.

Conclusions—These findings suggest that disruption in fronto-temporal neural circuitry may underlie memory difficulties frequently observed in patients with bipolar disorder.

Keywords

bipolar disorder; cognition; euthymia; medial temporal lobe; prefrontal cortex; working memory

There is growing evidence that at least a proportion of patients with bipolar disorder have significant cognitive impairments, even during periods of symptomatic remission (1–5). Working memory—defined as the temporary maintenance and manipulation of information—is among the most severely affected cognitive domains (1, 6, 7), with the level of deficit rising with increasing task difficulty (8). Both structural and functional abnormalities have been reported in bipolar patients in brain regions relevant for working memory function, including the dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), and medial temporal lobe (MTL) (9–11).

Most theoretical models of working memory distinguish between manipulation and maintenance processes, highlighting that these processes are differentially served by prefrontal regions, with dorsolateral prefrontal regions and superior parietal regions being differentially involved in the manipulation of information (12–14), and ventrolateral prefrontal regions in the maintenance of information (14). Recently, we developed a novel delayed-non-match-to-sample (DNMS) working memory task that highlights maintenance processes with separate conditions requiring the use of distinct mnemonic strategies to facilitate performance. Specifically, the task includes a condition that emphasizes the use of contextual information to organize familiar stimuli ('familiarity condition') and a condition where using holistic representations of novel stimuli ('novelty condition') is advantageous. While the former has been linked to prefrontal activation (15–17), the latter is thought to be associated more closely with MTL function (18). Previously, we employed this task behaviorally in a moderately symptomatic sample of patients with bipolar disorder and found that bipolar patients had deficits consistent with organizational dysfunction and poor detection of novel information relative to healthy controls (19). Although these results imply prefrontal and medial temporal dysfunction in bipolar disorder, direct assessment of neurophysiologic differences during task performance is necessary.

In the current experiment, we used functional magnetic resonance imaging (fMRI) to examine activity in remitted patients with bipolar I disorder and demographically matched healthy comparison subjects while performing our working memory task (19). We focused on patients in symptomatic remission to ensure that between-group neurophysiologic differences during task performance were not due to confounding effects of current mood symptoms. Thus, the present design allowed assessment of trait-related functional abnormalities within prefrontal and medial temporal regions. Consistent with the notion of working memory network dysfunction, particularly with regard to maintenance processes, implied by our prior behavioral findings utilizing this paradigm (19), we hypothesized that remitted patients with bipolar disorder would exhibit reduced neural activity compared to healthy subjects in prefrontal regions during the familiarity condition, and in MTL regions during the novelty condition.

Methods and materials

Participants

The University of Texas Health Science Center at San Antonio (UTHSCSA) Institutional Review Board approved this study and written informed consent was obtained from all individuals prior to participation. Fifteen remitted patients with bipolar disorder and 18 healthy comparison subjects were recruited. Patients were identified through outpatient clinics and community mental health facilities in the greater San Antonio area. Inclusion criteria for patients included: (i) diagnosis of bipolar I disorder as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID) (20), administered by experienced research clinicians; (ii) no history of a medical or neurological condition that might affect cognitive function; and (iii) no DSM-IV drug or alcohol abuse/dependence within the past six months. In order to increase representativeness of the patient sample, comorbid Axis I diagnoses of anxiety disorder, eating disorder, and/or past history of substance abuse (in full remission for at least six months prior to the study) were allowed. Healthy comparison subjects were recruited through local media advertisements and flyers posted in the medical center area. Inclusion criteria for healthy subjects were: (i) no lifetime Axis I psychiatric disorder as assessed by SCID; (ii) no history of any medical or neurological condition that might affect cognition; and (iii) no history of a psychotic or mood disorder in first-degree relatives (reported by detailed family history).

Three healthy comparison subjects were excluded from analysis, one for behavioral performance that deviated more than two standard deviations from the mean on the task, one due to a computer malfunction, and one for excessive motion (defined as relative or absolute motion greater than 2 mm). Remitted bipolar patients did not differ from healthy subjects in terms of age [mean $\pm$ SD: 39.00 $\pm$ 12.61 versus 36.20 $\pm$ 10.63, respectively; $F(1,28) = 0.43$, $p = 0.52$], gender (53 versus 47% female, respectively; $\chi^2 = 0.13$, $p = 0.72$), handedness (87% versus 93% right handed, respectively; $\chi^2 = 3.04$, $p = 0.22$), years of education [14.67 $\pm$ 2.26 versus 15.67 $\pm$ 1.72, respectively; $F(1,28) = 1.86$, $p = 0.18$], or ethnic composition ($\chi^2 = 6.14$, $p = 0.11$).

Clinical symptoms were assessed with the 21-item Hamilton Depression Rating Scale (HAMD) (21) and the Young Mania Rating Scale (YMRS) (22). Bipolar patients were considered to be in clinical remission at the time of the scan if they had minimal depressive (HAMD ≤ 10) and manic (YMRS ≤ 8) symptoms. The average HAMD score for the patient group was 3.93 $\pm$ 3.04 [range: 0–10] and the average YMRS was 1.6 $\pm$ 1.99 [range: 0–8]. The mean age when the patients experienced their first episode was 20.13 $\pm$ 10.11 years, with a mean duration of illness of 7.8 $\pm$ 7.20 years. Fourteen patients were on medication treatment at the time of the study (53% on antipsychotics, 47% on antidepressants, 80% on anticonvulsants) and one patient was drug free. No patients were on psychostimulants at the time of assessment. Eleven patients had a history of lifetime anxiety disorders, including two with current posttraumatic stress disorder. Nine of the bipolar patients (60%) had a history of past alcohol or substance abuse, but were in full remission for at least six months at the time of the study.

Delayed-non-match-to-sample (DNMS) task

Each trial of the DNMS task included four sequential presentations of stimuli (complex shapes). Participants were asked to remember the first three presentations of each trial (memory set), in which a single abstract shape was displayed for 500 ms (100 ms interstimulus interval). On the fourth presentation (after a 2300 ms delay interval), four shapes were displayed together (see Fig. 1 for depiction of the task). Participants were asked to select the shape on the last display that was new (i.e., the shape that was not shown on the three previous presentations).

The memory task was administered during fMRI scanning under two conditions ('familiarity' and 'novelty'). Each task condition included 30 trials per block with three blocks per condition and was designed to manipulate the relative importance of organizing existent memory traces ('familiarity condition') versus creating unique memory representations ('novelty condition'). Baseline conditions in which a fixation cross was presented for 15 seconds were interleaved throughout the entire memory task. The protocol lasted approximately nine minutes. Behavioral data were collected during the fMRI evaluation.

Familiarity condition

In this condition, the same four abstract stimuli were repeated, in a random position, on every trial. Performance on this condition depends on remembering whether a stimulus was part of the memory set on a given trial, rather than identifying it as an entirely new shape. This type of organizational demand has been associated with dorsolateral PFC activity in human and nonhuman primates (15, 16, 18, 23, 24).

Novelty condition

In this condition, each abstract stimulus appeared only once during the entire condition. The use of trial-unique stimuli, particularly novel and difficult-to-name shapes or visual scenes, has been shown to engage MTL structures, putatively for the creation of new memory representations (18).

Prior to performing the task, participants were administered a set of 20 practice trials, using stimuli later included in the familiarity condition. These example trials allowed participants to become accustomed to the test format and to learn the stimuli used in the familiarity condition.

Behavioral data

Behavioral data were analyzed using Statistical Package for the Social Sciences (SPSS, Version 10.0.5, SPSS, Inc., Chicago, IL, USA). All behavioral data were subjected to analysis of variance (ANOVA) with diagnostic group (remitted bipolar versus control) serving as the fixed factor and each behavioral measure as the dependent measure (i.e., number of errors and mean reaction time for correct responses for both conditions).

fMRI acquisition and analyses

Scanning was carried out on a Siemens 3T MRI (Siemens Medical Solutions, Erlangen, Germany) housed in the Research Imaging Center at UTHSCSA. Functional imaging used a gradient echo, echoplanar sequence, acquiring 26 slices (3 mm thick, 1 mm gap) parallel to the anterior commissure-posterior commissure (AC-PC) plane [repetition time (TR)/echo time (TE) = 3000/31 ms, $128 \times 128 \times 5$ mm, and field of view (FOV) = 256 mm]. For anatomical reference we acquired a higher resolution co-planar T1-weighted series (TR/TE = 500/20 ms, flip angle = 90 degrees, $128 \times 128 \times 5$ mm, FOV = 256 mm) and a high-quality 3D image (TR/TE = 33/12 ms, and flip angle = 60 degrees, 1 mm isotropic). The MRI evaluation lasted one hour, including all functional and anatomical scans.

Image analyses were performed using FSL software (<http://www.fmrib.ox.ac.uk/fsl/>) (25) and in-house utilities (<http://ric.uthscsa.edu/mango/> and <http://www.talairach.org/>). The following preprocessing steps were applied: six-parameter motion correction (26); non-brain removal (27); spatial smoothing using a Gaussian kernel of full-width-half-maximum (FWHM) 5 mm; mean-based intensity normalization of all volumes by the same factor; and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 90.0 s). Data were subjected to multiple-regression using a prewhitening technique to account for the intrinsic temporal autocorrelation of blood-oxygen-level-dependent (BOLD) signals. Least-squares coefficients were generated for each intracranial voxel independently for the novelty and familiarity conditions, and contrasts between these coefficients were used to create the statistical images. Medication effects were accounted for in whole-brain fMRI analyses by including regressors orthogonalized with regard to the patient group. Statistical images were spatially normalized (12-parameter model) to a standard stereotactic space (26) to facilitate multisubject analysis based on parameters derived from each subject's high-resolution anatomical image. Higher-level analyses were performed with a mixed-effects model (28, 29), where subject was treated as a random effect and images contrasting the familiarity and novelty conditions versus baseline, respectively, were generated. Spatial mixture modeling was applied to z statistical images of group differences within each condition and thresholded conservatively ($p < 0.0001$, $z > 2.3$) (30).

Results

Behavioral data

Behavioral performance did not differ between healthy subjects and patients for either the familiarity condition [errors: 3.87 ± 0.99 versus 4.07 ± 0.59 , respectively; $F(1,28) = 0.45$, $p = 0.51$; reaction time: 1358 ± 419 versus 1275 ± 478 ms, respectively; $F(1,28) = 0.26$, $p = 0.62$] or the novelty condition [errors: 4.60 ± 1.64 versus 4.87 ± 1.06 , respectively; $F(1,28) = 0.28$, $p = 0.60$; reaction time: 1513 ± 262 versus 1636 ± 307 ms, respectively; $F(1,28) = 1.40$, $p = 0.25$].

Activation patterns during the familiarity condition

In the overall sample, a network of eight brain regions was engaged during the familiarity condition compared to baseline (see Table 1 for local maxima during each condition and

Fig. 2 for a comparison of brain region activations between groups and conditions). These regions included the right inferior [Brodmann area (BA) 47], left medial (BA32), and bilateral middle frontal gyri; left precentral gyrus (BA6); and right thalamus. However, bipolar subjects had relatively greater activation in frontal regions, specifically in the right precentral gyrus (BA6), compared to healthy subjects. In contrast, bipolar patients showed reduced activation relative to healthy controls in parieto-occipital (BA17, 18, 19) and temporal lobes (BA20, 21, 37). See Table 2 for coordinates of the local maxima within the regions that displayed group differences.

Activation patterns during the novelty condition

A similar network of regions was evoked when the novelty condition was contrasted with baseline, but this condition additionally activated the parahippocampal region (see Table 1; Fig. 2). As in the familiarity condition, healthy subjects had greater activation in occipital and temporal lobe regions, but also showed relatively greater activation than bipolar patients in the posterior cingulate (BA31), left parahippocampal gyrus (BA36), left cuneus, left fusiform gyrus (BA37), and right fusiform gyrus (BA18) (Fig. 3). In contrast, patients with bipolar disorder showed greater activity than healthy subjects in PFC regions during this condition as well, particularly in the right precentral gyrus (BA6), right middle frontal gyrus (BA6), left medial frontal gyrus (BA9/10/11), right inferior frontal gyrus (BA9), and ACC (BA24/32) (see Fig. 3 for group differences between conditions).

Discussion

Despite similar behavioral performance, neural activation patterns in remitted bipolar patients differed from those of comparison subjects in brain regions involved in working memory. In particular, remitted bipolar patients showed differential recruitment of prefrontal regions compared to healthy controls, as well as relative hypoactivation in occipital and temporal regions, across both task conditions. This pattern of results suggests dysregulation of working memory (especially maintenance) circuitry in bipolar disorder, independent of the relative familiarity of the stimuli to be remembered. Similar behavioral performance between groups, but with increased prefrontal activation in the bipolar group, suggests that patients may recruit frontal regions to counterweigh reduced efficiency in temporal, parietal, and occipital regions of the working memory network.

By varying the relative frequency of stimuli to be remembered, we designed our experiment to engage prefrontal or medial temporal regions differentially. As discussed in more detail below, remitted patients with bipolar disorder did not activate these regions to the same level as comparison subjects, suggesting insensitivity to changing task demands. This also suggests that bipolar patients were less able to employ brain regions that have relative specificity for processing novel or familiar stimuli.

During the familiarity condition, the same four stimuli were repeated in each trial within a block, requiring the subject to recall when a particular stimulus appeared in a trial. Hence, good performance requires the organization of existing memory traces. Regions of the PFC have previously been implicated in the monitoring and matching of familiar stimuli (18). As anticipated, remitted bipolar patients differentially engaged the right inferior frontal gyrus

and bilateral middle frontal gyrus during the familiarity condition. These findings suggest inefficiency within the working memory system that impact the engagement of more specialized brain processes.

Tasks that involve memory for trial-unique stimuli are thought to engage MTL structures, particularly the hippocampus and parahippocampal gyrus (18, 31). These structures are important for maintaining memory of novel stimuli, and lesions within these regions in nonhuman primates have been shown to impair performance on delay-match-to-sample tasks (32, 33). Furthermore, previous functional neuroimaging studies in human subjects have shown that the MTL is activated to a greater extent than are prefrontal regions during working memory tasks that involve trial-unique stimuli (18). Remitted bipolar patients failed to engage these regions to the same extent as healthy subjects during the novelty condition. Others recently reported parahippocampal hypoactivation in patients with bipolar disorder during a working memory task with a familiarity judgment (34). Additionally, we found that remitted patients with bipolar disorder demonstrated hypoactivation relative to controls in the posterior cingulate (BA31), a brain region involved in emotional and motivational inputs from the limbic system (35). In contrast, remitted bipolar patients had relative hyperactivation in the ACC (BA24 and BA32), involved in response selection and monitoring, and bilateral frontal regions, including portions of the inferior (BA9), medial (BA9/11), and middle frontal gyri (BA6). These data suggest that bipolar patients and controls recruit different neural networks to accomplish this task, which may reflect different task performance strategies between groups. For example, remitted bipolar patients may use more cognitive control strategies that rely on prefrontal regions of the brain during the novelty condition, while healthy controls are using memory processes that are reliant on MTL structures.

Other studies, using different paradigms to examine working memory in remitted bipolar patients, have demonstrated alterations within this network as well, particularly in the PFC. Consistent with findings observed by Lagopoulos and colleagues (34), we found patterns of hypoactivation in lingual and fusiform gyri, concomitant with hypoactivation in medial temporal regions in bipolar patients while performing a working memory task, despite the differences in the tasks employed (i.e., a parametric Sternberg paradigm versus our DNMS task). In addition, Adler and colleagues (8) showed hyperactivation in remitted bipolar patients in regions of the PFC (BA10) as well as the temporal cortex, posterior parietal cortex, and the thalamus during performance on a two-back working memory task. Consistent with our findings in the novelty condition, Adler and colleagues (8) also found greater ACC activation in bipolar patients; however, after controlling for medication effects, this difference was no longer significant. Greater ACC activity (bilateral BA32, right BA24) has also been reported by Chang and colleagues (11) using a visuospatial working memory task in children and adolescents with familial bipolar disorder, as compared to controls. Using positron emission tomography (PET), increased ACC blood flow in bipolar patients has also been observed during a resting state (36) and while performing a decision-making task (37) during a manic state. Our results provide further evidence for abnormalities in ACC function in remitted patients with bipolar disorder. Collectively, these findings suggest alterations in fronto-temporal circuitry underlying working memory maintenance processes in bipolar patients, and provide evidence that such neurophysiologic alterations are not

limited to acutely symptomatic periods, but instead may reflect a trait marker of the disorder.

Limitations

In our prior behavioral study, symptomatic patients with bipolar disorder performed worse than healthy comparison subjects (15). However, task performance in the current study did not significantly differ between groups. Previous studies have reported that acute mood symptoms can impair working memory in bipolar individuals (38, 39), which could explain differences between the current and previous studies. Alternatively, it is possible that the task was not sufficiently sensitive to detect subtle group differences in this smaller sample. To fully account for the impact of affective symptoms on cognitive performance in bipolar disorder, longitudinal studies with serial neuropsychological assessments are warranted.

Our sample included patients with bipolar disorder taking one or more medications. As it is possible that psychotropic medications could alter fMRI activity, we examined medication effects at the whole-brain level. Specifically, we included medication regressors in our analyses. No significant medication effects were noted in our sample. Other studies have similarly observed neurophysiological differences in remitted bipolar disorder that could not be explained by the effects of medication (40). Thus, while there is no evidence that the observed group differences are attributable to medication effects, this is nevertheless a confound that could be more thoroughly investigated in future studies in which patients can be assessed both on and off medication.

Another important consideration is the effect of adapting the task to the scanner. It is possible that alterations in the task design may have altered characteristics that were sensitive to group differences. In addition, development of baseline conditions that isolate the desired cognitive process may help identify differences between populations of interest.

Conclusions

We demonstrated neurophysiological dysfunction within frontal-temporal circuits in symptomatically remitted patients with bipolar disorder despite normal task performance. These data suggest that brain systems supporting working memory are compromised in bipolar disorder, such that certain regions (i.e., the parahippocampus and occipito-parietal regions) are underutilized and others are relatively overengaged (i.e., prefrontal and anterior cingulate cortices). A parsimonious explanation for our findings is that the pathophysiology of bipolar disorder reduces the efficiency of the working memory network, resulting in the relative misutilization of multiple brain regions. Future research should examine working memory tasks in both affected individuals and their siblings or offspring to determine if these neural networks are compromised as a function of genetic liability. Such a design may help to further elucidate the pathoetiology underlying memory deficits in bipolar disorder.

Acknowledgments

This project was funded by NARSAD (Young Investigator Award to DCG).

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Fig. 1.
An example trial from the delayed-non-match-to-sample task.

Fig. 2.

Activation map for both the familiarity and novelty conditions thresholded at $z = 4.0$ for each group. Red indicates activation in the healthy control group, green indicates activation in the remitted bipolar disorder group, and yellow indicates regions activated by both groups.

Fig. 3.

Group differences in each of the two conditions. Maps reflect spatial mixture modeling thresholded conservatively at $p < 0.0001$ and $z > 2.3$. Blue indicates where remitted bipolar patients showed greater activation than controls, and red indicates where controls were hyperactive relative to remitted bipolar patients. ACC = anterior cingulate cortex; FFG = fusiform gyrus; LG = lingual gyrus; MFG = medial frontal gyrus; PH = parahippocampus; THAL = thalamus; VLN = ventrolateral nucleus.

Table 1

Local maxima determined from the familiarity and novelty conditions across the entire sample

Local maxima	Region	Familiarity condition				Novelty condition			
		Talairach coordinates				Talairach coordinates			
		z	x	y	z	z	x	y	z
Frontal lobe	Right cingulate gyrus (BA32)					5.79	6	22	36
	Right inferior frontal gyrus (BA46)					4.68	32	30	12
	Right inferior frontal gyrus (BA47)	5.37	34	18	-6				
	Left inferior frontal gyrus (BA10)					5.24	-40	48	4
	Right medial frontal gyrus (BA6)					6.81	4	12	46
	Right medial frontal gyrus (BA6)					5.76	32	-4	46
	Right medial frontal gyrus (BA6)					5.67	30	-4	56
	Right medial frontal gyrus (BA6)					5.33	24	-10	44
	Right medial frontal gyrus (BA6)					4.52	50	2	38
	Right medial frontal gyrus (BA9)	6.00	42	28	26	6.51	42	28	26
	Left medial frontal gyrus (BA6)					6.69	-4	14	46
	Left medial frontal gyrus (BA6)					5.88	-2	-4	58
	Left medial frontal gyrus (BA6)					5.54	0	-4	64
	Left medial frontal gyrus (BA32)	7.38	-4	6	46				
	Right middle frontal gyrus (BA46)	5.33	42	32	16	5.93	42	32	18
	Right middle frontal gyrus (BA9)	5.40	32	30	22				
	Left middle frontal gyrus (BA10)	4.64	-38	52	12	5.03	-38	52	10
	Right precentral gyrus (BA6)					5.33	38	2	26
	Right precentral gyrus (BA6)					4.79	42	-6	36
	Left precentral gyrus (BA6)	7.41	-38	2	26				
	Right superior frontal gyrus (BA9)					5.74	38	38	28
	Left superior frontal gyrus (BA6)					6.79	0	4	52
	Left superior frontal gyrus (BA10)					4.65	-34	54	12
	Right parahippocampal gyrus (BA27)					6.13	18	-32	-2
	Left parahippocampal gyrus (BA27)					6.04	-22	-30	-2
Anterior lobe	Left culmen					7.22	-32	-50	-18

Local maxima	Region	Familiarity condition			Novelty condition		
		Talairach coordinates			Talairach coordinates		
		z	x	y	z	x	y
Local maxima	Left culmen				5.49	-8	-28
	Right culmen	7.35	24	-56	-20	10	-24
	Right superior parietal lobule (BA7)				7.46	28	-66
Parietal lobe	Right superior parietal lobule (BA7)				7.45	28	-64
	Right declive				7.53	30	-80
Posterior lobe	Right lingual gyrus (BA18)				7.76	8	-88
Occipital lobe	Left fusiform gyrus (BA19)				7.74	-44	-72
	Right insula	5.72	32	16	8	7.04	32
Sub-lobar	Right insula (BA13)	6.57	34	16	2	5.63	34
	Right thalamus				5.43	20	-12
	Right thalamus (pulvinar)	6.48	20	-30	2	6.56	20
	Right thalamus (ventral lateral nucleus)	6.13	14	-16	10		
	Right thalamus (ventral lateral nucleus)	5.41	14	-18	0		
	Left thalamus (pulvinar)	6.30	20	-32	6	5.45	-22
	Left thalamus (medial dorsal nucleus)				6.25	-12	-20
	Left thalamus (ventral lateral nucleus)				6.24	-16	-16
	Left thalamus (mammillary body)				6.09	-12	-20
	Right lateral geniculum body				5.56	22	-26
	Left lentiform nucleus (putamen)				6.38	-18	-6
	Right lentiform nucleus (putamen)	5.31	22	-2	20		
	Right lentiform nucleus (putamen)	4.98	20	-2	14		
	Right midbrain (substantia nigra)	4.78	8	-22	-10	5.16	8
	Left midbrain (substantia nigra)				5.47	-8	-22

Images were thresholded at $z = 4.0$ and a cluster significance of $p = 0.0001$. Regions highlighted in gray were consistent across both conditions. BA = Brodmann area.

Table 2

Group differences in the novelty and familiarity condition

Contrast	Lobe	Region	Familiarity condition						Novelty condition						
			Talairach coordinates						Talairach coordinates						
			z	x	y	z	x	y	z	x	y	z	x	y	
HC > RBD	Anterior	Left culmen	4.10	-24	-30	-24	4.10	-36	-42	-18					
	Midbrain	Left subthalamic nucleus	3.50	-10	-18	-2									
	Occipital	Left cuneus (BA18)								3.42	-18	-92	12		
		Right fusiform gyrus (BA18)								2.69	30	-88	-14		
		Right fusiform gyrus (BA19)	2.60	34	-70	-10									
		Right inferior occipital gyrus (BA17)	3.44	14	-92	-6	2.96	14	-92	-6					
		Left lingual gyrus (BA17)	4.15	-20	-90	0	3.23	-20	-88	0					
		Right lingual gyrus (BA17)	3.30	18	-86	-2	2.60	18	-86	-2					
		Left lingual gyrus (BA18)	3.69	-12	-72	-6	3.34	-12	-86	-8					
		Right lingual gyrus (BA18)	3.21	34	-68	-4	2.45	16	-80	-6					
Limbic	Left middle occipital gyrus (BA18)	4.15	-18	-98	8	3.75	-18	-96	6						
	Right middle occipital gyrus (BA18)	3.53	24	-84	0	3.29	24	-82	0						
	Left parahippocampal gyrus (BA36)					3.81	-34	-28	-22						
	Right posterior cingulate (BA31)					2.55	28	-60	22						
Parietal	Right inferior parietal lobule (BA40)					2.34	38	-52	42						
	Right precuneus (BA7)	3.09	16	-60	44	3.65	30	-48	40						
Posterior	Right superior parietal lobule (BA7)	3.44	34	-58	54										
	Left declive	3.90	-36	-60	-14										
	Right declive	3.32	32	-80	-16										
Sub-lobar	Left lentiform nucleus (putamen)	3.66	-16	2	12										
	Left thalamus	3.83	-18	-30	0										
Temporal	Left fusiform gyrus (BA37)	3.74	-36	-52	-12	3.38	-42	-40	-14						
	Right fusiform gyrus (BA37)	2.92	40	-62	-8										
	Left fusiform gyrus (BA20)	3.53	-38	-34	-18										
	Left inferior temporal gyrus (BA20)	3.50	-60	-48	-14										
	Left inferior temporal gyrus (BA37)	3.16	-64	-50	-8										

Contrast	Lobe	Region	Familiarity condition			Novelty condition		
			Talairach coordinates			Talairach coordinates		
			z	x	y	z	x	y
RBD > HC	Frontal	Left middle temporal gyrus (BA21)	3.33	-66	-32	-2		
		Right inferior frontal gyrus (BA9)				2.76	54	6
		Left medial frontal gyrus (BA9)				2.88	-4	48
		Left medial frontal gyrus (BA11)				3.77	-6	34
		Left medial frontal gyrus (BA10)				2.54	-6	48
		Right middle frontal gyrus (BA6)				2.82	48	2
	Limbic	Right precentral gyrus (BA6)	3.69	54	2	36	54	-4
		Left anterior cingulate (BA24)				3.55	-2	32
		Left anterior cingulate (BA32)				3.00	-10	38

Maps, created through spatial mixture models, were thresholded at $z = 2.3$ and $p < 0.0001$. Highlighted rows indicate differences in activation that occurred during both conditions. RBD = remitted bipolar disorder patients; HC = healthy controls; BA = Brodmann area.