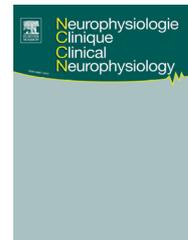Disponible en ligne sur

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ORIGINAL ARTICLE

Visual event-related potentials in external emotional conditions in bipolar disorders I and II

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Summary
Objectives. — Mutual influences of cognitive and emotional functions occur in bipolar disorder, but specific alterations in relation to external emotional stimuli in bipolar I (BD I) and II (BD II) subtypes remain unknown. This study aimed to explore the effects of external emotional stimuli on cerebral attentional function in BD I and BD II.
Methods. — We tested visual oddball event-related potentials (ERPs) during various external emotional stimuli (Disgust, Fear, Erotica, Happiness, Neutral and Sadness) in 31 patients with BD I, 19 BD II and 47 healthy volunteers. Participants' concurrent affective states were also evaluated.
Results. — The ERP N2 latencies during Fear and Happiness were prolonged, P3 amplitudes during Disgust and Erotica were decreased in BD I; P3 amplitudes during Disgust, Erotica, Happiness and Neutral conditions were decreased in BD II. Increased frontal and parietal and decreased temporal and occipital activations were found in BD I, while increased occipital and parietal and decreased frontal and limbic activations in BD II in relation to different external emotions. ERP components were not correlated with concurrent affective states in patients.
Conclusions. — Automatic attention during Happiness and Fear, and voluntary attention during Disgust and Erotica conditions were impaired in BD I; and voluntary attention during Disgust, Happiness, Erotica and Neutral conditions was impaired in BD II. Our study illustrates different patterns of visual attentional deficits associated with different external emotional stimuli in BD I and BD II.

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Introduction

Bipolar disorder, principally including types I (BD I) and II (BD II), is one of the most debilitating illnesses worldwide [24], being characterized by affective fluctuations from highs (mania or hypomania) to lows (depression) [2]. BD I is characterized by more anxious, irritable and impulsive symptoms [38], while BD II is more depressive [37], with suicidal ideas and behaviors [40]. However, effects of treatment targeting affective symptoms of individual patients vary considerably between BD I and BD II [16], which might be related to differences in cognitive processes under different environmental conditions of emotional stimuli.

The fundamental cognitive function of attention is impaired in bipolar disorder irrespective of the (hypo)manic, depressed, or euthymic phrase [17], but differences in attentional problems between BD I and BD II remain unclear. There are two main attentional systems in healthy people: one is the dorsal network which involves the superior frontal cortex and parts of the intraparietal cortex, in charge of top-down, goal-directed selective process; the other is the ventral network involving the inferior frontal cortex and temporoparietal cortex, responsible for bottom-up detection of salient or unexpected stimuli [10]. Compared to healthy volunteers, decreased activity of anterior temporal and lateral frontal regions during voluntary selective attention was found in BD I in a neuroimaging study [9], and prolonged latency and decreased amplitude of auditory mismatch negativity at the frontal electrodes during automated, pre-attentive cerebral processing were found in BD II in an event-related potential (ERP) study [3]. Neuropsychological studies have also shown decreased psychomotor speed in bipolar disorder [13], especially BD I [22].

There is also some evidence showing differences of cortical-brainstem or peripheral physiological reactions under conditions of external emotional stimuli in BD I and BD II. One study exploring the inhibitory brainstem reflex revealed prolonged latency of the second exteroceptive suppression period of temporalis muscle activity (ES2) under an external erotica stimulation in BD I, but prolonged ES2 latencies under disgust and happiness, and shortened ES2 durations under disgust, happiness and sadness conditions in BD II [48]. One study exploring the excitatory brainstem reflex disclosed smaller areas under the curve of the second component of the blink reflex under conditions of disgust, fear, and happiness in BD II compared to BD I [49]. Another study detected higher heart rate in BD I when an external fearful stimulus was presented immediately after external neutral stimuli; in addition, quicker eyeball movement in BD I than BD II occurred under the sadness condition immediately following disgust [30].

Behaviorally, emotional stimuli modulate attention or cognition in bipolar disorder. For instance, fear was shown to influence attentional state in subjects with bipolar disorder regardless of their manic, depressed, or euthymic state [15]. BD I had happy scene-related eyeball movement bias during initial orientation, but impairments in recognizing facial fear, disgust, and sadness [15,29]. Moreover, bipolar disorder subjects (mainly BD II) in depression overidentified negative facial emotions and poorly recognized positive ones [12]. These studies suggested that positive emotional stimuli predominantly affect automatic detection and negative stimuli predominantly influence voluntary processing stages in BD I, while both positive and negative stimuli affect voluntary processing more in BD II. Furthermore, neuroimaging studies revealed poor controllability of frontal regions, such as the inferior frontal or ventrolateral prefrontal, dorsolateral and medial prefrontal cortices, over limbic and emotion-related structures during emotional processing and regulation in bipolar disorder [23,39]. Literature also showed that these areas play an important role in attentional processes in healthy people [10]. However, the exact effects of external emotions on the early cognitive or attentional processing stages and their cerebral activations, as well as possible differences between BD I and BD II, so far remain unclear.

Visual oddball ERPs might be a candidate methodology for elucidating effects of external emotional stimuli on early attentional processes. The visual N1 and N2 components reflect encoding of elementary stimulus features [19,33] and involuntary attention to target or deviant stimulus [18,31] respectively, while the visual P3 reflects central resource utilization, that is, voluntary attention and evaluation of a stimulus [20,25]. Thus, in the current study, we tested visual ERPs in BD I and BD II under external emotional conditions of disgust, fear, sadness, erotica, and happiness. Based on previous documentation, we hypothesized that:

- BD I would have abnormal ERP components reflecting automatic attention under happiness or erotica conditions, and those reflecting voluntary attention under disgust, fear, or sadness, while BD II would have abnormal components reflecting voluntary attention under most external emotions;
- these abnormalities would have different cerebral activations under different external emotions in BD I and BD II, especially in frontal regions;
- and that these abnormalities would be associated with the concurrent affective states of BD I and BD II.

Methods

Participants

We enrolled 31 patients with BD I (16 men and 15 women; aged 19.81 years ± 1.68 S.D., ranged 18 ∼ 24 years), 19 BD II (7 men and 12 women; aged 19.26 ± 1.88, ranged 18 ∼ 26), and 47 healthy volunteers (controls; 18 men and 29 women; aged 19.85 ± 1.83, ranged 18 ∼ 25). All participants had normal or corrected-to-normal visual acuity, were right-handed, had received more than 12 years of education, and were free from any drug or alcohol for at least 72 hours prior to the test. No significant difference was found among groups regarding age (F [2,94] = .78, mean square effect (MSE) = 2.50, P = .462), gender (χ^2 = 1.34, df = 2, P = .512) or education level (χ^2 = 2.33, df = 2, P = .312). All patients were diagnosed by an experienced psychiatrist (WW) according to the DSM-5 criteria [2], and were confirmed to have no other psychiatric problems, such as personality disorder, substance use disorder, etc., and to have no brain lesions as determined using computerized tomography or magnetic resonance imaging scans. The study was carried out in

accordance with the Declaration of Helsinki as revised in 1989, approved by a local ethics committee and all participants gave their written informed consent to participate in this study.

Questionnaires

Sitting in a quiet room, participants were asked to answer the following 3 questionnaires.

The Mood Disorder Questionnaire (MDQ)
The MDQ is a self-report assessing the presence of symptoms and behaviors related to mania or hypomania [21]. It consists of three parts comprising 13 forced-choice (yes or no) questions, one question to determine whether two or more symptoms have been experienced at the same time, and one question to determine the extent to which symptoms have caused functional impairment on a scale ranging from ''no problems'' to ''serious problems''. The MDQ was demonstrated to be valid with an internal reliability of 0.79 in a sample of Chinese individuals [45].

The Hypomania Checklist-32 (HCL-32)
The HCL-32 is a self-assessment instrument with 32 forced-choice (yes or no) items describing hypomanic symptoms of emotions, thoughts, or behaviors, and questions regarding duration, impact of family, social and work life, or people's reactions [4]. The HCL-32 was demonstrated to be valid with an internal reliability of 0.88 in a sample of Chinese individuals [46].

The Plutchik-van Praag Depression Inventory (PVP)
The PVP is a self-report questionnaire including 34 items for detecting depressive symptoms [34]. Each item has three scale points (0, 1, 2) corresponding with increasing depressive tendencies. Participants have ''possible depression'' if they score between 20 and 25, or ''depression'' if they score above 25. The internal reliability of PVP was 0.94 in a sample of Chinese individuals [43].

External emotional stimuli. The external emotional stimuli, being composed of pictures and sounds of the same domain saturated with high arousal levels of emotional valence, were presented by *eevoke*™ software (ANT Software B.V., Enschede, The Netherlands). Pictures were from the International Affective Picture System [28], which were horizontally presented (768 × 512 pixels), sustaining about 19.8° × 13.5° of visual angles. Sounds were from the International Affective Digitized Sounds database [7], which were 40—50 dB in intensity, delivered through a headphone. The six emotional situations were Disgust (picture code: 9325; sound code: 255), Fear (3053; 275), Erotica (4680; 205), Happiness (2040; 110), Neutral (5390; 172) and Sadness (2205; 295).

ERP designs and recordings. Participants were seated in a dimly lit room at 100 cm from a computer screen. There were six successive sessions of experiment, with a two-minute interval between two sessions. Each session started with a fixation cross in the middle of a black background for 3000 ms, followed by 150 ERP trials (each trial lasting 2400 ms), with an inter-trial interval of 1200 ∼ 1500 ms. Within each ERP trial, there was an external emotional stimulus of either Disgust, Fear, Erotica, Happiness, Neutral, or Sadness (2000 ms each; emotion presentation order randomized between participants); and each emotion presentation was followed by either a standard (400 ms, a square of 40 mm × 40 mm) or target (400 ms, a circle of 40 mm in diameter) stimulus in the middle of the black background. The standard stimuli were delivered 120 times (80%) and the target stimuli were 30 times (20%) in a randomized order. Participants were asked to actively respond to the circle picture (target) by pressing a button with their right index finger as soon as possible.

EEG waves were recorded with 32 electrodes embedded in an elastic electrocap (Electro-Cap International, Inc., Eaton, OH, USA) according to the 10-20 International System, with a sampling rate of 1024 Hz, and were amplified by a DC amplifier (the ANT amplifier, Enschede, The Netherlands). The impedance of each electrode was kept below 10 kΩ. These recordings were made with an average reference and then referred again off-line to the average activity of the two mastoid electrodes (M1 and M2). Bipolar recordings of the electro-ocular activity were made with electrodes placed at the outer canthus and supraorbitally to the right eye. Potentials were analyzed offline with ASA software (ANT Software B.V., Enschede, The Netherlands), using a band-pass of .01 ∼ 30 Hz. The sampling epoch was 100 ms pre-stimulus and 600 ms post-stimulus. Any sweep in which the EEG exceeded ± 70 μv was excluded from averaging.

ERP waves were analyzed in terms of peak latency and baseline-to-peak amplitude determined by visual inspection. Latency ranges designated for potentials were 70 ∼ 200 ms for N1, 180 ∼ 400 ms for N2, and 300 ∼ 540 ms for P3. Moreover, the reaction times and accuracies to target in each participant were noted.

Statistical analyses. The mean reaction times to target stimuli, as well as scale scores of MDQ, HCL-32 and PVP in the three groups were analyzed by one-way ANOVA. ERP morphology data recorded at nine electrodes in frontal, central and parietal sites, i.e., F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were selected for analyzing. The mean ERP component latencies and amplitudes at nine selected electrodes were evaluated by two-way ANOVA, group (3) × electrode (9). Once a group effect was detected, the post-hoc Bonferroni test was used to evaluate parameter effects. Moreover, significant differences with $P \leq 0.05$ at no less than three coaxial electrodes (frontal, central, posterior in lateral axis; left, midline, right in sagittal axis) were required for meaningful group effects. Relationships between ERPs and the affective scale scores were analyzed using the Pearson correlation test, and only significant correlations with $P \leq 0.01$ at no less than three coaxial electrodes were considered stable and meaningful. With the present sample size, power to detect an effect was larger than 80% at $P \leq 0.05$, based on a sample of 19 participants per group (the smallest groups in the present study).

We also reconstructed the respective 3D sources, based on data obtained at the 32 electrodes, in order to look for cerebral areas involved in the significantly different processes of target stimuli under conditions of specific external emotional stimuli in three groups. The software used for the reconstruction was the SPM12 software package, running in Matlab R2013b (Mathworks Inc. Natick, MA, USA). The figures

Table 1 Mean scores ($\pm$ S.D.) of the Mood Disorder Questionnaire, the Hypomania Checklist-32, and the Plutchik-van Praag Depression Inventory, as well as reaction times and response accuracies to target in the healthy volunteers (controls, $n = 47$), bipolar I (BD I, $n = 31$) and bipolar II (BD II, $n = 19$) disorder patients.

	HC	BD I	BD II
Mood Disorder Questionnaire	4.15 ± 2.16	9.42 ± 1.03[a]	3.58 ± 2.09[b]
Hypomania Checklist-32	15.23 ± 3.44	22.61 ± 1.98[a]	20.47 ± 2.12[a,b]
Plutchik-van Praag Depression Inventory	9.68 ± 6.03	14.71 ± 7.02[a]	26.47 ± 6.89[a,b]
Reaction time to target (ms)			
Under Disgust	490.70 ± 73.78	530.52 ± 83.53	521.63 ± 70.67
Under Erotica	510.62 ± 85.74	541.04 ± 141.36	531.70 ± 84.13
Under Fear	498.04 ± 84.57	525.55 ± 91.55	535.99 ± 82.52
Under Happiness	494.31 ± 82.04	524.89 ± 93.98	510.67 ± 59.75
Under Neutral	495.16 ± 76.93	511.42 ± 92.69	509.42 ± 73.83
Under Sadness	495.68 ± 76.96	514.29 ± 99.21	525.08 ± 81.45
Accuracy (%)			
Under Disgust	96.82 ± 3.61	94.43 ± 7.63	96.72 ± 2.49
Under Erotica	98.23 ± 2.77	96.35 ± 6.51	97.89 ± 2.31
Under Fear	98.44 ± 3.25	97.64 ± 8.62	98.77 ± 2.28
Under Happiness	99.08 ± 2.38	98.17 ± 3.09	97.74 ± 3.69
Under Neutral	98.59 ± 3.24	99.15 ± 1.71	99.28 ± 1.84
Under Sadness	99.23 ± 1.86	97.74 ± 3.49	98.61 ± 2.26

[a] $P < 0.05$ vs. control
[b] $P < 0.05$ vs. BD I.

of the averaged source map were generated using xjView (http://www.alivelearn.net/xjview).

Results

Scale and behavioral results

The mean MDQ scores were significantly different between the three groups (F [2,94] = 90.97, MSE = 313.67, $P < 0.001$, $\eta^2 = 0.66$), with BD I patients scoring higher than BD II and controls ($Ps < .001$). The mean HCL-32 scores were significantly different among the three groups (F [2,94] = 69.53, MSE = 549.19, $P < 0.001$, $\eta^2 = 0.60$), with BD I and BD II scoring higher than controls ($P < 0.001$), and BD I higher than BD II ($P < 0.05$). The mean PVP scores were also significantly different among the three groups (F [2,94] = 44.74, MSE = 1908.17, $P < 0.001$, $\eta^2 = 0.49$), with BD II scoring higher than BD I and controls ($Ps < 0.001$), and BD I higher than controls ($P < 0.05$) (see Table 1). No group effect was detected regarding reaction time (F [2,94] = 0.44 $\sim$ 2.83, MSE = 2934.70 $\sim$ 16556.70; $Ps = 0.064 \sim 0.646$) or reaction accuracy ($\chi^2 = 0.36 \sim 4.37$, $df = 2$, $Ps = 0.112 \sim 0.837$) to target under external emotion conditions (also see Table 1).

ERP data

ERP components were clearly shown in three groups of participants; those recorded under Disgust conditions are shown as examples (Fig. 1). For the sake of brevity, only latencies/amplitudes of N2 and P3 with significant group effect are presented in Table 2, the remaining data regarding N1 latencies and amplitudes to target, and part of N2 and P3 latencies and amplitudes not being presented

here (though available upon request). There were significant group effects on N2 latencies under the conditions of Fear (F [2,88] = 3.79, MSE = 38877.13, $P < 0.05$, $\eta^2 = 0.08$) and Happiness (F [2,89] = 5.10, MSE = 53519.21, $P < 0.05$, $\eta^2 = 0.10$). Post-hoc testing showed that N2 latencies under Fear at parietal electrodes (all $Ps < 0.05$), and under Happiness at central electrodes (all $Ps < 0.05$) were prolonged in BD I compared to controls. In addition, significant group effects were found for P3 amplitudes under the conditions of Disgust (F [2,86] = 6.32, MSE = 2105.98, $P < 0.05$, $\eta^2 = 0.13$), Erotica (F [2,87] = 5.45, MSE = 1521.70, $P < 0.05$, $\eta^2 = 0.11$), Happiness (F [2,90] = 5.83, MSE = 1135.33, $P < 0.05$, $\eta^2 = 0.12$), and Neutral (F [2,87] = 10.02, MSE = 1935.97, $P < 0.001$, $\eta^2 = 0.19$). Post-hoc testing showed P3 amplitudes under Disgust at all nine electrodes in BD I (all $Ps \leq 0.05$) and BD II (all $Ps < 0.05$) that were lower than those in controls. P3 amplitudes under Erotica at all nine electrodes in BD I (all $Ps \leq 0.05$) and parietal electrodes in BD II (all $Ps < 0.05$) were lower than those in controls. P3 amplitudes under Happiness at all nine electrodes in BD II (all $Ps < 0.05$) were lower than those in controls. P3 amplitudes under Neutral in BD II were lower than those in BD I at frontal and parietal electrodes (all $Ps < 0.05$) and were lower than those in controls at all nine electrodes (all $Ps \leq 0.001$).

No significant group differences were found for N1 latencies to target under all six external emotional-stimuli (F [2,90] = 0.001 $\sim$ 2.10, MSE = 6.41 $\sim$ 8182.71, $Ps = 0.128 \sim 0.999$); nor N2 latencies under Disgust, Erotica, or Sadness (F [2,89] = 0.50 $\sim$ 2.40, MSE = 7844.42 $\sim$ 24904.07, $Ps = 0.097 \sim 0.606$); nor P3 latencies under Disgust, Erotica, Happiness, Neutral, or Sadness (F [2,90] = 0.12 $\sim$ 0.65, MSE = 2243.36 $\sim$ 10762.51, $Ps = 0.523 \sim 0.891$). There were no group differences among N1 amplitudes to target under conditions of Disgust, Erotica, Happiness, Neutral, or Sadness

Table 2 N2 latencies (mean ± S.D.) under Fear and Happiness and P3 amplitudes under Disgust, Erotica, Happiness and Neutral in the healthy volunteers (controls, $n = 47$), bipolar I (BD I, $n = 31$) and bipolar II (BD II, $n = 19$) disorder patients. Only part of the data are presented here, the remaining data being available upon request.

		Controls	BD I	BD II
N2 latency (ms)				
Fear	F3	285.80 ± 39.67	304.54 ± 30.38	303.55 ± 53.84
	Fz	288.27 ± 42.31	308.55 ± 29.92	307.37 ± 55.40
	F4	285.57 ± 41.61	303.57 ± 28.78	304.26 ± 56.83
	C3	279.03 ± 37.74	299.41 ± 32.99	301.39 ± 36.03
	Cz	283.24 ± 38.80	305.63 ± 29.95	288.89 ± 41.22
	C4	279.76 ± 39.65	300.92 ± 33.96	302.96 ± 43.94
	P3	272.14 ± 37.56	297.74 ± 32.96[a]	279.36 ± 40.34
	Pz	271.12 ± 37.71	299.10 ± 36.16[a]	270.99 ± 43.31
	P4	279.26 ± 35.86	302.04 ± 33.26[a]	284.99 ± 45.22
Happiness	F3	284.69 ± 42.55	305.50 ± 34.99	310.12 ± 46.54
	Fz	292.28 ± 41.98	312.57 ± 33.19	318.81 ± 42.94 [a]
	F4	285.32 ± 40.21	306.97 ± 33.85	315.10 ± 49.60 [a]
	C3	277.80 ± 42.46	310.73 ± 34.09[a]	293.62 ± 36.50
	Cz	281.69 ± 41.48	315.32 ± 31.99[a]	298.20 ± 39.83
	C4	280.32 ± 42.17	306.79 ± 32.80[a]	297.73 ± 41.81
	P3	273.39 ± 42.91	296.04 ± 35.62	286.48 ± 37.59
	Pz	275.93 ± 40.59	299.00 ± 38.28[a]	285.29 ± 33.81
	P4	276.27 ± 40.06	301.02 ± 37.89[a]	288.53 ± 37.18
P3 amplitude (μv)				
Disgust	F3	8.94 ± 7.26	5.02 ± 4.26 [a]	3.92 ± 4.07[a]
	Fz	8.92 ± 7.46	5.03 ± 4.51[a]	4.64 ± 4.00[a]
	F4	9.12 ± 6.13	5.64 ± 4.69[a]	4.54 ± 4.02[a]
	C3	10.61 ± 8.27	6.53 ± 5.17[a]	5.48 ± 4.75[a]
	Cz	12.22 ± 8.99	7.64 ± 5.31[a]	6.93 ± 4.60[a]
	C4	12.22 ± 8.14	7.65 ± 5.35[a]	6.38 ± 4.28[a]
	P3	12.36 ± 8.26	8.40 ± 5.20[a]	6.76 ± 4.29[a]
	Pz	14.10 ± 8.30	9.70 ± 6.09[a]	8.47 ± 5.06[a]
	P4	12.07 ± 7.68	8.06 ± 5.81[a]	6.28 ± 4.27[a]
Erotica	F3	7.39 ± 5.53	4.17 ± 5.44[a]	4.25 ± 4.03
	Fz	7.41 ± 6.16	4.04 ± 6.26	4.48 ± 3.71
	F4	7.66 ± 5.22	4.67 ± 5.68[a]	4.20 ± 3.69
	C3	8.75 ± 6.15	5.18 ± 6.99[a]	5.02 ± 4.07
	Cz	10.07 ± 6.72	5.95 ± 7.90[a]	6.10 ± 4.20
	C4	9.76 ± 5.69	5.43 ± 7.71[a]	5.66 ± 3.72
	P3	10.47 ± 5.16	6.50 ± 7.27[a]	5.53 ± 3.34[a]
	Pz	11.84 ± 5.67	7.28 ± 8.06[a]	6.43 ± 4.82[a]
	P4	9.74 ± 5.14	5.74 ± 7.92[a]	4.84 ± 4.13[a]
Happiness	F3	9.10 ± 6.17	7.08 ± 4.59	5.26 ± 5.23[a]
	Fz	9.40 ± 6.40	6.84 ± 3.26	5.63 ± 5.05[a]
	F4	10.13 ± 8.06	7.39 ± 3.36	5.77 ± 4.45 [a]
	C3	10.67 ± 5.79	8.80 ± 3.78	6.86 ± 4.94[a]
	Cz	12.08 ± 6.76	9.79 ± 4.90	7.60 ± 5.02[a]
	C4	11.75 ± 6.48	10.26 ± 4.36	7.13 ± 4.69[a]
	P3	10.49 ± 4.20	9.60 ± 3.84	6.74 ± 4.60[a]
	Pz	13.27 ± 5.82	11.34 ± 4.78	8.09 ± 5.16[a]
	P4	10.36 ± 4.64	9.62 ± 4.22	5.36 ± 3.80[a,b]
Neutral	F3	8.28 ± 5.37	7.24 ± 4.68	2.92 ± 4.86[a,b]
	Fz	8.80 ± 5.58	7.44 ± 4.81	3.51 ± 4.83[a,b]
	F4	8.90 ± 4.68	7.45 ± 4.61	3.78 ± 4.33[a,b]
	C3	10.31 ± 5.92	8.37 ± 5.39	4.81 ± 3.81[a]
	Cz	12.10 ± 6.15	9.86 ± 6.27	5.95 ± 4.54[a]
	C4	11.26 ± 4.61	9.43 ± 5.35	5.98 ± 4.26[a]
	P3	11.26 ± 5.07	9.87 ± 5.26	4.95 ± 3.88[a,b]
	Pz	13.45 ± 5.42	11.44 ± 6.07	6.51 ± 4.00[a,b]
	P4	10.72 ± 4.40	9.28 ± 5.63	5.08 ± 4.80[a,b]

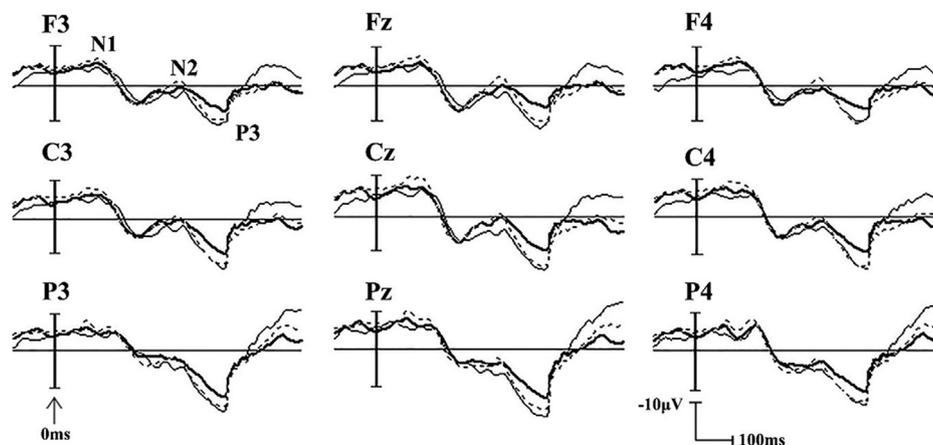[a] $P \leq 0.05$ vs controls
[b] $P \leq 0.05$ vs BD I.

Fig. 1 Grand averages of ERPs elicited by target under external emotional condition of Disgust at nine electrodes in the healthy volunteers (thin line; $n = 47$), patients of bipolar I (dashed line; $n = 31$) and bipolar II (thick line; $n = 19$) disorders.

(F [2,90] = 0.16 ~ 1.99, MSE = 12.30 ~ 873.35, Ps = 0.143 ~ 0.851); nor N2 amplitudes under all six external emotional-stimuli (F [2,90] = 0.34 ~ 2.43, MSE = 38.69 ~ 1279.59, Ps = 0.094 ~ 0.711); nor P3 amplitudes under Fear or Sadness (F [2,88] = 1.73 ~ 2.51, MSE = 333.29 ~ 1935.81, Ps = 0.087 ~ 0.183). Group differences were found for N2 latencies under Neutral (F [2,87] = 3.17, MSE =31946.37, $P < 0.05$), P3 latencies (F [2,88] = 3.56, MSE = 46297.72, $P < 0.05$) and N1 amplitudes to target (F [2,88] = 4.14, MSE = 232.58, $P < 0.05$) under Fear; however, post-hoc testing showed no significance for any three electrodes on a given axis.

Source reconstructions

After significant group effects for N2 latencies and P3 amplitudes under different external emotions, we tried to locate the possible neural sources for these components in the three groups by performing 3D source reconstruction in their corresponding time-windows.

Compared to controls, decreased activation of inferior temporal gyri under Happiness during N2 time window was found in BD I. During the P3 time window, decreased activations of inferior temporal gyri under all external emotions except Fear, increased activations of inferior frontal region under Disgust, increased inferior and middle frontal under Erotica, increased parietal under Happiness, and increased medial prefrontal and insula under Neutral conditions were found in BD I; and increased middle occipital under Disgust, decreased inferior frontal under Happiness, and increased inferior frontal, superior parietal and occipital under Neutral conditions were found in BD II. In addition, decreased activation of inferior occipital under Fear during the N2 time window, and increased activations of occipital and parietal under Erotica in the P3 time window were found in both BD I and BD II. Furthermore, a significant group effect was shown for the Neutral condition, with lower activations of bilateral postcentral gyri ($P < 0.001$), left parahippocampal gyrus ($P < 0.001$), uncus ($P < 0.001$) and inferior temporal gyrus ($P < 0.001$) in BD II than those in controls. Taking the P3 in the Disgust condition as an example, the source map for the three groups is shown in Fig. 2. For the sake of brevity, only

the inverse solute results under external emotional stimuli with significant group effects are shown in Table 3.

Relationships between ERPs and affective states

The P3 amplitudes under Disgust at frontal electrodes ($n = 47$; F3, $r = -0.40$, $P = 0.009$; Fz, $r = -0.40$, $P = 0.008$; F4, $r = -.044$, $P = 0.003$) were negatively correlated with HCL-32 in controls. No other relationship between ERP components and affective states was found in a given group.

Discussion

This is the first study addressing the specific effects of external emotional stimulation on cerebral attentional function in bipolar disorder. We found that N2 latencies under Fear and Happiness conditions were prolonged and P3 amplitudes under Disgust and Erotica decreased in BD I; while P3 amplitudes under Disgust, Erotica, Happiness and Neutral conditions were decreased in BD-II. We detected generalized abnormal activation of frontal regions especially inferior frontal gyrus, and inferior temporal, parietal, occipital, and limbic regions in bipolar disorder, as previously reported [1]. We consistently found that both BD I and BD II scored higher on MDQ, HCL-32 and PVP, similar to previous reports [44,45], but changes in cerebral potentials were not associated with the concurrent affective states of BD I and BD II. Therefore, two of our three hypotheses were confirmed, while rebuttal of our third hypothesis suggests that different patterns of attentional dysfunction are the primary characteristics of BD I and BD II under external emotional stimuli conditions.

In controls, negative correlation between P3 amplitudes under the Disgust condition and HCL-32 score suggests that the hypomania-like trait is linked to hypovigilance to negative social cues, such as the fearful facial gaze as previously reported [35], and by the association between attentional avoidance and disgust sensitivity [5]. In BD I, prolonged N2 latencies under Fear and Happiness conditions might also be explained by the following two result sets. One set was the lower attention-executive function when recognizing facial fear found in these patients [32,41], and that of our own
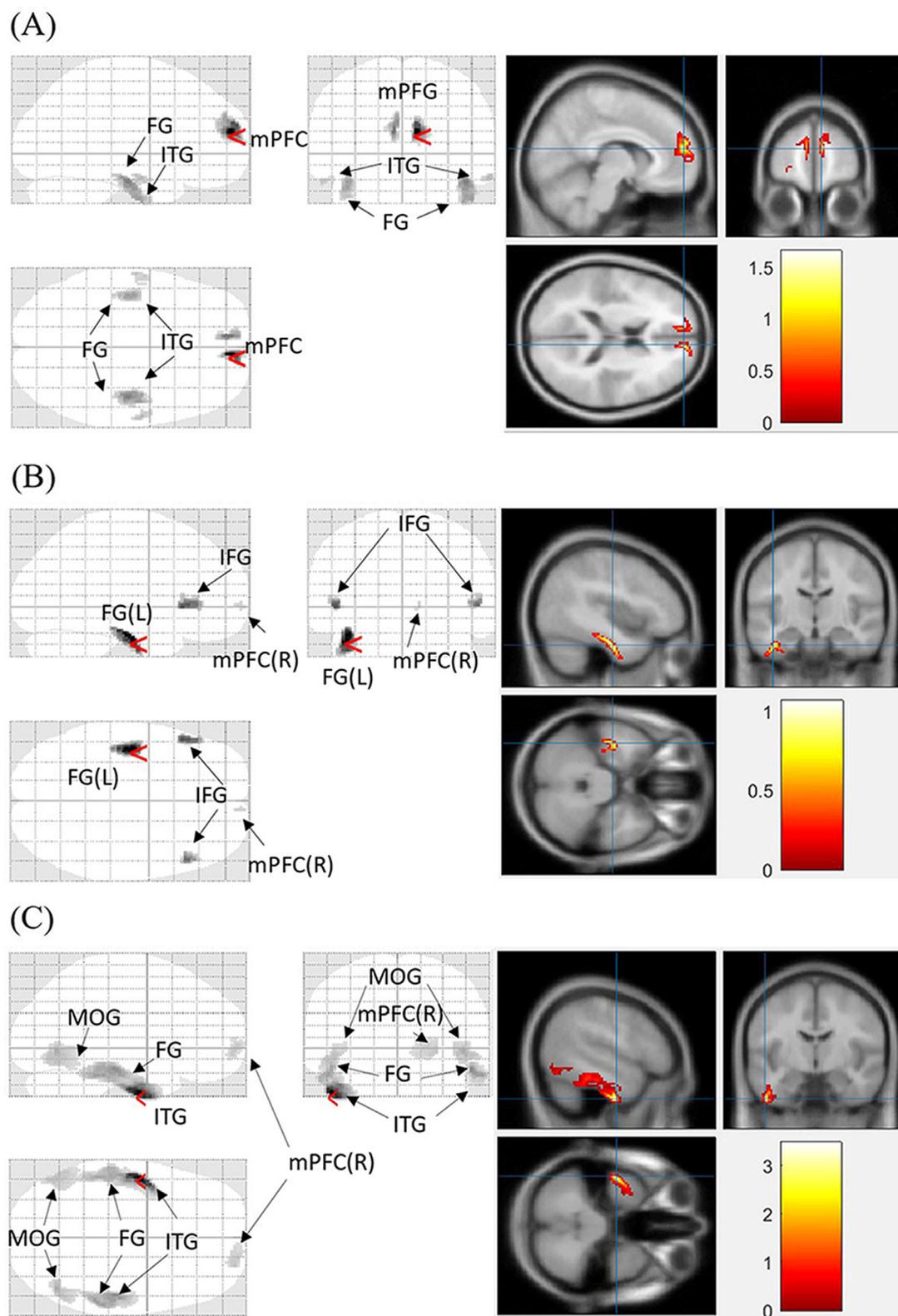
Fig. 2 Source map of P3 (time window: 300 ~ 540 ms) to the target stimuli under Disgust in (A) healthy volunteers, (B) bipolar I, and (C) bipolar II disorder patients. Left panels show sources overlaid on a glass brain. Right panels show sources overlaid on a T1 template brain. The red arrowheads and blue cross hairs indicate source regions of peak intensity in the three groups were the right medial prefrontal cortex, left fusiform gyrus, and left inferior temporal gyrus respectively. Note: FG (L), left fusiform gyrus; mPFC (R), right medial prefrontal cortex; IFG, bilateral inferior frontal gyri; ITG, bilateral inferior temporal gyri; MOG, bilateral middle occipital gyri. For missing data information, see text. The bar in each panel on the right side indicates the intensity of cerebral activities, with white as the highest and black the lowest.

Table 3 Putative N2 and P3 generators in the N2 and P3 time windows in the healthy volunteers (controls, $n = 47$), bipolar I (BD I, $n = 31$) and bipolar II (BD II, $n = 19$) disorder patients.

Component	Group	Source region
N2 under Fear [180 ∼ 400 ms]	Controls	fusiform gyri (Temporal Lobe)*
		inferior temporal gyrus (R) (Temporal Lobe)
		inferior occipital gyrus (R) (Occipital Lobe)
	BD I	fusiform gyri (Temporal Lobe)*
		inferior temporal gyri (Temporal Lobe)
	BD II	fusiform gyrus (R) (Temporal Lobe)*
		inferior temporal gyrus (R) (Temporal Lobe)
P3 under Disgust [300 ∼ 540 ms]	Controls	medial prefrontal cortex (Frontal Lobe)*
		fusiform gyri (Temporal Lobe)
		inferior temporal gyri (Temporal Lobe)*
	BD I	fusiform gyrus (L) (Temporal Lobe)*
		medial prefrontal cortex (R) (Frontal Lobe)
		inferior frontal gyri (Frontal Lobe)*
	BD II	inferior temporal gyri (Temporal Lobe)*
		medial prefrontal cortex (Frontal Lobe)
		fusiform gyri (Temporal Lobe)
		middle occipital gyri (Occipital Lobe)
P3 under Erotica [300 ∼ 540 ms]	Controls	inferior temporal gyri (Temporal Lobe)*
	BD I	inferior frontal gyri (Frontal Lobe)*
		middle frontal gyri (Frontal Lobe)
		inferior parietal lobules (Parietal Lobe)
		middle occipital gyrus (R) (Occipital Lobe)
	BD II	middle temporal gyri (Temporal Lobe)*
		fusiform gyri (Temporal Lobe)
		superior temporal gyri (Temporal Lobe)
		postcentral gyri (Parietal Lobe)
		cuneus (Occipital Lobe)
		middle occipital gyrus (L) (Occipital Lobe)
N2 and P3 under Happiness [180 ∼ 540 ms]	Controls	inferior frontal gyrus (L) (Frontal Lobe)*
		inferior temporal gyri (Temporal Lobe)
		cuneus (Occipital Lobe)
	BD I	inferior frontal gyrus (R) (Frontal Lobe)*
		postcentral gyri (Parietal Lobe)
		fusiform gyri (Temporal Lobe)
		cuneus (Occipital Lobe)
	BD II	inferior temporal gyrus (R) (Temporal Lobe)*
		inferior occipital gyrus (R) (Occipital Lobe)
P3 under Neutral [300 ∼ 540 ms]	Controls	inferior temporal gyrus (R) (Temporal Lobe)*
	BD I	medial prefrontal cortex (Frontal Lobe)*
		fusiform gyri (Temporal Lobe)
		Insula (R) (Sub-lobar)
	BD II	fusiform gyri (Temporal Lobe)*
		inferior frontal gyri (Frontal Lobe)
		superior parietal lobules (Parietal Lobe)
		cuneus (Occipital Lobe)

Source regions of peak intensity under different emotional stimuli in the three groups are indicated with an asterisk. Time windows for N2 and P3 under Happiness in the three groups were merged due to their conjoint activated regions. L, only the left side was activated; R, only the right side was activated.

results of decreased right inferior occipital gyrus activity under Fear, which was involved in the basic visual processing. The other set was the happy stimuli influence on the initial attentional orientation in manic patients [15], and our results of decreased inferior temporal gyri under Happiness which played a role in object recognition [11]. In BD II, the decreased P3 amplitudes and hypoactivation in inferior

temporal gyri and limbic regions but increased inferior frontal activation under Neutral conditions, might suggest increased impulse control over the prepotent response which leads to reduced voluntary attention to non-emotional stimuli as previously reported [6]. The hypoactivation in inferior frontal gyri and decreased P3 amplitudes under Happiness conditions suggested insufficient voluntary evaluation
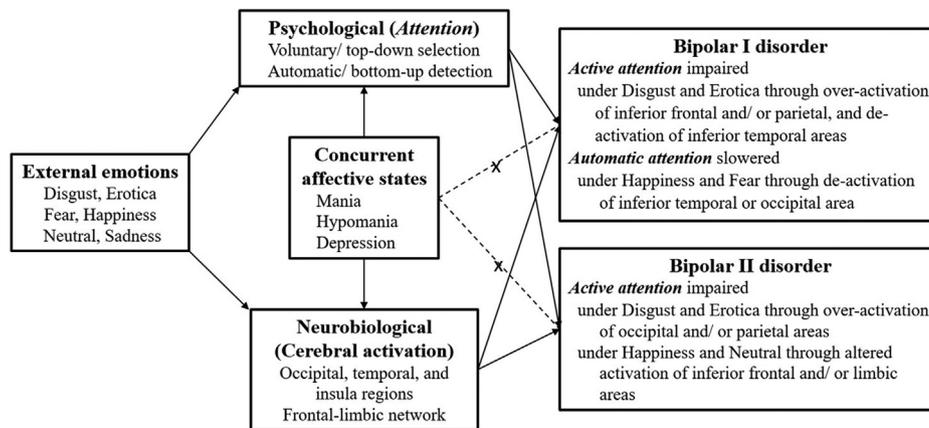
Fig. 3 Cerebral information processing styles were influenced by external emotional stimuli through psychological and neurobiological pathways in bipolar disorder: both active and automatic attentions were impaired in bipolar I, while only active attention was impaired in bipolar II; both bipolar I and II disorders were impaired through different brain areas under different external-emotions; and these differences were independent from the concurrent affective states.

and modulation of response to happy cues in our BD-II, in line with their poor performance and decreased activation of the inferior frontal region in happy face processing and recognition tasks [8,12], which might lead to ignorance of subsequent targets in the attentional task [47].

Both BD I and BD II showed decreased P3 amplitudes under Disgust and Erotica conditions, implying that they had lower voluntary evaluation during disgust or sexual stimulations. The impaired active attention, decreased inferior temporal gyri and increased inferior frontal gyri activations under the Disgust condition in BD I suggested that attentional resources were excessively occupied by inhibition of emotion, causing impaired object recognition [11,36]; results were also in line with previous observations that disgust stimuli hold attention easily [42]. In BD II, the increased inferior occipital activation under Disgust suggested that more primary visual processing was involved in the procedure [11], while the decreased P3 amplitude suggested that this might merely be the after-effect of the previous disgust situation instead of attention to target [42]. Moreover, decreased P3 amplitudes, increased activation of occipital and parietal regions and decreased inferior temporal gyri under Erotica conditions in our BD I and BD II groups support the idea that erotic stimuli exaggerate individuals' perception and interpretation of sensory information [11], and that erotica readily distracts goal-directed behavior [27]. The increased inferior frontal activation in our BD I suggests that these patients devote more attentional resources to the processing of erotic information and intensity regulation of their responses as previously investigated [14], and supports the high sensitivity to erotic stimuli in bipolar disorder, especially BD I [26].

However, the limitations of our study design should be borne in mind. Firstly, we only used visual ERPs to study attentional functions under external emotions; other sensory modalities of ERPs or other techniques assessing broader attentional functions would be helpful to elucidate the phenomena. Secondly, we did not include anger, contempt, and surprise as external emotions; their involvements might help to show more complicated emotional effects on attentions in bipolar disorder. Thirdly, we did not

recruit control groups with other pathologies such as unipolar major depression or personality disorder, and hence whether our findings are unique to bipolar disorder remains to be seen. Nevertheless, we found that BD I patients had slower automatic attention under Happiness and Fear conditions, and decreased cerebral activation for object recognition or primary visual processing, lower voluntary attention under Disgust and Erotica, and over-activation in regions dealing with emotional modulation. BD II patients on the other hand, had lower voluntary evaluation ability under Disgust, Happiness, Erotica and Neutral conditions, and excessively activated areas responsible for visual processing and emotional perception or regulation.

Conclusions

Our study implies that external emotional stimuli trigger the processing of both psychological and neurobiological pathways and elicit different responses in BD I and BD II which are independent from their concurrent affective states (Fig. 3). Therefore, our study demonstrates different visual processing mechanisms under external emotional conditions in different types of bipolar disorder, which could provide a basis for developing emotional intervention therapy.

Disclosure of interest

The authors declare that they have no competing interests.

Acknowledgments

Références

[1] Adler CM, Sax KW, Holland SK, Schmithorst V, Rosenberg L, Strakowski SM. Changes in neuronal activation with increasing

attention demand in healthy volunteers: an fMRI study. Synapse 2001;42:266—72.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

[3] Andersson S, Barder HE, Hellvin T, Lovdahl H, Malt UF. Neuropsychological and electrophysiological indices of neurocognitive dysfunction in bipolar II disorder. Bipolar Disord 2008;10:888—99.

[4] Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord 2005;88:217—33.

[5] Armstrong T, McClenahan L, Kittle J, Olatunji BO. Don't look now ! Oculomotor avoidance as a conditioned disgust response. Emotion 2014;14:95—104.

[6] Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004;8:170—7.

[7] Bradley MM, Lang PJ. The International Affective Digitized Sounds (IADS-2): affective ratings of sounds and instruction manual. Gainesville, FL: University of Florida Tech Rep; 2007. p. B—B3.

[8] Brotman MA, Tseng WL, Olsavsky AK, Fromm SJ, Muhrer EJ, Rutenberg JG, et al. Fronto-limbic-striatal dysfunction in pediatric and adult patients with bipolar disorder: impact of face emotion and attentional demands. Psychol Med 2014;44:1639—51.

[9] Calhoun VD, Maciejewski PK, Pearlson GD, Kiehl KA. Temporal lobe and ''default'' hemodynamic brain modes discriminate between schizophrenia and bipolar disorder. Hum Brain Mapp 2008;29:1265—75.

[10] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews. Neuroscience 2002;3:201—15.

[11] Creem SH, Proffitt DR. Defining the cortical visual systems: ''What'', ''Where'', and ''How''. Acta Psychol (Amst) 2001;107:43—68.

[12] Cusi AM, Nazarov A, Holshausen K, MacQueen GM, McKinnon. Systematic review of the neural basis of social cognition in patients with mood disorders. J Psychiatry Neurosci 2012;37:154—69.

[13] Dittmann S, Hennig-Fast K, Gerber S, Seemuller F, Riedel M, Emanuel SW, et al. Cognitive functioning in euthymic bipolar I and bipolar II patients. Bipolar Disord 2008;10:877—87.

[14] Fuster JM. The prefrontal cortex - an update: time is of the essence. Neuron 2001;30:319—33.

[15] García-Blanco A, Salmerón L, Perea M. Inhibitory control for emotional and neutral scenes in competition: an eye-tracking study in bipolar disorder. Biol Psychol 2017;127:82—8.

[16] Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet 2013;381:1672—82.

[17] Goodwin F, Jamison K. Manic-depressive illness. 2nd ed. New York: Oxford University Press; 2007.

[18] Hansen JC, Hillyard SA. Endogenous brain potentials associated with selective auditory attention. Electroencephalogr Clin Neurophysiol 1980;49:277—90.

[19] Heinze HJ, Mangun GR. Electrophysiological signs of sustained and transient attention to spatial locations. Neuropsychologia 1995;33:889—908.

[20] Heit G, Smith ME, Halgren E. Neuronal activity in the human medial temporal lobe during recognition memory. Brain 1990;113:1093—112.

[21] Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the mood disorder questionnaire. Am J Psychiatry 2000;157:1873—5.

[22] Hsiao Y, Wu Y, Wu JY, Hsu M, Chen H, Lee S, et al. Neuropsychological functions in patients with bipolar I and bipolar II disorder. Bipolar Disord 2009;11:547—54.

[23] Jeganathan J, Perry A, Bassett DS, Roberts G, Mitchell PB, Breakspear M. Fronto-limbic dysconnectivity leads to impaired brain network controllability in young people with bipolar disorder and those at high genetic risk. Neuroimage Clin 2018;19:71—81.

[24] Kessler RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, et al. Individual and societal effects of mental disorders on earnings in the United States: results from the national comorbidity survey replication. Am J Psychiatry 2008;165:703—11.

[25] Kok A. Event-related potential (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 1997;45:19—56.

[26] Kopeykina I, Kim HJ, Khatun T, Boland J, Haeri S, Cohen LJ, et al. Hypersexuality and couple relationships in bipolar disorder: a review. J Affect Disord 2016;195:1—14.

[27] Lane RD. Theory of emotional awareness and brain processing of emotion. International Congress Series 2006;1287:116—21.

[28] Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Tech. Rep 2008:A—A8.

[29] Lembke A, Ketter TA. Impaired recognition of facial emotion in mania. Am J Psychiatry 2002;159:302—4.

[30] Ma G, Wang C, Jia Y, Wang J, Zhang B, Shen C, et al. Electrocardiographic and electrooculographic responses to external emotions and their transitions in bipolar I and II disorders. Int J Environ Res Public Health 2018;15:884.

[31] Mangun GR, Hillyard SA. Mechanisms and models of selective attention. In: Rugg MD, Coles MGH, editors. Electrophysiology of mind: Event-related potentials and cognition. Oxford: Oxford University Press; 1995 [40-85p].

[32] Martino DJ, Strejilevich SA, Fassi G, Marengo E, Igoa A. Theory of mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders. Psychiatry Res 2011;189:379—84.

[33] Näätänen R. Attention and brain function. Hillsdale, NJ: Lawrence Erlbaum Associates; 1992.

[34] Plutchik R, van Praag HM. Interconvert ability of five self-report measures of depression. Psychiatry Res 1987;22: 243—56.

[35] Putman P, Saevarsson S, van Honk J. Hypomanic trait is associated with a hypovigilant automatic attentional response to social cues of danger. Bipolar Disord 2007;9:779—83.

[36] Roberts G, Green MJ, Breakspear M, McCormack C, Frankland A, Wright A, et al. Reduced inferior frontal gyrus activation during response inhibition to emotional stimuli in youth at high risk of bipolar disorder. Biol Psychiatry 2013;74:55—61.

[37] Rosa AR, Bonnín CM, Vázquez GH, Reinares M, Solé B, Tabarés-Seisdedos R, et al. Functional impairment in bipolar II disorder: is it as disabling as bipolar I? J Affect Disord 2010;127:71—6.

[38] Serretti A, Olgiati P. Profiles of ''manic'' symptoms in bipolar I, bipolar II and major depressive disorders. J Affect Disord 2005;84:159—66.

[39] Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. Bipolar Disord 2012;14:326—39.

[40] Undurraga J, Baldessarini RJ, Valenti M, Pacchiarotti I, Vieta E. Suicidal risk factors in bipolar I and II disorder patients. J Clin Psychiatry 2011;73:778—82.

[41] Uono S, Sato W, Kochiyama T, Kubota Y, Sawada R, Yoshimura S, et al. Time course of gamma-band oscillation associated with face processing in the inferior occipital gyrus and fusiform gyrus: a combined fMRI and MEG study. Hum Brain Mapp 2017;38:2067.

[42] van Hooff JC, Devue C, Vieweg PE, Theeuwes J. Disgust- and not fear-evoking images hold our attention. Acta Psychol (Amst) 2013;143:1—6.

[43] Wang W, Cao M, Zhu S, Gu J, Liu J, Wang Y. Zuckerman-Kuhlmans personality questionnaire in patients with major depression. Soc Behav Pers 2002;30:757—64.

[44] Xu S, Gao Q, Ma L, Fan H, Mao H, Liu J, et al. The Zuckerman—Kuhlman personality questionnaire in bipolar I and II disorders: a preliminary report. Psychiatry Res 2015;226:357—60.

[45] Yang HC, Yuan CM, Liu TB, Li LJ, Peng HJ, Rong H, et al. Validity of the Chinese version mood disorder questionnaire (MDQ) and the optimal cutoff screening bipolar disorders. Psychiatry Res 2011;189:446—50.

[46] Yang HC, Yuan CM, Liu TB, Li LJ, Peng HJ, Liao CP, et al. Validity of the 32-item hypomania checklist (HCL-32) in a clinical sample with mood disorders in China. BMC Psychiatry 2011;11:84.

[47] Yiend J. The effects of emotion on attention: a review of attentional processing of emotional information. Cogn Emot 2010;24:3—47.

[48] Zhu Q, Wang J, Shen C, Fan H, Zhang B, Ma G, et al. Inhibitory brainstem reflexes under external emotional-stimuli in bipolar I and II disorders. BMC Psychiatry 2017; 17:224.

[49] Zhu Q, Wang J, Wang W, Fan H, Ma G, Zhang B, et al. Blink reflex under external emotional-stimuli in bipolar I and II disorders. Psychiatry Res 2018;259:520—5.