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Altered functional connectivity among frontal eye fields, thalamus and cerebellum in bipolar disorder

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Summary

Objectives: The aim of our study is to evaluate functional connectivity of cerebello-thalamo-cortical networks linking frontal eye fields (FEF) and cerebellar regions associated with oculomotor control: nodulus (X), uvula (IX), flocculus (H X) and ventral paraflocculus (H IX) in bipolar disorder (BD) with the use of resting state functional magnetic resonance imaging (rsfMRI).

Methods: 19 euthymic BD patients and 14 healthy controls underwent rsfMRI examination. Functional connectivity between bilateral FEF, thalamus and cerebellar regions associated with oculomotor control was evaluated.

Results: BD patients revealed decreased functional connectivity between following structures: right FEF and bilateral thalamus, flocculus (H X), uvula (IX); right thalamus and right FEF; between right flocculus (H X) and right FEF, left thalamus; between left thalamus and bilateral FEF and right flocculus (H X).

Conclusions: BD patients presented decreased functional connectivity among FEF, thalamus and cerebellar structures associated with eye movements control. Oculomotor evaluation of BD patients assessed with rsfMRI may help to determine whether altered functional connectivity observed in our study is associated with eye movements deficits in BD.

Key words: vermin, neuroimaging, affective disorders

Introduction

Bipolar disorder (BD) is a chronic mental illness characterized by occurrence of recurrent depressive, hypomanic, manic or mixed episodes. It has been shown that in BD there are cognitive impairments that can also be demonstrated between affective episodes [1–3]. Furthermore, growing number of research results indicate that patients present significant motor deficits in the form of neurological soft signs [4–6], implicit motor learning impairment [2] and eye movement deficits [7]. A systematic review of oculomotor studies indicates that BD patients present significant impairments during tasks evaluating: smooth pursuits eye movements (i.e., tracking a moving target); fixation tasks and antisaccade tests, during which subjects are instructed to make a saccade away from the target [7]. Presence of such deficits in BD has been associated with structural and functional disturbances of central nervous system regions subserving oculomotor control [7, 8].

Magnetic resonance imaging (MRI) studies performed on the group of 6,503 participants have shown, among others, significant grey matter reductions in frontal lobes of BD patients [9, 10]. The frontal eye fields (FEF) found in these regions are the structures responsible for the conscious control of eye movements [11]. FEF are active during functional MRI (fMRI) studies evaluating smooth pursuit eye movements or antisaccades [12]. Resting state fMRI (rsfMRI) studies measure hemodynamic brain response by blood-oxygen-level dependent (BOLD) contrast, when a participant lies without performing any specific task. rsfMRI allows to visualize brain regions characterized by synchronized hemodynamic response associated with their resting neural activity. The value of correlation coefficient between the BOLD contrast of these brain regions is the measure of their functional connectivity [13].

rsfMRI studies have shown decreased amplitude of low-frequency fluctuation (ALFF) in the area of FEF, supplementary eye fields and thalamus in the group of patients with BD with psychotic symptoms in the past, schizoaffective disorder and schizophrenia [14]. Decreased functional connectivity of FEF was associated with error rates in antisaccade task [14]. Xu et al. [15] have shown that increased ALFF in FEF, prefrontal cortex regions, insula and putamen differentiates BD patients from healthy controls.

Another important structure involved in the control of eye movements is the cerebellum, especially regions of the nodulus (X), uvula (IX), flocculus (H X), and ventral paraflocculus (H IX) [11,16]. fMRI examination of BD patients during smooth pursuit eye movement task showed hyperactivity of the uvula in the group of patients [8]. Structural studies have shown decreased volume of the cerebellar vermis in BD patients [17–19]. Growing number of studies indicate that the role of the cerebellum is not limited to motor functions [20]. Numerous connections of this structure with cortical areas, in the form of cerebello-thalamic-cortical tracts, are associated with the cerebellar control of cognitive functions and emotions [21–25]. Damage of those connections are associated with the presence of emotional disorders

[26, 27]. The results of the studies carried out so far point out the role of deficits in those networks in mental illnesses, i.e., BD, schizophrenia, depression, and autism spectrum disorders [28–31].

It has been shown that the regions of the cerebellum associated with the control of eye movements create connections to FEF through the dentate nucleus and the thalamus [11, 32]. The aim of our study is to evaluate the activity of the cerebello-thalamo-cortical network connecting FEF and oculomotor structures of the cerebellum in BD patients with the use of rsfMRI. BD patients reveal disturbed structures of aforementioned networks [17–19, 33], oculomotor deficits [7], and associations between decreased functional connectivity of FEF and eye movement disorders [14]. Thus, we hypothesize that BD patients show decreased functional connectivity between FEF, thalamus and cerebellar regions associated with oculomotor control, particularly: nodulus (X), uvula (IX), flocculus (H X) and ventral paraflocculus (H IX).

Methodology

38 participants were enrolled to this study. We have recruited 21 euthymic BD patients diagnosed according to DSM-5 and ICD-10. Inclusion criterion was treatment with antipsychotic drugs from the group of dibenzoxazepine: clozapine, olanzapine or quetiapine. Chosen antipsychotics provided comparable profile of neurological side effects. The aforementioned criterion was chosen due to the participation of the subjects in ongoing oculometric studies. Additionally, treatment with valproic acid was accepted in the BD group. Exclusion criteria were as follows: (a) history of alcohol or drug abuse; (b) severe, acute or chronic neurological and somatic diseases; (c) severe personality disorders; (d) or treatment other than mentioned in inclusion criteria; (e) patients treated with lithium were excluded from the study, since, as described in Chrobak et al. [34] – it may affect cerebellar structure and function; (f) diseases, injuries or underwent eye surgeries; (g) contraindications for magnetic resonance imaging.

The second examined group consisted of 17 healthy controls, matched in terms of sex and age with BD patients. Exclusion criteria for the control group were identical to the criteria for BD patients. In addition, participants with a diagnosis of mental illness or the history of mental illness in the first-degree relatives were excluded from the study. All participants signed a written informed consent prior to the assessment. The study was approved by the Jagiellonian University Bioethics Committee.

Due to the occurrence of head movements significantly interfering with the interpretation of rsfMRI results, it was decided to exclude the results of two participants from the BD group and three healthy controls. As a result, 33 subjects were examined, 19 BD patients and 14 healthy controls. The description of the studied group is presented in Table 1.

Table 1. **The description of the studied group**

	BD group	Control group
Age (years, mean (SD))[a]	36 (6.4)	35 (10.2)
Sex (men/women)[b]	7/12	5/9
BD type (I/II)	10/9	-
Number of psychotic BD patients	5	-
Medication	Number of patients (%)	Dose (mean mg (SD))
Quetiapine	6 (32%)	367.7 (233.8)
Olanzapine	7 (37%)	9.6 (4.7)
Valproic acid	9 (47%)	977.7 (334.6)

BD – bipolar disorder; SD – standard deviation; [a)] T-test, ns.; [b)] Chi-square test, ns.

MRI data acquisition

MRI data were acquired using a 3T Siemens Skyra MR system. Sagittal T1 MPRAGE sequence was used in order to obtain anatomical images. Total of 13-minute functional resting state BOLD images were acquired using an echo planar imaging sequence with the following parameters: TR = 2060 ms; TE = 27 ms; FOV = 256 mm; slice thickness = 3 mm; voxel size = 4 mm^3. A total of 39 interleaved transverse slices and 400 volumes were acquired. During resting state procedure, subjects were instructed to keep their eyes open, to think of nothing particular, and not to fall asleep. Due to the limited access to the MRI scanner, subjects were tested at different times of the day, ranging between 12 pm and 9 pm.

Imaging data processing

The rsfMRI data processing was performed using MATLAB v. 2016a and SPM12 software. All functional images were slice-time corrected and realigned, and 12 rigid-body parameters were estimated. ART-based software package was used in order to identify outlier scans. The data were then normalized to MNI space. No smoothing was used due to reports on the risk of detecting the false connectivity values [35]. Component-based noise correction (CompCor) method was used for extraction of 5 principal components from WM and CSF identified via a segmentation of the anatomical images.

Functional connectivity analysis

Pre-processed data underwent connectivity analyses using CONN v17.f [36]. Further steps involved removing confounding variables using linear regression (white

matter, cerebrospinal fluid and outlier volumes) and using a band-pass filter in the range of 0.008–0.09 Hz to remove frequencies unrelated to resting brain activity.

First level functional connectivity analysis was performed using ROI-to-ROI approach. Following bilateral brain regions were selected as ROIs (Region of Interest – ROI): thalamus, cerebellum 10 (flocculus – H X), cerebellum 9 (ventral paraflocculus – H IX), vermis 9 (uvula – IX), and vermis 10 (nodulus – X), which were defined based on the Harvard-Oxford atlas, as well as left and right FEF, defined based on work of Luna et al. [37]. After that, 12 x 12 connectivity matrix consisting of bivariate Pearson correlation coefficients was created and raw correlation values were then transformed to Fisher Z-scores.

First-level connectivity maps were then used in a second-level analysis where *t*-test for independent samples implemented in CONN was performed in order to investigate differences in functional connectivity between patients and controls.

We predicted smaller functional connectivity between ROIs in bipolar group, therefore one-tailed testing was used. The significance level was set at FDR-corrected $p < 0.005$.

Results

We found weaker functional connectivity in patients compared to controls between the right FEF seed and bilateral thalamus, bilateral flocculus (H X) as well as uvula (IX). Weaker functional connectivity was found also between the left thalamus and right flocculus (H X) (Figure 1). Detailed results are displayed in Table 2.

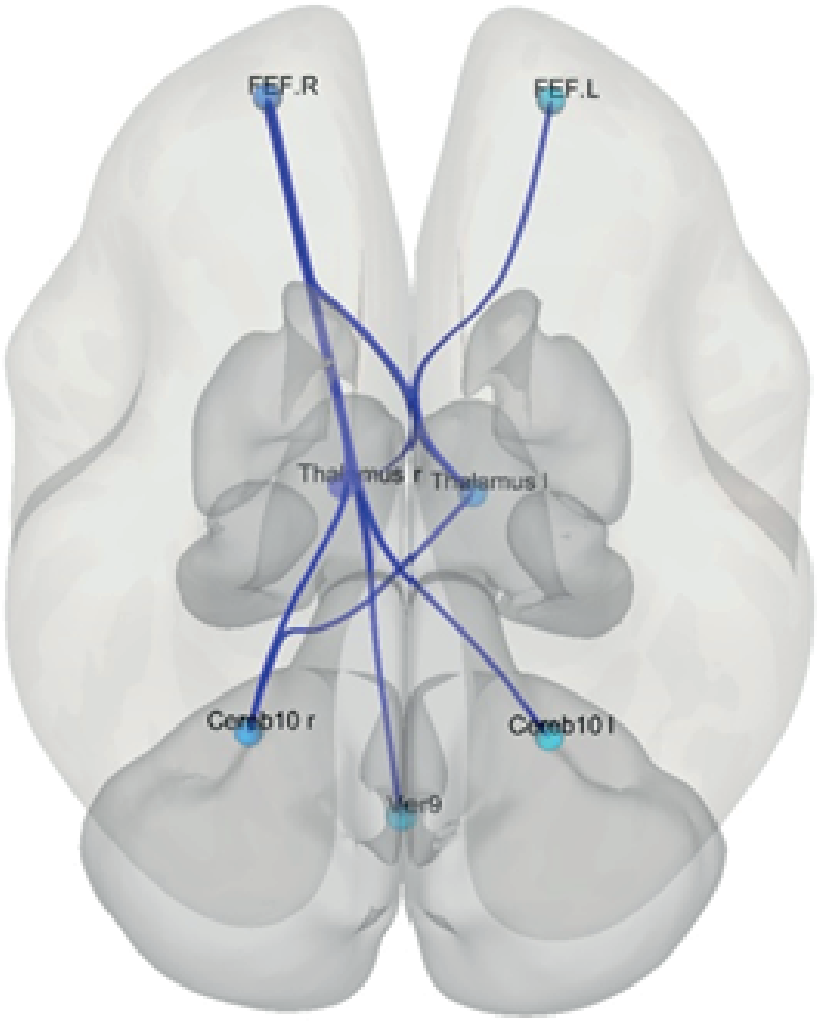
Table 2. **Functional connectivity differences among selected regions of interest between bipolar disorder patients and healthy controls**

ROI	T	p-unc	p-FDR
Seed FEF.R			
FEF.R – Thalamus R	-4.18	<0.001	0.001
FEF.R – Cerebellum10 R	-3.43	0.0009	0.0031
FEF.R – Thalamus L	-3.36	<0.001	0.0031
FEF.R – Cerebellum10 L	-2.02	0.026	0.0483
FEF.R – Vermin 9	-2.01	0.0268	0.0483
Seed Thalamus L			
Thalamus L – FEF.R	-3.36	0.001	0.0094
Thalamus L – Cerebellum10 R	-2.99	0.0027	0.0123
Seed Thalamus R			
Thalamus R – FEF.R	-4.18	<0.001	0.001
Seed Cerebellum10 R			

table continued on the next page

Cerebellum10 R – FEF.R	-3.43	<0.001	0.0079
Cerebellum10 R – Thalamus L	-2.99	0.0027	0.0123

ROI – region of interest; t – t-statistics; p-unc – uncorrected p value; p-FDR – p values with false discovery rate correction; R – right side; L – left sight; FEF – frontal eye fields; cerebellum 10 – flocculus (H X); cerebellum 9 – ventral paraflocculus (H IX); vermis 9 – uvula (IX), vermis 10 – nodulus (X)



Ver9 – vermin 9 (uvula – IX), Cereb10 – Cerebellum 10 (flocculus – X), FEF – frontal eye field

Figure 1. **Altered functional connectivity among frontal eye fields, thalamus and cerebellum in bipolar disorder**

Discussion

To our best knowledge, we have conducted the first study evaluating the functional connectivity among FEF, thalamus and structures of the cerebellum related to eye movements in BD. Patients showed significantly decreased functional connectivity between these structures, precisely between: right FEF and bilateral thalamus and bilateral flocculus (H X) and uvula (IX); between right thalamus and right FEF; between right flocculus (H X) and right FEF and left thalamus; and between left thalamus and bilateral FEF and right flocculus (H X). Brain regions with weaker functional connectivity in BD identified by our work directly translate into lower, compared to healthy participants, correlation coefficient between time series among distinct atomically separated brain regions [13].

The results of our research refer to the observations of FEF dysfunction in BD patients. Xu et al. [15] have shown increased ALFF in selected frontal regions, including FEF in BD patients compared with healthy controls. Lencer et al. [14] have shown decreased ALFF in bilateral FEF, supplementary eye fields, thalamus, left orbitofrontal cortex and left superior temporal gyrus in the heterogenic group of patients with the diagnosis of schizophrenia, schizoaffective disorder or psychotic BD. It has been shown that error rate during antisaccade task is negatively associated with the decrease of functional connectivity between the left FEF, left inferior parietal gyrus, bilateral precuneus, left middle temporal gyrus and right fusiform gyrus, and with the increased functional connectivity between FEF and left angular gyrus. A relationship between the number of errors in the antisaccade test and functional connectivity between the thalamus and regions of supplementary eye field, right parahippocamp and left temporal gyrus, has also been found. In opposite to our findings, Lencer et al. [14] showed increased functional connectivity between the right FEF and bilateral thalamus. Differences between obtained results may be due to heterogeneous group of patients in the aforementioned study [14], a larger number of subjects and a greater number of analyzed structures. Nevertheless, these results also indicate that altered functional connectivity of FEF may differentiate patients with psychotic BD, schizophrenia, schizoaffective disorder and healthy individuals, and may be associated with oculomotor disorders.

To our best knowledge, for the first time we showed reduced functional connectivity between the right FEF and bilateral flocculus (H X) and uvula (IX) as well as between the right flocculus (X) and right FEF. It has been proposed that networks between FEF, thalamus and oculomotor cerebellar structures may constitute a feedback system whose task is to estimate the velocity of the observed target and to adjust accordingly the velocity of eye movements [11]. Martin et al. [8] showed altered activation of the uvula (IX) during smooth pursuit eye movement task in BD patients. Growing number of studies indicate disturbances of cerebellar functional connectivity with cortical and subcortical structures in BD [38–40]. Our results suggest that altered activity of this region may be associated with dysfunction of its functional connectivity with

FEF during resting state. Currently, our research group is conducting fMRI study of BD patients during smooth pursuit eye movements. We hypothesize that the altered functional connectivity of cerebello-thalamo-cortical networks may be associated with oculomotor deficits and impaired activity of the central nervous system during smooth pursuit eye movements.

The limitations of our study are as follows: (a) a relatively small number of subjects, additionally limited by the necessity to exclude some participants due to the occurrence of excessive head motions during the examination; (b) heterogeneity of BD patients group, consisting of BD I and BD II, and patients with a history of psychotic symptoms; (c) the use of pharmacotherapy in the studied group of patients, which could affect the results; (d) the small size of the sample prevented comparisons between different BD types or taken medication; (e) the lack of oculomotor data makes it impossible to directly link functional connectivity alterations of structures involved in the control of eye movements with the presence or absence of oculomotor deficits in the studied group; (f) Due to the limited access to the MRI scanner, subjects were tested at different times of the day, ranging between 12 pm and 9 pm (low number of participants prevented controlling the impact of this variable on obtained results).

Presented results indicate that euthymic BD patients show reduced functional connectivity among FEF, thalamus and structures of the cerebellum associated with oculomotor control compared to the healthy participants. Our observations require replication on a larger number of subjects, evaluating the role of BD type and the effect of medication. Oculometric evaluation of participants evaluated with the use of rsfMRI could help to determine whether the functional abnormalities observed in our study are associated with the eye movement deficits in BD.

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