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Abstract:	Abstract Bipolar disorder (BD) is emerging as an illness marred by heterogeneous profile of cognitive impairments. Increased cognitive dysfunction is correlated with greater symptom severity. However, the psychopathology foundation of cognitive impairment remains under-explored. The aim of this study is to assess whether there are differences in brain activation during tasking-state between BD patients with and without working memory (WM) deficit. 2-back tasking-state functional magnetic resonance images were obtained from twenty-seven BD patients and thirteen well matched healthy controls. Based on 2-back task performance, all the patients were subdivided into two groups. Image analysis were proceeded to obtain significantly activated regions in each group as well as significant differential activations between any two groups. Compared to healthy controls, BD patients with WM deficit exhibit peak decreased task-related activation at two brain areas: middle frontal gyrus and superior frontal gyrus (medial), which were not observed in BD patients without WM deficit. BD patients with WM deficit can not achieve WM task successfully mainly related with dysfunctional prefrontal cortex.

Attention Deficit Contribute to Working Memory Deficit in Bipolar Disorder

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Abstract

Background. Bipolar disorder (BD) is emerging as an illness marred by heterogeneous profile of cognitive impairments. Increased cognitive dysfunction correlated with greater symptom severity. However, the psychopathology foundation of cognitive impairment remains under-explored. The aim of this study is to assess whether there are differences in brain activation during tasking-state between BD patients with and without working memory (WM) deficit.

Methods. 2-back tasking-state functional magnetic resonance images were obtained from twenty-seven BD patients and thirteen well matched healthy controls. Based on 2-back task performance, all the patient samples were subdivided into two groups. Those scoring more than one standard deviation below the normative mean were defined as WM deficit. Image analysis were proceeded to obtain significantly activated regions in each group as well as significant differential activations between any two groups.

Results. Compared to healthy controls, BD patients with WM deficit exhibit peak decreased task-related activation at two brain areas: middle frontal gyrus and superior frontal gyrus (medial), which were not observed in BD patients without WM deficit.

Conclusions. BD patients with WM deficit can not achieve WM task successfully mainly related with dysfunctional prefrontal cortex.

Key Words: Bipolar Disorder, Cognitive impairments, Working memory deficit, N-back

Background

Impairment in cognitive function has been identified as one of the core features of Bipolar Disorder (BD) [1]. Increased cognitive dysfunction is often associated with greater symptom severity [2]. Cognitive deficits were found to persist even during remission or euthymic phases predicts poor long-term recovery [3, 4]. Among these

neurocognitive deficits, working memory (WM) deficit has been consistently reported in patients with BD in particular [3, 5, 6]. Several studies have reported that dysfunctions in WM are the underlying cause of cognitive impairments [5].

On the contrary, many studies indicated significant portion of BD patients do not show significant cognitive impairments. Bipolar patients and healthy subjects has been reported to have similar performance on the task, although with significantly different patterns of brain activation or additionally activated brain regions perhaps as a compensatory mechanism [6-8].

Some studies revealed differences in terms of cognitive performance versus healthy controls (HC), whereas others present a mixed picture of hyper-activation and hypo-activation in the specific brain regions traditionally involved in WM circuits [3]. Patiens with BD failed to suppress activation in the left anterior insula during WM task (n-back) [9]. Bipolar subjects have been reported to exhibit a significant reduction in neural activation in WM (n-back) circuits (right dorsolateral prefrontal cortex and right posterior parietal cortex), independent of mood state [6]. Similar to this research, BD patients showed reductions in bilateral frontal, temporal and parietal activation, and increased activations in the left precentral, right medial frontal and left supramarginal gyri [10]. Some other research findings focused on the aberrant activation in BD patient's first-degree relatives in order to discover biomarkers or endophenotype of genetic risk during WM task [9, 11, 12]. Meanwhile, some studies focused on the alteration in patterns of activation along with increased WM load [3, 12, 13].

Available data from neuroimaging studies assessing neural response in BD patients performing an n-back task are inconsistent [3]. Methodological issues such as the inconsistency of samples or paradigms may have contributed to discrepant results.

To date, the neurophysiological basis for WM deficit remain under-explored. Many functional magnetic resonance imaging (fMRI) studies explored BD patients and WM deficit based on bipolar subtypes [6]. These studies assigned bipolar patients into different groups based on mood episodes or bipolar subtypes (BP Ⅰ and BP Ⅱ) [14]. No research has examined how WM deficit is related to discrepant brain

activation in HC and patients of two BD subtypes grouped by their WM performance. It is possible that heterogeneous cognitive profiles (specifically WM) in BD samples also contributed to the above controversial conclusion. To date, the neurophysiological foundation for these cognitive impairments remain under-explored .

In this study we sought to classify BD patients into two subgroups according to their WM performance. The aim of this study was to explore the neural substrate accounted for WM deficit in BD. We hypothesize that dysfunction of prefrontal brain areas would contribute to WM deficit in BD patients.

Methods

Participants

Using Structured Clinical Interview patient version for DSM-IV (SCID-P), Twenty-seven patients with bipolar disorder were recruited from individuals undergoing thorough fMRI scans with both structural and functional imaging. BD patients were recruited from inpatients and outpatients psychiatry units at the Second Xiangya Hospital of Central South University, Hunan province, China. Eligible subjects fulfilled the following inclusion criteria: a) age between 18-45; b) met DSM-IV criteria for bipolar disorder without psychotic features; c) nine years of education or above; d) right-handed by a determination of hand preference, and the following exclusion criteria: a) any contraindications to MRI scanning; b) lifetime or present comorbidities of alcohol or substance abuse history; c) history of electroconvulsive therapy; d) chronic neurological illness.

Thirteen HC were recruited from a community sample. The inclusion and exclusion criteria for these subjects were the same as those of the bipolar disorder group except that they did not meet the DSM-IV diagnostic criteria of any psychiatric disorders by SCID non-patient version, and their first degree relatives had no history of any psychiatric disorders.

All BD subjects were diagnosed by at least two experienced psychiatrists. None

of the subjects had psychotic symptoms at the time of the scan.

Written informed consent was obtained from all subjects after thorough explanation of the study [15]. All methods of this study was approved by the ethics committee of the Second Xiangya Hospital. All the subsequent research analyses were carried out in accordance with the approved guidelines and rugulations.

Cognitive Tasks

The n-back task is one of the most common fMRI paradigms used to observe WM function [6]. In the present study, WM performance was assessed by a classical latin letter variant of the n-back task. Single white letters were presented on a black background on a computer screen at 2 s intervals in 40 s blocks using NordicNeurolab's fMRI hardware system. The n-back task consisted of three different conditions: plus mark fixation as a baseline condition, 0-back condition, and 2-back condition, respectively. During the 0-back condition, subjects were instructed to respond every time the letter "X" or "x" appeared. During the 2-back condition, they were required to press the right button when the letter presented was identical to the one presented two trials back [15]. The letters were in a pseudo-randomized order, each letter was presented for 500 ms, followed by 1500-ms delay. The experiment utilized a blocked design with four epochs for each of the two experimental conditions (8 epochs total) with 20 letters per epoch and seven targets in each epoch [16]. At the beginning of each epoch, a visual instruction indicated the condition (0-back or 2-back) for 2 s. A fixation epoch, in which one crossing for fixation (+) was presented for 20 s, was inserted after every epoch, resulting in a total of eight fixation epochs. The data from these fixation epochs was defined as the baseline condition. At the beginning of the session, a short fixation epoch presented for 4 s was inserted to allow the magnetization to reach equilibrium amplitude. The functional task-state session lasted for 8 minutes and 20 seconds [16]. The reaction time and the accuracy of the responses were recorded electronically by computer. All the subjects were thoroughly instructed before the scanning procedure and experimented for many times until they reached more than 80 percent accuracy both 0-back and 2-back task.

Image Acquisition

All image data were acquired using a Philips Gyroscan Achieva 3.0 Tesla MRI scanner. 250 volumes images were collected axially, using a gradient-echo echo-planar imaging (EPI) sequence: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, matrix = 64×64, slice thickness = 4 mm, gap = 0 mm, slices = 36. Each functional task-state session lasted 8 minutes and 20 seconds [16].

Statistical Analysis

Each raw cognitive score of 2-back was standardized to a z score (with a mean of 0 and a standard deviation of 1) using the values of the healthy comparison group as reference. Patients were then classified as cognitive function deficit if performance was more than 1 standard deviation below the normative mean. Pearson's chi-square for categorical data and ANOVA analysis for continuous variables were used to compare demographic data among cognitively impaired, unimpaired and healthy control groups [17]. The three groups were well matched by age (χ^2=3.983, p=0.137), education level (χ^2=1.235, p=0.539), and gender (χ^2=0.714, p=0.700) (see Table 1).

Image Processing

For image pre-processing and statistical analysis, we used the SPM8 software package (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, http://www.fil.ion.ucl.ac.uk/spm). First, fMRI data were converted from DICOM to NIFTII format using MRIcroN with the first two volumes discarded to allow scanner stabilization. The remaining 248 images were corrected differences in image acquisition time between slices (reference slice=35), spatially realigned to the first image for head-motion correction, then eliminated the image that a maximum displacement of exceed 1.5mm at each axis and an angular motion of exceed 1.5° for each axis. Subsequently, the images were spatially normalized to the standard template of the Montreal Neurological Institute (MNI) and resampled to 3*3*3 mm^3 voxel. Finally, the volumes were spatially smoothed with an 8 mm full width half maximum Gaussian kernel.

Single subject' data were analyzed voxel-wise within the general linear model

(GLM) to calculate statistical parametric maps of t-statistics for condition-specific effects. Then the contrast images of each subject were entered into a second-level analysis, statistical inference was conducted by using the summary statistical approach. Regions consisted of ten or more voxels at a *p* threshold of 0.001(uncorrected) showing significant activation in each group were identified using one-sample t-tests. Regions showing significant difference were identified using two-sample t-tests between any two groups, the statistical threshold was set to $p<0.005$(uncorrected), minimum cluster size is ten voxels.

Results

Task Performance

Analysis of variance (ANOVA) analysis of reaction time (RT) revealed all fell short of significance among three groups, suggesting similar levels of engagement. On the converse, the accuracy either 0-back or 2-back showed significant statistical differences, all ≤ 0.001 (see table 2).

Neuroimaging: Between-group fMRI Comparisons

Comparison of BD patients with WM deficit and HC (Group 1-HC)

The comparison of brain activations in patients with WM deficit and HC indicated that the patient group exhibited enhanced activation in temporal lobe, parietal lobe, frontal lobe, but showed decreased WM (2 back minus fixation) associated responses in calcarine fissure and surrounding cortex right (CAL.R), middle frontal gyrus left (MFG.L), the supplementary motor area right (SMA.R), Superior frontal gyrus medial left, (SFGmed.L). (see Fig. 1-a, Table 3).

Comparison of BD patients without WM deficit and HC (Group 2-HC)

The comparison of brain activations in patients without WM deficit and HC indicated that the patients group revealed enhanced activation only in Parietal

Lobe/postcentral gyrus (voxel size=16, x,y,z=54 -19 55) during the completion of WM task (2-back minus fixation); But patients subjects showed reduced activation in a wide range of brain areas including fusiform gyrus, superior and middle occipital gyrus, superior parietal gyrus, lingual gyrus, calcarine cortex, cuneus, posterior cingulate. (Fig. 1-b, Table 4).

Comparison of BD patients with and without WM deficit (Group 1-2)

Compared with BD patients without WM deficit, those with WM deficit showed increased activation in parietal lobe (voxel size=17 x,y,z= 24 -40 49). Meanwhile, BD patients with WM deficit showed reduced activation in Superior Temporal Gyrus (voxel size= 11, x,y,z= -51 -40 13)，and Frontal_Middle_R (aal) (voxel size= 12 x,y,z= 30 56 19). (Fig. 1-c, Table 5).

Discussion

In this study, we compared two subgroups of BD patients, those with WM deficit and without, as compared to HC group, applying an optimized activation pattern analysis, including correlations with mood symptoms and activated brain areas. Relative to HC, BD patients with WM deficit exhibited significant reduced activation in Frontal_Middle_L and Frontal_Superior_Medial_L. These findings may add fresh insights to the psychopathological mechanisms underlying poorer WM performance in BD patients.

The MFG contain brodman areas (BA) 46, BA46 roughly corresponds with the DLPFC. The DLPFC plays an important role in sustaining attention and WM. N-back paradigm is a reliable method to activate DLPFC [18]. MFG is also involved in attention network [19]. Therefore the alteration of the MFG activation in the present research may mainly be associated with attention deficit. Attentional control is fundamental to WM and sustained attention [20]. Patients with BD perform poorly on tasks of selective attention [21]. This is in agreement with our results.

Furthermore, our finding of attention deficit is supported by poorer 0-back

performance (see Table 2) in WM deficit patients. As 0-back blocks is a task for participants to maintain baseline vigilance and selective attention [3, 22]. BD patients with WM deficit exhibit significant attention deficit compared with HC, and even BD patients without WM deficit. We therefore infer that attention deficit (0-back) contributes to the poorer WM performance (2-back) in WM deficit BD patients. This is consistent with prior finding-many of the group differences (from 0-back to 2-back) were driven by differences in activity in the low-level (0-back) baseline task [11].

We observed some discrepancies between our results and a previous report. There has been report that MFG as well as inferior frontal gyrus, superior parietal gyrus, inferior parietal lobule were all involveded in attention network [19]. Reduced activation were observed in the superior and inferior parietal lobules in Stroop Colour Word Task in BD patients [21]. In our study, parietal lobe activation was increased. We believe that in order to stay on task, patients may need to engage in additional temporal lobe activation (eg increased deactivation of superior temporal gyrus) and increased parietal lobe activation to achieve the n-back task successfully. This maybe a compensating mechanism to achieve adequate WM performance.

Medial frontal gyrus is a region associated with high-level executive functions and decision-related processes [23]. The superior medial frontal area is involved in episodic memory retrieval, monitor and manipulate information within WM [24]. Increased demands on stable task-set maintenance were associated with increased sustained activity in medial superior frontal gyrus [25]. Anatomical and functional data suggest that the left medial superior frontal gyrus is a critical region that integrates multi-sensory information [26]. We think these above views can well elucidate that the dysfunctional superior medial frontal area will lead to WM deficit in some subtype BD patients.

Finally, a Voxel-wise meta-analysis summarized that high-risk patients showed reduced neural activation in a cluster spanning the bilateral medial frontal gyrus (BA 8,6), bilateral superior frontal gyrus (BA 8,6) compared with controls [27]. Therefore, the current findings suggest that the reduced neural activation in the medial superior frontal gyrus maybe a psychotic diathesis which has already been existed before BP

onset and promote the exacerbation process.

Primary study indicate linearization process in Speech Production may be supported by a neural network connecting the left middle temporal gyrus with the medial superior frontal gyrus and left MFG [28]. The MFG and medial superior frontal gyrus were both involved in two neural networks mapping the meaning to the new word. These two networks share a common node-the MFG, suggesting that these two networks communicate in WM [29]. Thus it is possible that the deactivation of MFG and medial superior frontal gyrus may have cooperated in one network and contributed to WM impairment.

The sensitivity to sadness of the MFG was strongly correlated with activity in the left medial superior frontal gyrus (BA 8), an area associated with the regulation of negative emotion [30]. The limbic system is involved in human higher brain functions, such as memory, recognition and emotion [31]. Research demonstrates that the hippocampus is connected with medial superior frontal gyrus and orbitofrontal cortex providing new insight into the human limbic network [31]. Maybe the left MFG and medial superior frontal gyrus both connected with limbic network and consisted in not only emotion processing and regulation circuit but WM network. Further research are needed to explore the functional connectivities between these regions of interested (ROIs).

2-back nontarget RT Correct reflects the response speed of subjects, which depends on individual's WM capacity. WM comprises temporally separated biological processes that involve the on-line retention and manipulation of information [5]. In the present study, the WM capacity of HC group is the best among three groups, the RT is (677.093±94.103ms), the BP patients without WM deficit need more time (690.516±130.120ms) to retrieval, because the memory is a little more ambiguous than HC. Interstingly, the RT of BP patients with WM deficit was (622.552± 162.821)ms, maybe due to the extensive reduction of WM capacity in this group of patients leaving almost no memory for retrieval. So these patients do not need to recall and omit the retrieval process. As consequence, patients with severe WM deficit decide in random yet with fastest speed.

In summary, in the present study, we creatively classified BP patients into two subgroups-with or without WM deficit. We identified some significant aberrant activated brain areas implicated in the WM deficit in BD patients. Ongoing research will be needed to clarify the differences implicated in WM deficit by using this proposed classification method to other psychiatric illness, such as schizophrenia. To verify whether WM deficit is an endophenotype for a broad spectrum of mental illness, even whether WM deficit dictate diagnostic specificity and inclusion of WM deficit criterion [32].

Conclusions

BD patients with WM deficit can not achieve WM task successfully mainly related with dysfunctional prefrontal cortex, especially decreased activation at two brain areas: middle frontal gyrus and superior frontal gyrus (medial).

Abbreviations

BD: Bipolar disorder; WM: working memory; HC: healthy controls; fMRI: functional magnetic resonance imaging; EPI: echo-planar imaging; MNI: Montreal Neurological Institute; GLM: general linear model; ANOVA: Analysis of variance; RT: reaction time; CAL.R: calcarine fissure and surrounding cortex right; MFG.L: middle frontal gyrus; SMA: the supplementary motor area; SFGmed: Superior frontal gyrus medial; BA: brodman areas; ROIs: regions of interested;

Declaration

Ethics approval and consent to participate

Written informed consent was obtained from all subjects after thorough explanation of the study. All methods of this study was approved by the ethics committee of the Second Xiangya Hospital. All the subsequent research analyses were carried out in accordance with the approved guidelines and rugulations.

Consent for publication

Not applicable

Availability of data and materials

The datastes used and analysed during the current study are avaible from the corresponding author on reasonable request.

Competing interests

The authors declare no competing financial interests.

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Authors' Contributions

LC designed the experiments protocals, collected data and carried out the experiments, took part in analyzing the image data, draw the picture, wrote the main manuscript text. JX analyzed the image data. XH analyzed the image data. HL helped to prepare the figure. TEM analyzed the image data. AH participated in collecting data and carrying out the experiments. CZh also helped to collect data and carry out the experiments. ZX participated in designing the experiment protocols. BSh also guided me to designed the experiment protocols. ZL is the most important professor who guided me to designed the experiment protocols. All authors reviewed the manuscript. All authors have approved the manuscript.

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References:

1. Pompei F, Dima D, Rubia K, Kumari V and Frangou S: **Dissociable functional connectivity**

changes during the Stroop task relating to risk, resilience and disease expression in bipolar disorder. *Neuroimage*, 2011. **57**(2):576-82.

2. Marvel CL and Paradiso S: **Cognitive and neurological impairment in mood disorders**. *Psychiatr Clin North Am*, 2004. **27**(1):19-36, vii-viii.
3. Cremaschi L, Penzo B, Palazzo M, Dobrea C, Cristoffanini M, Dell'osso B, et al: **Assessing Working Memory via N-Back Task in Euthymic Bipolar I Disorder Patients: A Review of Functional Magnetic Resonance Imaging Studies**. *Neuropsychobiology*, 2013. **68**(2):63-70.
4. Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, et al: **Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy**. *Nat Rev Drug Discov*, 2012. **11**(2):141-68.
5. Lagopoulos J, Ivanovski B and Malhi GS: **An event-related functional MRI study of working memory in euthymic bipolar disorder.** *J Psychiatry Neurosci.*, 2007. **32**(3):174-84.
6. Townsend J BS, Foland-Ross LC, Sugar CA, Altshuler LL.: **fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects.** *Psychiatry Res.*, 2010. **182**(1):22-9.
7. Strakowski SM, Adler CM, Holland SK, Mills N and DelBello MP: **A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder**. *Neuropsychopharmacology*, 2004. **29**(9):1734-40.
8. Hamilton LS, Altshuler LL, Townsend J, Bookheimer SY, Phillips OR, Fischer J, et al: **Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task**. *Hum Brain Mapp*, 2009. **30**(12):3958-69.
9. Thermenos HW, Goldstein JM, Milanovic SM, Gabrieli SW, Makris N, Laviolette P, et al: **An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder**. *Am J Med Genet B Neuropsychiatr Genet*, 2010. **153B**(1):120-31.
10. Monks PJ, Thompson JM, Bullmore ET, Suckling J, Brammer MJ, Williams SC, et al: **A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction**. *Bipolar Disord*, 2004. **6**(6):550-64.
11. Thermenos HW, Makris N, Whitfield-Gabrieli S, Brown AB, Giuliano AJ, Lee EH, et al: **A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: preliminary findings**. *Bipolar Disord*, 2011. **13**(3):272-86.
12. Drapier D, Surguladze S, Marshall N, Schulze K, Fern A, Hall MH, et al: **Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task**. *Biol Psychiatry*, 2008. **64**(6):513-20.
13. Jansma JM, Ramsey NF, van der Wee NJ and Kahn RS: **Working memory capacity in schizophrenia: a parametric fMRI study**. *Schizophr Res*, 2004. **68**(2-3):159-71.
14. Harkavy-Friedman JM, Keilp JG, Grunebaum MF, Sher L, Printz D, Burke AK, et al: **Are BPI and BPII suicide attempters distinct neuropsychologically?** *J Affect Disord*, 2006. **94**(1-3):255-9.
15. Jansen A, Krach S, Krug A, Markov V, Eggermann T, Zerres K, et al: **A putative high risk diplotype of the G72 gene is in healthy individuals associated with better performance in working memory functions and altered brain activity in the medial temporal lobe**. *Neuroimage*, 2009. **45**(3):1002-1008.
16. Zhang H, Wei X, Tao H, Mwansisya TE, Pu W, He Z, et al: **Opposite effective connectivity in the posterior cingulate and medial prefrontal cortex between first-episode**

schizophrenic patients with suicide risk and healthy controls. *PLoS One*, 2013. **8**(5):e63477.

17. Perez-Iglesias R, Tordesillas-Gutierrez D, McGuire PK, Barker GJ, Roiz-Santianez R, Mata I, et al: **White matter integrity and cognitive impairment in first-episode psychosis**. *Am J Psychiatry*, 2010. **167**(4):451-8.
18. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, et al: **Prefrontal dopamine D1 receptors and working memory in schizophrenia**. *J Neurosci*, 2002. **22**(9):3708-19.
19. Fan J, McCandliss BD, Fossella J, Flombaum JI and Posner MI: **The activation of attentional networks**. *Neuroimage*, 2005. **26**(2):471-9.
20. Mullin BC, Perlman SB, Versace A, de Almeida JR, Labarbara EJ, Klein C, et al: **An fMRI study of attentional control in the context of emotional distracters in euthymic adults with bipolar disorder**. *Psychiatry Res*, 2012. **201**(3):196-205.
21. Pompei F, Jogia J, Tatarelli R, Girardi P, Rubia K, Kumari V, et al: **Familial and disease specific abnormalities in the neural correlates of the Stroop Task in Bipolar Disorder**. *NeuroImage*, 2011. **56**(3):1677-84.
22. Paulus FM, Bedenbender J, Krach S, Pyka M, Krug A, Sommer J, et al: **Association of rs1006737 in CACNA1C with alterations in prefrontal activation and fronto-hippocampal connectivity**. *Hum Brain Mapp*, 2013.
23. Talati A and Hirsch J: **Functional specialization within the medial frontal gyrus for perceptual go/no-go decisions based on "what," "when," and "where" related information: An fMRI study**. *Journal Of Cognitive Neuroscience*, 2005. **17**(7):981-993.
24. Nagahama Y, Okina T, Suzuki N and Matsuda M: **Neural correlates of psychotic symptoms in dementia with Lewy bodies**. *Brain*, 2010. **133**(Pt 2):557-67.
25. Wilk HA, Ezekiel F and Morton JB: **Brain regions associated with moment-to-moment adjustments in control and stable task-set maintenance**. *Neuroimage*, 2012. **59**(2):1960-7.
26. Ueyama T, Donishi T, Ukai S, Ikeda Y, Hotomi M, Yamanaka N, et al: **Brain regions responsible for tinnitus distress and loudness: a resting-state FMRI study**. *PLoS One*, 2013. **8**(6):e67778.
27. Fusar-Poli P: **Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis**. *J Psychiatry Neurosci*, 2012. **37**(2):106-12.
28. Ye Z, Habets B, Jansma BM and Munte TF: **Neural basis of linearization in speech production**. *J Cogn Neurosci*, 2011. **23**(11):3694-702.
29. Ye Z, Mestres-Misse A, Rodriguez-Fornells A and Munte TF: **Two distinct neural networks support the mapping of meaning to a novel word**. *Hum Brain Mapp*, 2011. **32**(7):1081-90.
30. McLellan TL, Wilcke JC, Johnston L, Watts R and Miles LK: **Sensitivity to posed and genuine displays of happiness and sadness: a fMRI study**. *Neurosci Lett*, 2012. **531**(2):149-54.
31. Kubota Y, Enatsu R, Gonzalez-Martinez J, Bulacio J, Mosher J, Burgess RC, et al: **In vivo human hippocampal cingulate connectivity: a corticocortical evoked potentials (CCEPs) study**. *Clin Neurophysiol*, 2013. **124**(8):1547-56.
32. Bora E, Yucel M and Pantelis C: **Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond**. *Schizophr Bull*, 2010. **36**(1):36-42.

Figure1 Between-group fMRI Comparisons. (a): Comparison of BD patients with deficit and HC (Group1-HC). (b): Comparison of BD patients without deficit and HC (Group 2-HC). (c): Comparison of BD patients with and without deficit (Group1-2). The brain areas in blue signify decreased activation when the former group compared with the later group, meanwhile, the brain areas in red signify increased activation when the former group compared with the later group.

Table 1: BD patients and HC demographics characteristics

	Patients With Deficits (n=14)	Patients without Deficits (n=13)	Healthy Controls (n=13)	statistical analysis	
				F/χ^2	p
sex	6/8	6/7	4/9	0.714	0.700
age (SD), year	26.714 (5.060)	27.154 (4.318)	24.154 (4.413)	1.609	0.214
education (SD), year	14.429 (2.954)	14.000 (2.345)	13.538 (2.295)	0.407	0.668

SD=Standard Deviation

Table 2: BD Patients and HC clinical and neuropsychological characteristics

	Patients With Deficits (n=14)	Patients without Deficits (n=13)	Healthy Controls (n=13)	statistical analysis	
				$F/\chi^2/Z$	*p*
Illness duration (SD), months	49.443(38.302)	54.054(49.932)	-	-0.270	0.789
HAMD score (SD)	13.930(10.111)	13.615 (10.469)	-	-0.170	0.865
YMRS score (SD)	5.000(8.029)	3.308(5.879)	-	-0.494	0.621
HAMA score (SD)	12.143(8.132)	10.692(9.724)	-	0.422	0.677
Cpz100 (SD)	167.855(223.462)	112.821(176.665)	-	-0.814	0.416
WAIS-inf (SD)	18.964(4.630)	19.231(3.919)	19.615(4.104)	0.080	0.923
WAIS-Dig (SD)	72.357(18.521)	76.000(15.748)	94.077(12.731)	7.075	0.003
0-back target accuracy	0.866(0.168)	0.950(0.068)	0.979(0.025)	15.551	0.000
0-back target RT, ms	538.744(115.901)	483.453(76.056)	466.884(43.372)	2.313	0.123
0-back nontarget accuracy	0.811(0.312)	0.963(0.056)	0.976(0.018)	78.512	0.000
0-back nontarget RT, ms	559.971(114.578)	506.222(96.557)	510.529(54.755)	2.866	0.239
2-back target accuracy	0.518(0.212)	0.878(0.063)	0.828(0.055)	36.652	0.000
2-back target RT, ms	755.363(158.057)	666.125(110.534)	678.427(119.951)	1.833	0.174
2-back nontarget accuracy	0.691(0.303)	0.913(0.073)	0.917(0.086)	42.618	0.000
2-back nontarget RT, ms	622.552(162.821)	690.516(130.120)	677.093(94.103)	0.845	0.655

WAIS-inf: WAIS-information, WAIS-Dig: WAIS-Digital symbol

Table 3: Significant between-group difference in activation during WM task in BD patients with deficit compared to HC

Cerebral region	BA	Side	T-score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients with deficit> healthy controls							
Middle Temporal Gyrus	38	R	3.74	10	30	5	-41
Middle Temporal Gyrus	38	L	4.53	98	-36	14	-41
Middle Temporal Gyrus	38	L	3.96		-33	5	-38
Fusiform_L (aal)		L	3.32		-30	-4	-32
Thalamus_L(aal)		L	3.46	18	-21	-19	4
Putamen_L (aal)		L	3.13		-30	-16	-2
Postcentral_R (aal)	1	R	4.38	312	54	-19	52
Postcentral_R (aal)	6	R	4.34		63	-10	37
Rolandic_Oper_R (aal)		R	3.80		45	-7	10
Supp_Motor_Area_R (aal)	6	R	3.37	17	6	-7	64
bipolar disorder patients with deficit< healthy controls							
Lateral Ventricle//undefined		R	-3.62	21	30	-46	1
Calcarine_R (aal)		R	-2.96		30	-55	10
Frontal_Mid_L(aal)	9	L	-3.27	11	-33	11	34

Supp_Motor_Area_R(aal)	6	R	-3.24	11	12	20	52
Frontal_Sup_Medial_L (aal)	8	L	-3.79	11	-3	29	52

Table 4: Significant between-group difference inactivation during WM task in BD patients without deficit compared to HC

Cerebral region	BA	Side	T-Score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients without deficit > healthy controls							
Postcentral_R (aal)	1	R	3.48	18	54	-19	55
bipolar disorder patients without deficit < healthy controls							
Lateral Ventricle		R	-4.08	118	30	-43	1
Temporal Lobe		R	-3.88		42	-49	-2
Fusiform_R (aal)		R	-3.27		21	-46	-11
Precuneus	31	L	-3.17	52	-21	-73	16
Lingual_L (aal)		L	-3.16		-15	-64	1
Calcarine_R (aal)		R	-2.97	17	21	-61	7
Occipital_Sup_L (aal)	19	L	-3.63	38	-18	-94	19
Occipital_Mid_L (aal)		L	-3.48		-18	-94	10
Cuneus_R (aal)	19	R	-3.15	36	6	-82	28
Cuneus_R (aal)		R	-2.91		21	-70	22
Occipital Lobe		R	-2.83		27	-70	13
Occipital_Mid_L (aal)		L	-3.13	10	-24	-61	28
Parietal_Sup_R (aal)		R	-3.40	21	15	-67	61

Table 5: Significant between-group difference in activations during WM task in BD patients with deficit compared to BD patients without deficit

Cerebral region	BA	Side	T-Score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients with deficit> bipolar disorder patients without deficit							
Parietal Lobe		R	3.09	23	24	-40	49
Precentral_R (aal)		R	3.02		33	-28	58
Postcentral_R (aal)		R	2.88		30	-28	46
bipolar disorder patients with deficit < bipolar disorder patients without deficit							
Frontal_Mid_R (aal)	BA10	R	-3.63	19	30	56	19
Temporal_Mid_L (aal)		L	-3.49	11	-51	-40	13

Table 1: BD patients and HC demographics characteristics

	Patients With Deficits (n=14)	Patients without Deficits (n=13)	Healthy Controls (n=13)	statistical analysis	
				F/χ^2	p
Gender(Male/Female)	6/8	6/7	4/9	0.714	0.700
Age (SD), year	26.714 (5.060)	27.154 (4.318)	24.154 (4.413)	1.609	0.214
Education (SD), year	14.429 (2.954)	14.000 (2.345)	13.538 (2.295)	0.407	0.668

SD=Standard Deviation

Table 2: Clinical and neuropsychological characteristics

	Patients with Deficits (n=14)	Patients without Deficits (n=13)	Healthy Controls (n=13)	Statistical Analysis	
				$F/\chi^2/Z$	*p*
Illness duration (SD), months	49.443 (38.302)	54.054 (49.932)	-	-0.270	0.789
HAMD score (SD)	13.930 (10.111)	13.615 (10.469)	-	-0.170	0.865
YMRS score (SD)	5.000 (8.029)	3.308 (5.879)	-	-0.494	0.621
HAMA score (SD)	12.143 (8.132)	10.692 (9.724)	-	0.422	0.677
Cpz100 (SD)	167.855 (223.462)	112.821 (176.665)	-	-0.814	0.416
WAIS-inf (SD)	18.964 (4.630)	19.231 (3.919)	19.615 (4.104)	0.080	0.923
WAIS-Dig (SD)	72.357 (18.521)	76.000 (15.748)	94.077 (12.731)	7.075	0.003
0-back target accuracy	0.866 (0.168)	0.950 (0.068)	0.979 (0.025)	15.551	0.000
0-back target RT, ms	538.744 (115.901)	483.453 (76.056)	466.884 (43.372)	2.313	0.123
0-back nontarget accuracy	0.811 (0.312)	0.963 (0.056)	0.976 (0.018)	78.512	0.000
0-back nontarget RT, ms	559.971 (114.578)	506.222 (96.557)	510.529 (54.755)	2.866	0.239
2-back target accuracy	0.518 (0.212)	0.878 (0.063)	0.828 (0.055)	36.652	0.000
2-back target RT, ms	755.363 (158.057)	666.125 (110.534)	678.427 (119.951)	1.833	0.174
2-back nontarget accuracy	0.691 (0.303)	0.913 (0.073)	0.917 (0.086)	42.618	0.000
2-back nontarget RT, ms	622.552 (162.821)	690.516 (130.120)	677.093 (94.103)	0.845	0.655

WAIS-inf: WAIS-information, WAIS-Dig: WAIS-Digital symbol

Table 3: Significant between-group difference in activation during working memory task in bipolar disorder patients with deficit compared to healthy controls

Cerebral region	BA	Side	T-score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients with deficit > healthy controls							
Middle Temporal Gyrus	38	R	3.74	10	30	5	-41
Middle Temporal Gyrus	38	L	4.53	98	-36	14	-41
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bipolar disorder patients with deficit < healthy controls							
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Frontal_Mid_L(aal)	9	L	-3.27	11	-33	11	34

Supp_Motor_Area_R(aal)	6	R	-3.24	11	12	20	52
Frontal_Sup_Medial_L (aal)	8	L	-3.79	11	-3	29	52

Table 4: Significant between-group difference in activation during working memory task in bipolar disorder patients without deficit compared to healthy controls

Cerebral region	BA	Side	T-Score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients without deficit > healthy controls							
Postcentral_R (aal)	1	R	3.48	18	54	-19	55
bipolar disorder patients without deficit < healthy controls							
Lateral Ventricle		R	-4.08	118	30	-43	1
Temporal Lobe		R	-3.88		42	-49	-2
Fusiform_R (aal)		R	-3.27		21	-46	-11
Precuneus	31	L	-3.17	52	-21	-73	16
Lingual_L (aal)		L	-3.16		-15	-64	1
Calcarine_R (aal)		R	-2.97	17	21	-61	7
Occipital_Sup_L (aal)	19	L	-3.63	38	-18	-94	19
Occipital_Mid_L (aal)		L	-3.48		-18	-94	10
Cuneus_R (aal)	19	R	-3.15	36	6	-82	28
Cuneus_R (aal)		R	-2.91		21	-70	22
Occipital Lobe		R	-2.83		27	-70	13

Occipital_Mid_L (aal)	L	-3.13	10	-24	-61	28
Parietal_Sup_R (aal)	R	-3.40	21	15	-67	61

Table 5: Significant between-group difference in activations during working memory task in bipolar disorder patients with deficit compared to bipolar disorder patients without deficit

Cerebral region	BA	Side	T-Score		Center of mass		
			Max.	Size	x	y	z
bipolar disorder patients with deficit > bipolar disorder patients without deficit							
Parietal Lobe		R	3.09	23	24	-40	49
Precentral_R (aal)		R	3.02		33	-28	58
Postcentral_R (aal)		R	2.88		30	-28	46
bipolar disorder patients with deficit < bipolar disorder patients without deficit							
Frontal_Mid_R (aal)	BA10	R	-3.63	19	30	56	19
Temporal_Mid_L (aal)		L	-3.49	11	-51	-40	13

Figure

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