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Regular Article

Psychosocial functioning is correlated with activation in the anterior cingulate cortex and left lateral prefrontal cortex during a verbal fluency task in euthymic bipolar disorder: A preliminary fMRI study

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Aim: Cognitive impairment may account for functional and occupational disability in patients with bipolar disorder even during periods of euthymia. While imaging suggests structural, neurochemical, and functional abnormalities in bipolar disorder patients, the pathophysiology of these deficits has not been elucidated. It was hypothesized that euthymic bipolar patients would have different cortical activation during a verbal fluency task compared to healthy controls, and that psychosocial functioning would be associated with prefrontal cortical activation during the task in the bipolar group.

Methods: Ten euthymic bipolar patients and 10 healthy control participants (matched for age, gender, and years of education) underwent functional magnetic resonance imaging (fMRI) during a verbal fluency task, tapping task and visual task. Correlational analysis between the fMRI brain activation and clinical variables of the participants, including Global Assessment of Functioning (GAF) score, was performed.

Results: Compared to the controls, euthymic bipolar patients had significantly greater activation in the bilateral precuneus with similar behavioral performance during the verbal fluency task. There were no significant differences between the groups for the visual task or the simple motor task. Activation in both the left anterior cingulate cortex (ACC) and the left dorsolateral prefrontal cortex (PFC) were significantly positively correlated with GAF score in the euthymic bipolar patients.

Conclusion: Both the ACC and lateral PFC regions are components of a neural network that plays a critical role in psychosocial functioning, and are often found to be affected in bipolar patients.

Key words: bipolar disorder, euthymia, functional magnetic resonance imaging, prefrontal cortex, psychosocial functioning.

ALTHOUGH PATIENTS WITH bipolar disorder (BD) have historically been characterized as returning to baseline function between affective episodes,[1] it is increasingly apparent that this view is somewhat inaccurate. Euthymic BD patients, although clinically in remission, often continue to be functionally compromised.[2] Some studies point to a significant degree of psychosocial dysfunction even when patients are euthymic.[3,4] Other reports have emphasized the impact of cognitive dysfunction on psychosocial functioning in BD patients.[5,6] In addition, psychosocial functioning seems to be more strongly associated with cognitive impairment than

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most other clinical variables.[7] Verbal fluency is an aspect of higher executive function, a spectrum of cognitive processes that are essential to control and regulate lower-level processing and goal-directed behavior.[8] A recent meta-analysis of cognitive deficits in euthymic BD patients found a small impairment in phonetic fluency.[9]

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), are now widely used to study BD.[10] Studies of executive functioning in BD patients have included working memory tasks, continuous performance tasks, Stroop and language tasks. Some functional neuroimaging studies found blunted activation of the prefrontal cortex (PFC) during cognitive tasks in BD patients.[11,12] Other studies did not find hypoactivation but reported enhanced or unchanged activation.[13,14] Although there has been variability of results depending on the clinical state of the patients and the task design, the PFC has been consistently involved.[15] Psychosocial functioning is a sophisticated construct that encompasses interactions and activities in personal, occupational, and recreational contexts. The biological underpinnings of psychosocial impairment are unclear. Few studies have specifically examined psychosocial functioning using brain activation and neuropsychological tasks.

The present study analyzed the association between psychosocial functioning and brain activation during higher cognitive functions in euthymic BD patients. We hypothesized that euthymic BD patients would exhibit different cortical activation during a verbal fluency task, but not during lower motor or sensory tasks, compared to healthy controls. More specifically, euthymic BD patients would have a more extended pattern of brain activation compared to the controls to achieve similar behavioral performance, reflecting insufficient processing in the anterior cingulate cortex (ACC) and left lateral PFC, which have been consistently reported to be activated during verbal fluency tasks. In addition, psychosocial functioning, known to be impaired in BD even during remission, was hypothesized to be associated with ACC and left lateral PFC activation during the task.

METHODS

Participants

The present study included 10 patients who met DSM-IV criteria for bipolar I disorder and 10 healthy volunteers with no history of neurological or psychiatric illness. Participants were all Japanese, and pairwise matched for age, sex, and years of education (Table 1). Healthy volunteers were required to be free of any recent use of any psychotropic medication. All participants were right-handed as assessed on the Edinburgh Handedness Inventory.[16] All patients were outpatients at the Hiroshima University Medical Hos-

Table 1. Demographics and behavioral performance

	BD patients mean ± SD	Normal controls mean ± SD	
n	10	10	
Gender (M/F)	4/6	4/6	
Age (years)	48.4 ± 8.8	54.6 ± 5.6	n.s. ($P = 0.12$)
Years of education	14.1 ± 2.0	13.5 ± 2.3	n.s. ($P = 0.38$)
Age at onset of first episode	35.0 ± 13.9		
Duration of illness (years)	13.6 ± 8.1		
HRSD score	2.8 ± 2.0	1.2 ± 1.1	n.s. ($P = 0.07$)
YMRS score	0.3 ± 0.6	0.1 ± 0.3	n.s. ($P = 0.50$)
GAF score	78.7 ± 7.9	90.8 ± 2.3	BD < controls ($P = 0.012$)
No. episodes	13.8 ± 14.9		
Mania	6.3 ± 5.8		
Depression	7.6 ± 9.4		
No. hospitalizations	2.7 ± 2.6		
Word fluency task	11.6 ± 4.2	10.2 ± 3.6	n.s. ($P = 0.52$)

BD, bipolar disorder; GAF, Global Assessment of Functioning; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

pital. They had been diagnosed by two senior psychiatrists (including Y.O.) as having bipolar I disorder, using the Mini-International Neuropsychiatric Interview (MINI)[17] according to DSM-IV criteria. Healthy participants were recruited via advertisements. Exclusion criteria for both groups were current or past history of any psychiatric illness (other than BD for patients), organic disorder of the central nervous system, or a serious physical disorder, and standard MRI contraindications.[18] General functioning was assessed with the Global Assessment of Functioning (GAF) scale.[19] The GAF scale was administered by trained clinicians focusing on functioning instead of symptoms, and the assessment of the patients was based on individual interviews with the patients and with one of their family members.

Euthymia was defined as a score <7 on both the 17-item Hamilton Rating Scale for Depression (HRSD)[20] and the Young Mania Rating Scale (YMRS)[21] at the initial assessment and on the day of fMRI. All patients were euthymic for >1 month prior to scanning. All patients were receiving maintenance therapy at the time of the study. They had a stable pharmacotherapeutic regimen for a minimum of 6 weeks prior to study entry. Patients with BD were medicated as follows: lithium carbonate (400–800 mg) was taken by nine patients, sodium valproate (400–1600 mg) by four patients, olanzapine (2.5–20 mg) by two patients, and quetiapine (200 mg) by one patient. No patients were taking any antidepressants. Of the 10 BD patients, seven were taking two or more medications.

The study was conducted under a protocol approved by the Ethics Committee of the Hiroshima University School of Medicine. All participants provided written informed consent prior to their participation.

Experimental paradigm

We used a periodic design involving the presentation of a baseline condition for 30 s followed by an activation condition for 30 s. Each cycle was repeated three times over the course of 3 min.

Word fluency task

During the activation condition, participants were cued by the visual presentation of one of three letters (the Japanese phonetic characters that are pronounced 'sa', 'ta', and 'te') and asked to generate as many different words as they could beginning with that letter and to internally articulate the word. One of the three letters was presented every 3 s. During the baseline condition, participants were cued by visual presentation of the word 'yasumi' (which means 'rest') every 3 s and asked to internally articulate that word.

Before the scanning, all participants underwent a performance test outside of the scanner using the same design as described, with three different letters ('ka', 'na', and 'to'). On this test, participants were instructed to articulate the words audibly, not internally, and the number of different words generated was recorded.

Tapping task

During the activation condition, participants were cued by the visual presentation of the word 'yubiawase' (which means 'finger tapping') and asked to tap the thumb of the right hand to the forefinger, the middle finger, the third, and the little in order. This word was presented every 3 s. During the baseline condition, participants were cued by the visual presentation of a mosaic pattern every 3 s and asked only to watch the pattern without thinking about anything.

Visual task

During the activation condition, participants were cued by the visual presentation of a blinking checkered pattern every 3 s. During the baseline condition, they gazed at a fixed red cross in the center of the screen every 3 s. Throughout both conditions, the participants were asked only to watch the display without thinking about anything.

Image acquisition

Functional magnetic resonance imaging was performed using a 1.5-T Magnetom Symphony Maestro Class scanner (Siemens, Tokyo, Japan) at Kajikawa Hospital (Hiroshima, Japan). A time-course series of 64 volumes was acquired with T2*-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 38 slices, and the slice thickness was 4 mm with no gap, and covered the entire cerebral and cerebellar cortices. The interval between two successive acquisitions of the same image (TR) was 3000 ms, the echo time (TE) was 48 ms, and the flip angle was 90°. The field of view (FOV) was 256 mm,

and the matrix size was 64 × 64, giving voxel dimensions of 4 × 4 × 4 mm. Scan acquisition was synchronized to the onset of the trial. After functional scanning, structural scans were acquired using a T1-weighted gradient echo pulse sequence (TR, 2050 ms; TE, 3.93 ms; flip angle, 15°; FOV, 256 mm; voxel dimensions, 1 × 1 × 1 mm), which facilitated localization.

Data analysis

Statistical analysis for demographic data and task performance of each group was performed using PASW 18.0 (Tokyo, Japan). To compare the age, years of the education, mood symptoms (HRSD and YMRS), GAF scores, and task performance of the word fluency task (WFT), Mann–Whitney *U*-test was used. Significance was defined as $P < 0.05$.

For image processing and statistical analysis we used statistical parametric mapping (SPM5) software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.1 (Mathworks, Sherborn, MA, USA). The first (pre-task-period) and the last three (post-task-period) volumes were discarded, and the remaining 60 volumes were used for statistical analysis. Images were corrected for motion and realigned with the first scan of the session as a reference. T1 anatomical images were registered to the first functional image in each subject and aligned to a standard stereotaxic space, using the Montreal Neurological Institute (MNI) T1 template. The calculated non-linear transformation was applied to all functional images for spatial normalization. Finally, the functional images were smoothed with an 8-mm full-width, half-maximum Gaussian filter.

Using group analyses according to a random effect model that allowed inference to the general population,[22] we identified brain regions that showed significant responses during (i) word generation compared with word repetition; (ii) finger tapping compared with looking at a mosaic pattern; and (iii) looking at a blinking checkered pattern compared with looking at a red cross.

The group analysis consisted of two levels. In the first level, the signal time course of each subject was modeled with a delayed box-car function convolved with a hemodynamic response function in the context of a general linear model. One contrast image per subject was created by contrasting word generation with word repetition. In the second step, these images were entered into a one-sample *t*-test and then a two-sample *t*-test. Activations were reported if they exceeded $P < 0.05$, corrected for whole-brain false discovery rate at the single-voxel level and cluster extent of ≥50 contiguous voxels. In addition, voxel-wise correlational analysis (linear regression implemented in SPM5) between the activation of the WFT and clinical variables (BD group only and whole group) was applied for the voxels masked by the positive effect of WFT (inclusive mask threshold set at $P < 0.05$ uncorrected). This means that correlation analysis was performed for the regions that were related to the WFT. We used a relatively liberal threshold of $P < 0.01$ at the voxel level and cluster size >25 for this analysis, and limited inspection to a priori hypothesized regions. These a priori regions included the ACC and lateral PFC, because these regions are typically of interest for cognitive function and pathophysiology of BD. We then extracted the activation of each peak voxel, and used scatter plots for the activation and clinical variable only for visualization purpose. The xyz coordinates used in the present study are from the MNI brain space. Labels for brain activation foci were obtained in Talairach coordinates, which were converted from MNI coordinates, using the Talairach Daemon software, which provides accuracy similar to that of neuroanatomical experts.[23] The areas identified as labeled areas by this software were then confirmed by comparison with activation maps overlaid on MNI-normalized structural MRI.

RESULTS

Demographics

As shown in Table 1, there were no statistically significant differences between the two groups in terms of gender, age, years of education, HRSD score, or YMRS score. BD patients had significantly lower GAF score than normal controls.

Behavioral performance

All participants were able to complete the three tasks. There was no significant group difference in offline verbal fluency performance (Table 1).

Neuroimaging data

As shown in Figure 1, for both groups all tasks produced robust activations within the cerebral regions

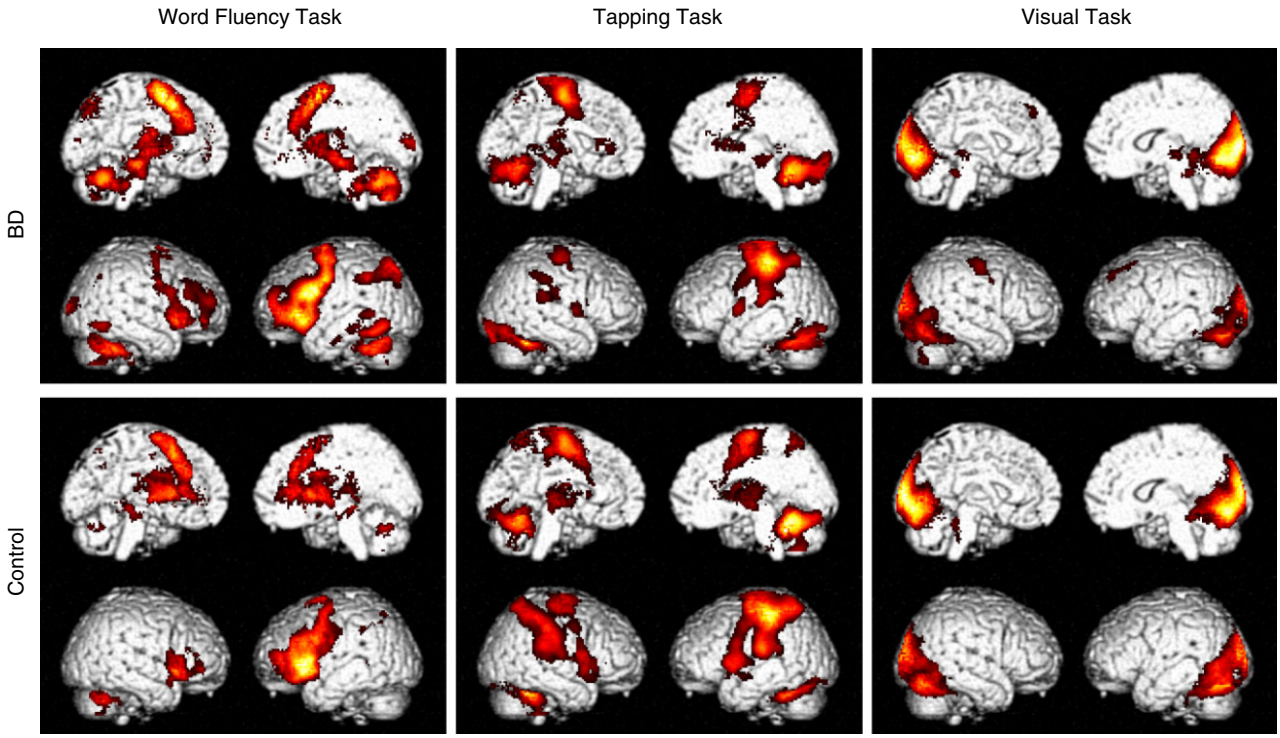

Figure 1. Brain activation during the verbal fluency task, tapping task and visual task in each group. For the word fluency task, healthy controls had activation in the lateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), and cerebellum. Patients with euthymic bipolar disorder (BD) had a similar pattern of brain activation, with more widespread changes. Each group had significant activation in the left primary motor area for the tapping task, and in the bilateral primary visual area for the visual task (false discovery rate-corrected $P < 0.05$ and voxels >50).

that have previously been implicated in neuroimaging studies. A one-sample *t*-test for each group indicated significant activation in the left primary motor area for the tapping task, and in the bilateral primary visual area for the visual task. For the WFT, healthy controls had activation in the lateral PFC, ACC, and cerebellum. Patients with euthymic BD had a similar pattern of brain activation in these regions. Furthermore, additional regions including the bilateral precuneus were significantly activated in the BD patients.

Direct comparison between the two groups, using a two-sample *t*-test at each voxel of the brain activation, for the WFT showed that the BD patient group had significantly greater activation than the control group in the bilateral precuneus (left: [−14 −82 46], BA7, T = 5.21, voxels = 142; right: [16 −82 46], BA7, T = 5.21; voxels = 67). No other differences in significantly activated areas were seen for the control and the BD patient group (Fig. 2). There were no significant differences between the two groups for the visual task and the simple motor task.

Correlations in fMRI activation and clinical variables in BD patients

In the euthymic BD participants, activation in both the left ACC and the left lateral PFC were significantly positively correlated with GAF score (Fig. 3; ACC: [−10 38 24], BA32, T = 4.97, voxels = 75; left lateral PFC: [−50 14 4], BA45, T = 4.79, voxels = 34). No significant correlations were evident between brain activation and the offline performance or other clinical variables, such as age, years of education, onset age, duration of illness, number of episodes, or number of hospitalizations to the patient group. In addition, for all participants including the healthy controls, there was a significantly positive correlation between GAF score and activity in both brain areas (data not shown).

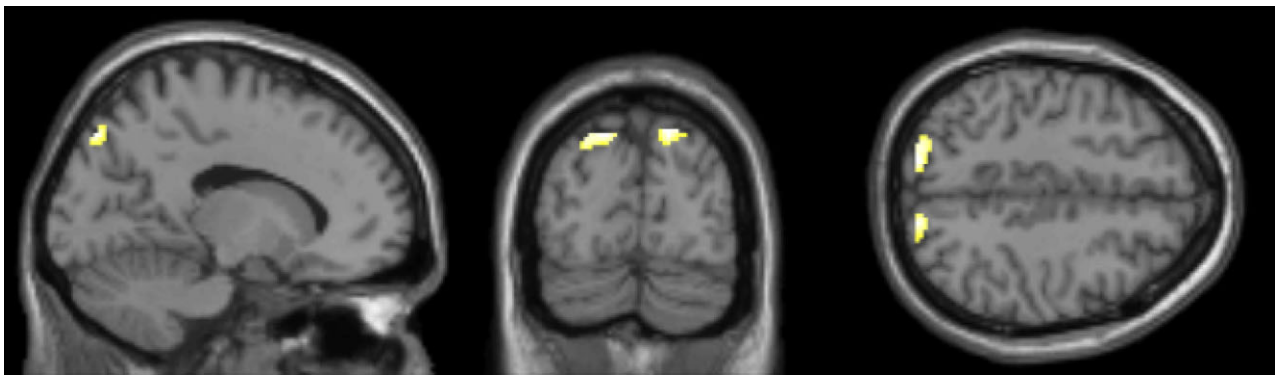

Figure 2. Word fluency task results. The bipolar disorder group had significantly greater activation than the control group in the bilateral precuneus (false discovery rate-corrected $P < 0.05$ and voxels >50).

DISCUSSION

The principal findings of this study are twofold. First, euthymic BD patients had greater activation in the bilateral precuneus compared to the controls, with similar behavioral performance during the verbal fluency task. There were no significant differences in patterns of brain activation between the two groups for the visual task and the simple motor task. Second, activation of both the left ACC and the left lateral PFC were significantly positively correlated with GAF score in the euthymic BD participants. There was no significant group difference, however, in the activations of the regions with which GAF score was correlated. This suggests that changes in the activation of these regions are associated with the current general functioning of BD patients, but are not the trait abnormality of BD. To our knowledge, this is the first study to show a clear relationship between functional brain activation and GAF in daily life in euthymic BD patients.

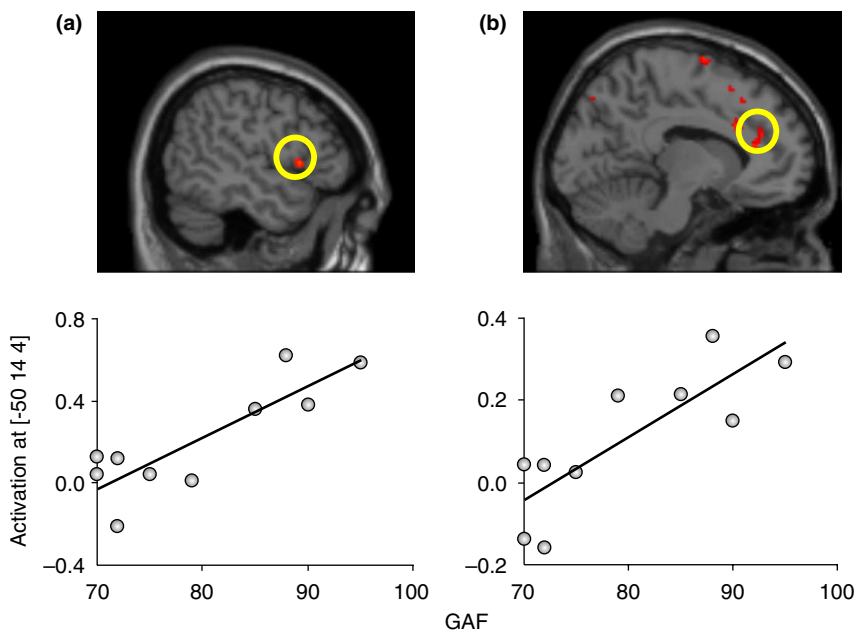

Figure 3. Correlations in brain activation and psychosocial functioning in bipolar disorder (BD) patients. In the BD group, activation in both the (a) left lateral prefrontal cortex (PFC) and (b) left anterior cingulate cortex (ACC) were significantly positively correlated with Global Assessment of Function (GAF) score (uncorrected $P < 0.01$ and voxels >25 masked by word fluency task activation $P < 0.05$).

Although the cross-sectional nature of the present study precludes definitive conclusions about a causal relationship, the present findings suggest that the poorer general psychosocial functioning found in euthymic BD patients may be attributable to attenuation of ACC and left lateral PFC activation during the higher cognitive task. Consistent with the present results at the behavioral level, verbal fluency has been reported to be a predictor of psychosocial functioning in BD patients.[24] Difficulty in retrieving verbal information may represent a serious problem for BD patients in their occupational functioning as well as in their interpersonal relationships. The ACC has been considered a key cortical area during the processing of cognitively demanding information. It has been shown to be associated with a number of functions including response selection, inhibition, vocalization and attention.[25] In contrast, the lateral PFC has been related to working memory, cognitive-set shifting, and planning.[26] Preceding neuroimaging studies have found alterations in the ACC–dorsolateral PFC system in both unipolar depressed and BD patients, putatively reflecting an abnormal interplay of monitoring and executive neurocognitive functions.[27]

One contradictory finding in the present study is that we failed to find a difference in the offline verbal fluency performance between the two groups, even though there was significant activation in the precuneus in euthymic BD patients compared to healthy controls. One explanation of this finding may be that the BD patients were able to produce similar numbers of words by activating more brain regions other than the usually activated areas such as the ACC, left lateral PFC, and cerebellum. This suggests that the patients used an alternative neural strategy to process verbal information to improve their performance. The present findings are in agreement with other studies that have found greater activation in different regions during cognitive tasks in patients with BD.[28,29] The precuneus has traditionally received little attention, mainly because of its hidden location and the virtual absence of focal lesion studies. Recent functional imaging findings in healthy individuals, however, suggest that the precuneus is a multimodal association area that is involved in episodic memory retrieval. It has been suggested that the prefrontal regions drive memory retrieval and that successful retrieval prompts the reactivation of engrams stored in the precuneus.[30] In the present study, BD patients had hyperactivation in the dorsoposterior portion of the precuneus near the parieto-occipital fissure during the verbal fluency task. This portion is functionally connected to adjacent visual cortical regions,[31] and related to visual and spatial attention. Therefore, the present results suggest that the BD patients required greater attention resources to perform the same task, possibly because of an inefficiency of the neural systems supporting verbal fluency performance. Interestingly, a considerable number of previous studies have indicated the differential recruitment of the precuneus between BD patients and controls, during various cognitive tasks. Greater activation in the precuneus of euthymic BD patients compared to controls during the verbal fluency task corroborates a previous study suggesting that BD patients have reduced deactivation in the precuneus, in comparison to healthy controls.[32] Significantly, studies using tasks other than the verbal fluency task have also suggested the diminished, or absent activity in the precuneus, as compared to healthy controls.[33,34] Although there is a lack of consistency in the direction of the effects observed across tasks, possibly because of differences in samples, imaging tasks, and analysis protocols among others, a study using voxel-based morphometry has also suggested that the precuneus is affected in BD.[35] It is suggested that the role of the precuneus in BD is an important issue for future investigation.

Several limitations must be considered when interpreting the present study. First, the overall number of participants is relatively small, which limits the generalizability of the study findings. The patient sample, however, consisted of well-diagnosed, stable individuals with chronic BD, and the sample size provided enough power to detect between-group differences. This sample size limitation is particularly true for correlation analysis, although the results for all participants are similar to those for BD patients. Nonetheless, this study provides some hypotheses for future research with larger samples. Second, the patients receiving medications were being treated with a variety of drug combinations, so that specific medication effects could not be determined given the number of patients available. Medications, however, may alter brain activation in regions that are associated with cognitive tasks, so the study of specific drug effects on cognition (and corresponding brain activation) in a larger patient sample is warranted. Third, the task performance data were obtained in an offline condition, but not in an online condition, because of the risk of verbal movement confounding the data. All participants, however, performed the same task using different phonemic characters outside of the scanner,

although there is no guarantee that the task performance at each session was the same. Fourth, the present paradigm had no sufficient baseline prior to the active block. This means that we cannot exclude the possibility that the early MRI data may include unstable magnetization. But we demonstrated that the activations on the WFT corresponded with the findings of previous studies. The effect of unstable magnetization seems to be small.

In conclusion, patients with euthymic BD had significant positive correlations between psychosocial functioning and activations in the ACC and the left lateral PFC during a verbal fluency task. Thus, the hidden cognitive disturbance, detected only on functional brain imaging with neuropsychological tests, is always present in BD, even though bipolar patients exhibit minimal affective symptoms during periods of euthymia. These results suggest that the precuneus may be sensitive to the impact of BD, and are also indicative of an association between the general functioning of euthymic BD patients and the function of the ACC and the lateral PFC. Further studies of brain activity using neuropsychological tasks as probes for psychosocial functioning in BD and other neuropsychiatric disorders are warranted.

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REFERENCES

1. Kraepelin E. *Manic-Depressive Insanity and Paranoia*. Livingstone, Edinburgh, 1921.
2. Malhi GS, Yatham LN. Mania Matters! *Acta Psychiatr. Scand.* 2007; **434** (Suppl.): 1–2.
3. Tohen M, Hennen J, Zarate JCM *et al*. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am. J. Psychiatry* 2000; **157**: 220–228.
4. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: A longitudinal follow-up study. *Am. J. Psychiatry* 1995; **152**: 379–384.
5. Martinez-Aran A, Vieta E, Colom F *et al*. Cognitive impairment in euthymic bipolar patients: Implications for clinical and functional outcome. *Bipolar Disord.* 2004; **58**: 224–232.
6. Zubieta JK, Huguelet P, O'Niel RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. *Psychiatry Res.* 2001; **102**: 9–20.
7. Martinez-Aran A, Vieta E, Reinares M *et al*. Cognitive function across manic or hypomanic, depressed, and euthymic status in bipolar disorder. *Am. J. Psychiatry* 2004; **161**: 262–270.
8. Alvarez JA, Emory E. Executive function and the frontal lobes: A meta-analytic review. *Neuropsychol. Rev.* 2006; **16**: 17–42.
9. Robinson LJ, Thompson JM, Gallagher P *et al*. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J. Affect. Disord.* 2006; **93**: 105–115.
10. Kupferschmidt DA, Zakzanis KK. Toward a functional neuroanatomical signature of bipolar disorder: Quantitative evidence from the neuroimaging literature. *Psychiatry Res.* 2011; **193**: 71–79.
11. Curtis VA, Dixon TA, Morris RG *et al*. Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *J. Affect. Disord.* 2001; **66**: 111–121.
12. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology* 2004; **29**: 1734–1740.
13. Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, Strakowski SM. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disord.* 2004; **6**: 540–549.
14. Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. *Am. J. Psychiatry* 2005; **162**: 1697–1705.
15. Bearden CE, Hoffman KM, Cannon TD. The neuropsychology and neuroanatomy of bipolar affective disorder: A critical review. *Bipolar Disord.* 2001; **3**: 106–150.
16. Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 1971; **9**: 97–113.
17. Sheehan DV, Lecrubier Y, Sheehan KH *et al*. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* 1998; **59** (Suppl. 20): 22–33.
18. Dempsey MF, Condon B, Hadley DM. MRI safety review. *Semin. Ultrasound CT MR* 2002; **25**: 392–401.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)*. American Psychiatric Association, Washington, DC, 1994.

20. Hamilton M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 1960; **23**: 56–62.
21. Young RC, Biggs JT, Zieger VE, Meyer DA. A rating scale for mania: Reliability, validity, and sensitivity. *Br. J. Psychiatry* 1978; **133**: 429–435.
22. Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? *NeuroImage* 1999; **10**: 1–5.
23. Lancaster JL, Woldorff MG, Parsons LM *et al*. Automated Talairach atlas labels for functional brain mapping. *Hum. Brain Mapp.* 2000; **10**: 120–131.
24. Martinez-Aran A, Vieta E, Colom F *et al*. Neuropsychological performance in depressed and euthymic bipolar patients. *Neuropsychobiology* 2002; **46** (Suppl. 1): 16–21.
25. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain* 1995; **118** (Pt. 1): 279–306.
26. Rogers MA, Kasai K, Matsuo K *et al*. Executive and prefrontal dysfunction in unipolar depression: A review of neuropsychological and imaging evidence. *Neurosci. Res.* 2004; **50**: 1–11.
27. Melcher T, Falkai P, Gruber O. Functional brain abnormalities in psychiatric disorders: Neural mechanisms to detect and resolve cognitive conflict and interference. *Brain Res. Rev.* 2008; **59**: 96–124.
28. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP, Eliassen JC. Abnormal fMRI activation in euthymic bipolar disorder patients during a counting Stroop interference task. *Am. J. Psychiatry* 2005; **162**: 1697–1705.
29. Wessa M, Houenou J, Paillere-Martinot ML *et al*. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/no-go task. *Am. J. Psychiatry* 2007; **164**: 638–646.
30. Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* 2006; **129**: 546–583.
31. Margulies DS, Vincent JL, Kelly C *et al*. Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc. Natl Acad. Sci. U.S.A.* 2009; **106**: 20 069–20 074.
32. Costafreda SG, Fu C, Picchioni M *et al*. Pattern of neural responses to verbal fluency shows diagnostic specificity for schizophrenia and bipolar disorder. *BMC Psychiatry* 2011; **11**: 18.
33. Strakowski SM, Adler CM, Cerullo M *et al*. Magnetic resonance imaging brain activation in first-episode bipolar mania during a response inhibition task. *Early Interv. Psychiatry* 2008; **2**: 225–233.
34. Malhi GS, Lagopoulos J, Owen AM, Ivanovski B, Shnier R Sachdev P. Reduced activation to implicit affect induction in euthymic bipolar patients: An fMRI study. *J. Affect. Disord.* 2007; **97**: 109–122.
35. Malhi GS, Lagopoulos J, Das P, Moss K, Berk M, Coulston CM. A functional MRI study of theory of mind in euthymic bipolar disorder patients. *Bipolar Disord.* 2008; **10**: 943–956.