P300 component in euthymic patients with bipolar disorder type I, bipolar disorder type II and healthy controls: a preliminary event-related potential study

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The aim of the present study was to investigate P300 event-related potential components in euthymic bipolar disorder type I (BDI) and bipolar disorder type II (BDII) patients and matched controls. A total of 10 BDI patients, 10 BDII patients and 10 healthy individuals were enrolled in the study. Event-related potential data were collected according to a standard auditory 'oddball' paradigm. A significant groups effect in both the peak amplitude ($P < 0.001$) and the mean amplitude ($P < 0.001$) was observed; post-hoc comparisons showed that the peak and mean amplitudes of BDI and BDII patients were significantly lower than the peak and mean amplitudes of the healthy controls. The neurophysiological patterns found in the present study might at least partially reflect the presence of a mild selective cognitive impairment in euthymic BDI and BDII patients. From a clinical point of view, these evidences support the potential role of cognitive interventions in the treatment of BD. *NeuroReport* **26:206–210**

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Introduction

Bipolar disorder (BD) is a chronic and disabling disorder characterized by manic/hypomanic and depressive episodes [1]. The course of BD has traditionally been viewed as episodic, with symptomatic and functional recovery between mood episodes; however, recent clinical and epidemiological studies document how, despite symptomatic improvements or recovery following mood episodes, many BD individuals experience cognitive disturbances even during the euthymic phase of the disease [2–7].

Both the 4th and the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) divide BD into two types labelled as bipolar disorder type I (BDI) and bipolar disorder type II (BDII) [1,8,9]; BDI is defined by manic or mixed episodes that last at least 7 days or by manic symptoms that are so severe that the patient needs immediate hospital care, whereas BDII is defined by a pattern of depressive and hypomanic episodes, but no full-blown manic or mixed episodes [1,8,9].

Cognitive disturbances may affect patients with both the subtypes of BD [5,6]; in particular, it has been reported that BDII patients show a level of neuropsychological performances intermediate between BDI and healthy individuals, specifically in frontal executive functioning and verbal learning working memory [6].

From a neurophysiological point of view, event-related potentials (ERPs) allow the identification of specific neurocognitive deficiencies [10,11]. In particular, the P300 component has been studied widely and it is believed to be related to stimuli categorization as an indicator of selective attention and memory updating [10]. The P300 consists of two main subcomponents named P3a and P3b; whereas the p3a, which is elicited by a distracter stimulus, has been interpreted as a neural correlate of the orienting response, the P3b component, which is elicited by a target rare stimulus, reflects neuronal activity associated with revision of the mental representation of the previous event within the stimulus environment [10].

This component has been found to be abnormal in a range of psychiatric afflictions including BD; in particular, the reduction in the amplitude of P300 components represents the most common neurophysiological abnormality observed in euthymic BD patients [12–15]. However, most of the studies considered only BDI patients or did not consider the two subtypes of BD patients independently; in addition, no studies have so far carried out a comparison of P300 components between euthymic BDI patients, BDII patients and matched healthy controls.

Given the above, the aim of the present paper was to evaluate the differences in P3b components between

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patients with BDI, BDII and healthy controls. It is hypothesized that, similar to what has previously been found in relation to neuropsychological disturbances [6], BDII patients may show neurophysiological characteristics intermediate between BDI patients and healthy individuals.

Materials and methods

Participants

A total of 10 BDI patients (four men and six women, aged 31–64 years mean age: 47.20 ± 8.90) and 10 BDII patients (four men and six women, aged 33–65 years mean age: 48.50 ± 14.26) referring at the Policlinico Umberto I University Hospital, Sapienza University of Rome, were consecutively enrolled in the study. Patients were diagnosed using research modules of the Structured Clinical Interview for the DSM-IV [16]; they were in the euthymic phase of the disease, as assessed by Hamilton Depression Rating Scale score less than 7 [17] and Young Mania Rating Scale less than 7 [18].

A control group of healthy individuals (with no Axis I and II DSM-IV diagnosis) comparable for age and sex was also included (four men and six women, aged 31–65 years mean age: 46.20 ± 13.05). Patients' exclusion criteria were as follows: left handedness, history of neurologic diseases, other Axis I diagnosis, hospitalization in the last 12 months, patients on stable pharmacological treatment from at least 2 months, pharmacological treatment with typical antipsychotics, presence of electroencephalographic (EEG) abnormalities at the baseline recording, Hamilton Depression Rating Scale score greater than 7, Young Mania Rating Scale greater than 7 and mental retardation (IQ < 70) measured by Raven Progressive Matrices (PM38) [19].

The research protocol was approved by the Ethical Committee of Human Experimentation of Policlinico Umberto I University Hospital; after receiving information on the aims of the study, all participants provided their written consent.

EEG recording and event-related potentials

The ERP data were collected according to a standard auditory 'oddball' paradigm consisting of a sequence of two tones (duration: 200 ms; rise–fall times: 10 ms; intensity: 80 dB SPL) delivered in a random order, with one tone (1000 Hz) being the standard stimulus ($P = 0.8$) and the other being the infrequent target stimulus (frequency: 2000 Hz; $P = 0.2$). Participants were instructed to mentally count the target tones. The interstimulus interval varied randomly between 2 and 3 s.

Participants were seated in an anatomic chair in a faradized and light-attenuated room. The electrophysiological signals were recorded by Ag/AgCl electrodes fixed on the scalp at the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 sites, according to the International 10–20 System, referred to linked mastoids and grounded at Fpz. The bipolar electrooculogram was recorded from above and below the left eye. All interelectrode impedances were maintained below 3 kΩ. EEG signals and electrooculogram were filtered using a 0.01–30 Hz. A notch filter (50 Hz) was also applied. The data were digitized using an analog/digital converter at a sampling rate of 1024 Hz and stored on a hard disk. A Mizar Sirius EEG-EP Galileo NT multifunctional system (EB NEURO-Firenze) was used.

ERP analysis

Trials containing eye movements were automatically rejected. A further selection was performed in the offline analysis to reject other kinds of artefacts according to the clinical guidelines [20]. For each participant, all artefact-free trials were averaged per stimulus (standard and target) and filtered with a low-pass digital filter of 20 Hz for each stimulus. Scalp electrode activity was measured at all electrode sites, of which Fz, Cz and Pz were analysed.

The P3b amplitude and latency at Fz, Cz and Pz electrode sites for target tones were measured from baseline to peak using a 250–500 ms interval. Furthermore, the P3b amplitude was also measured as the mean voltage between 250 and 500 ms after target stimulus and P3b timings were also quantified as midpoint latency, the time point that divided the area under the curve into two equal halves. It is known [21] that assessment of these measures provides several advantages, that is compared with the peak amplitude, the mean amplitude is not biased by the number of trials.

Statistical analysis

The data were analysed using the IBM (Armonk, New York, USA) SPSS Statistics software, version 20. Analysis of variance (ANOVA) for continuous variables and χ^2 tests for dichotomous variables were used to examine differences between BDI, BDII patients and controls.

P3b maximum peak-to-peak latency and amplitude, midpoint latency and the mean amplitude were analysed separately using repeated-measures ANOVA, including the between-subject factor grouping (BDI patients, BDII patients and healthy controls) and the within-subject factor electrodes location (Fz, Cz and Pz). Greenhouse–Geisser-corrected P-values are reported. Bonferroni post-hoc tests were used where relevant.

Results

Pharmacological treatments and other characteristics of the participants are presented in Table 1. The three groups (BDI, BDII and healthy controls) did not significantly differ in age [$F(2, 27) = 0.09$; $P = 0.92$] and educational level [$F(2, 27) = 2.25$; $P = 0.13$]. The two

Table 1 Demographic variables, clinical characteristics and ERP data of the sample

	Mean (SD)		
	BDI (10)	BDII (10)	Control (10)
Age	47.70 ± 8.90	48.50 ± 14.26	46.20 ± 13.05
Educational level[a]	13.44 ± 3.68	16.14 ± 2.27	12.70 ± 3.71
Duration of disease[a]	15.00 ± 9.71	13.10 ± 9.62	–
Number of hospitalizations	3.30 ± 6.06	0.90 ± 0.99	–
Age of onset[a]	29.60 ± 15.84	33.60 ± 8.97	–
Familiarity to BD [*N* (%)]	3 (30)	5 (50)	–
Pharmacological treatment [*N* (%)]			–
Anticonvulsants	7 (70)	5 (50)	–
Antipsychotics	6 (60)	7 (70)	–
Antidepressants	3 (30)	5 (50)	–
Two or more psychotropic medications [*N* (%)]	7 (70)	6 (60)	–
Fz latency peak	379.18 ± 21.439	414.58 ± 59.76	373.48 ± 28.23
Cz latency peak	383.68 ± 23.45	400.57 ± 62.28	350.90 ± 59.07
Pz latency peak	391.18 ± 28.77	397.81 ± 57.87	372.07 ± 30.29
Fz midpoint latency	368.18 ± 23.94	360.31 ± 27.10	355.96 ± 32.18
Cz midpoint latency	369.17 ± 26.91	370.44 ± 30.73	365.14 ± 29.91
Pz midpoint latency	370.53 ± 17.60	368.37 ± 20.46	377.34 ± 22.43
Fz amplitude peak	5.11 ± 2.67	4.64 ± 3.10	10.30 ± 4.39
Cz amplitude peak	4.87 ± 4.11	6.68 ± 4.24	13.69 ± 7.80
Pz amplitude peak	6.17 ± 3.22	9.68 ± 5.66	16.78 ± 8.32
Fz mean amplitude	2.19 ± 0.76	1.83 ± 0.51	4.94 ± 2.14
Cz mean amplitude	3.78 ± 1.56	2.63 ± 1.59	8.40 ± 3.73
Pz mean amplitude	6.86 ± 1.94	8.48 ± 6.14	13.38 ± 2.86

BDI, bipolar disorder type I; BDII, bipolar disorder type II; BD, bipolar disorder; ERP, event-related potential.
[a]Years.

patient groups did not differ in age of onset [$F(1, 18) = 0.48$; $P = 0.50$], duration of disease [$F(1, 18) = 0.19$; $P = 0.67$], number of hospitalizations [$F(1, 18) = 1.53$; $P = 0.23$], family history of BD [χ^2 $(1) = 0.83$; $P = 0.36$] and pharmacological treatment.

Repeated-measures ANOVA showed a significant location effect in midpoint latency [$F(1.87, 50.41) = 5.03$; $P = 0.01$]. Post-hoc comparisons showed that midpoint latency was significantly longer at Pz than at Fz ($P = 0.03$). No significant difference was observed for P3b peak latency.

Repeated-measures ANOVA also showed a significant location effect in both the peak amplitude [$F(1.67, 44.94) = 10.22$; $P < 0.001$] and the mean amplitude [$F(1.35, 36.54) = 50.96$; $P < 0.001$]. Post-hoc comparisons showed that the peak and mean amplitudes at Pz were significantly higher than those at Fz ($P < 0.001$) and Cz ($P < 0.001$) (see Fig. 1).

Finally, repeated-measures ANOVA showed a significant groups effect in both peak amplitude [$F(2, 27) = 12.72$; $P < 0.001$] and mean amplitude [$F(2, 27) = 19.01$; $P < 0.001$]. Post-hoc comparisons showed that the peak and mean amplitudes of BDI and BDII patients were significantly lower than the peak and mean amplitudes of healthy controls.

Discussion

The main aim of the present study was to investigate P300 components in euthymic BDI and BDII patients and matched controls.

Consistent with previous findings [12–15], patients with BDI and BDII had significantly smaller P3b peak and mean amplitudes than healthy controls. Different from the hypothesis of the study, no significant differences were found between BDI and BDII patients; this finding confirms the results of Jahshan *et al.* [13], who reported no significant differences in mismatch negativity and P3a between BPI and BPII patients.

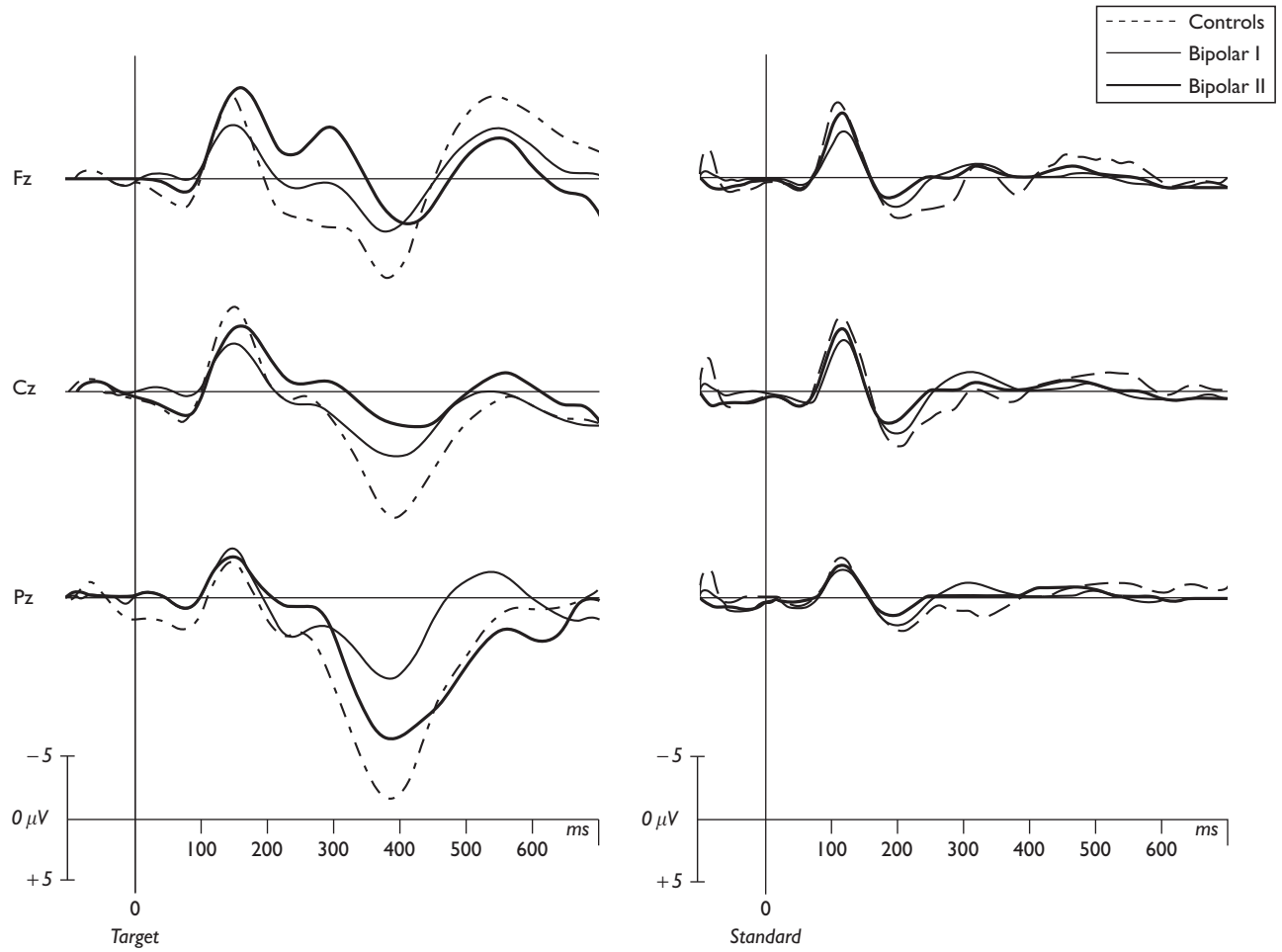
It is possible to speculate that the neurophysiological patterns found in the present study might at least partially reflect the presence of a mild selective cognitive impairment in euthymic BDI and BDII patients [6]. In particular, the smaller P3b amplitude may indicate a difficulty in allocating the attentional resources during a discriminative task. However, it is important to evidence that our interpretation remains largely speculative because of the absence of cognitive task/behavioural data in the present study.

In the present study, a main effect of location was observed for Pz electrodes. This is consistent with previous findings suggesting that parietal areas are crucial for the generation of the scalp recorded P300 component [22,23] and play an important role in different cognitive processing such as working memory, attention and executive function [5,6,24–26] that are known to be potentially impaired in BD patients [5,6,27].

From a clinical point of view, our results raise some relevant issues: the relapse rate for many psychiatric disorders including BD is staggeringly high, indicating that treatment methods combining psychotherapy with pharmacological interventions are not entirely effective; indeed, cognitive deficits have gained considerable importance in the field as critical features of mental illness, and it is now believed that they might represent valid therapeutic targets. Therefore, it may be hypothesized that specific 'ERP-oriented' cognitive interventions could be planned in addition to standard medications and psychotherapies on the basis of each patient's needs for an 'individualized' or 'personalized' therapy that may have the potential to reduce relapse rates and to improve functional outcomes [11,28].

The most important limitation of the present study is the small sample size, which makes it very difficult to draw definitive conclusions from our data; the findings of the present paper are promising, but they must be considered only as preliminary. Future researches are needed to assess potential neurophysiological differences in larger samples of BDI and BDII patients and their association with neuropsychological and clinical disturbances.

Fig. 1



Grand-averaged P3b traces at mid-line scalp sites for target and standard stimuli for bipolar I (thin line), bipolar II (thick line) and healthy controls (dashed line). The analysis time was 800 ms with a 100 ms prestimulus baseline.

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Conflicts of interest

There are no conflicts of interest.

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