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P300 event-related potential in euthymic patients with bipolar disorder

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ABSTRACT

Auditory P300 event-related potential (ERP) and performance on Sustained Attention were evaluated in 24 euthymic bipolar patients and 38 healthy volunteers. There were no significant differences between groups, and performance in sustained attention had no significant influence in the P300 responses. P300 response might be driven by the presence of mood symptoms.

1. Introduction

Compared to schizophrenia, there have only been a handful of studies of the P300 event related potential (ERP) component in bipolar disorder, and the relationship of P300 abnormalities and patient state is not well characterized. Muir et al. (1991) reported that patients with bipolar disorder exhibited increase in P300 latency and reduction inP300 amplitude, similar to patients with schizophrenia but not to control subjects. This observation was corroborated by Souza et al. (1995) and Vilela et al. (1999), although it should be noted that, in this last study, a large proportion of the bipolar patients had prominent mood symptoms. There are also reports of reduced P300 amplitude in patients with psychotic mania (Salisbury et al., 1999) and of prolonged P300 latency in patients with manic or mixed episodes (O'Donnell et al., 2004; Strik et al., 1998). Prolonged P300 latency in patients with major depression has been described by some authors (Roschke et al., 1996; Gangadhar et al., 1993), but not by others (Bruder et al., 1991; Swanwick et al., 1996; Hansenne et al., 1994. Salisbury et al. (1998) reported that patients with first-episode schizophrenia had reduced P300 amplitude compared to both patients with first-episode affective psychosis and control subjects. Interestingly, Muir et al. (1991) observed P300 latency prolongation in patients with bipolar disorder and psychotic symptoms but not in patients with unipolar depression, and Santosh et al. (1994) found P300 reduction only in depressed patients with hallucinations. In recent years, Pierson et al. (2000) reported latency prolongation in 19 first-degree relatives of patients with bipolar disorder, and Hall et al. (2007) found a genetic correlation between P300 amplitude reduction and bipolar disorder. A very recent study has shown that bipolar patients with a history of psychosis and their unaffected relatives showed significantly delayed P300 latency compared to controls (Schultze et al., 2008). These observations place P300 on the select list of candidate endophenotypes for bipolar disorder (Lenox et al., 2002), although it is still unclear whether P300 event-related potentials fulfill the requisite of being state independent because, as also occurs in neurocognitive studies of bipolar patients, mood—a crucial confounding factor—is not always monitored.

The main aim of this study was to compare P300 abnormalities in bipolar patients in a strictly defined euthymic state when compared to healthy volunteers of similar characteristics. We also assessed the correlation between P300 abnormalities and sustained attention.

2. Materials and methods

2.1. Patients and control subjects

Twenty-four euthymic patients with bipolar disorder were recruited from 3 outpatient clinics. The patients all met the DSM-IV-TR criteria for type I bipolar disorder, and they had been euthymic for the previous three months. Evaluation was completed with the life-time version of the standardised interview Schedule for Affective Disorders and Schizophrenia (SADS, Spitzer et al., 1978). Euthymia was defined as a score of less than 7 on both the Hamilton Rating Scale for Depression (1960) and the Young Mania Rating Scale (1978). Exclusion

Abbreviations: dB, decibel; DSM-IV-TR, Diagnostic And Statistical Manual of Mental Disorders, 4th edition, Text Revision; ERP, event-related potential; Hz, Hertz; kΩ, kiloohm; ms, millisecond; SADS, Schedule for Affective Disorders and Schizophrenia; SD, standard deviation.

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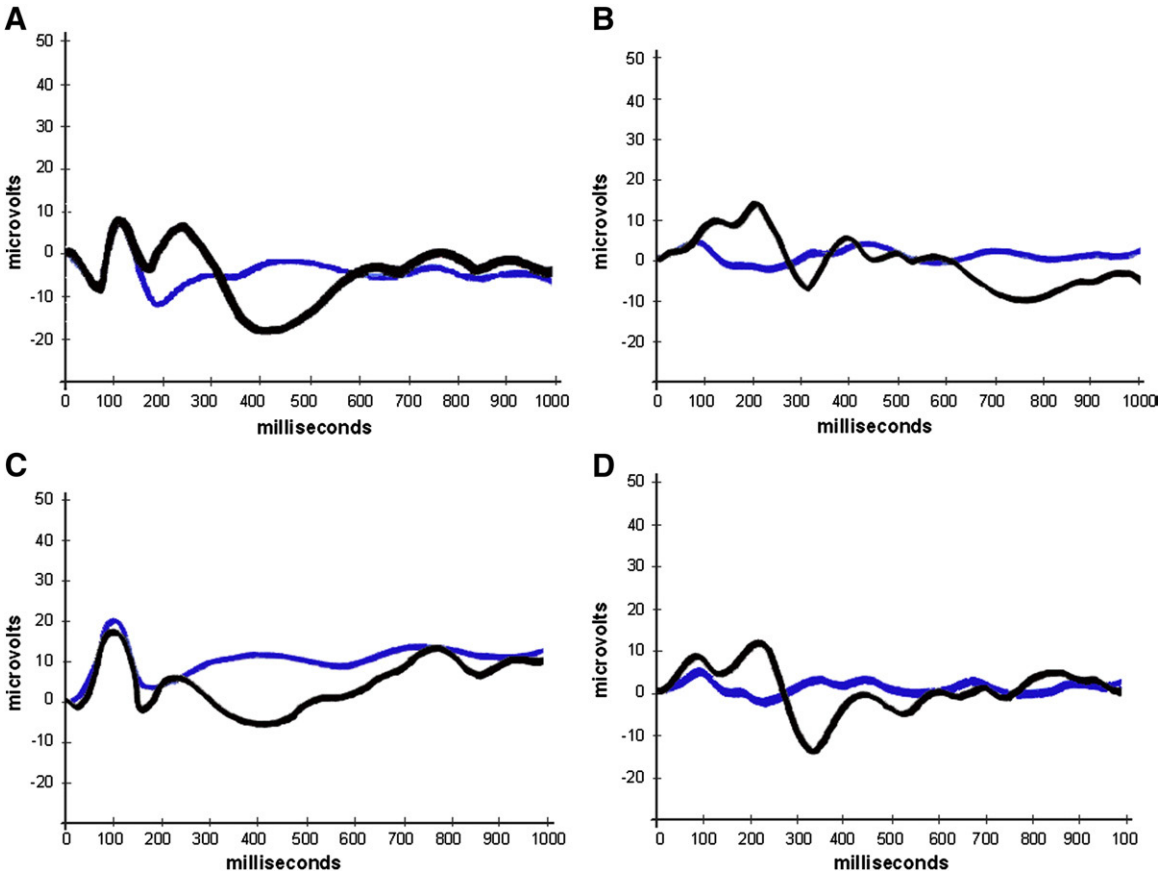

Fig. 1. Black line: ERP obtained from the average of responses to infrequent target tones. Blue line: evoked potential obtained from the average of responses to frequent not target tones. A and C: Patients with delayed P300. B: Control. C: Patient with normal latency of P300 wave. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

criteria included a personal history of schizophrenia, schizoaffective or other psychotic disorders, the current presence of a comorbid psychiatric condition (including substance abuse/dependence, since smoking or alcohol abuse have been demonstrated as confusing factors on auditory P300 potential (Neuhaus et al., 2006; Sanchez-Turet et al., 2002), any physical illness potentially impairing cognitive performance, and a history of head trauma with loss of consciousness. On the contrary, past history of substance abuse/dependence (12 months prior to the test) was not excluded, since it is a very common feature in bipolar disorder.

We also enrolled 38 healthy subjects who were not undergoing psychiatric treatment and who were similar to the study group in terms of age, sex, and level of education. Informed consent was obtained from all the participants and the study was approved by the ethics committee at the University Hospital Príncipe de Asturias in Madrid, Spain.

2.2. Auditory event-related potentials

P300 was elicited using auditory stimuli. An oddball paradigm was used and stimuli were delivered binaurally as tones with an intensity of 85 dB, a rise–fall time of 10 ms, and a plateau of 50 ms. The subjects were asked to distinguish between a frequent tone of 1000 Hz and a rare tone of 2000 Hz, presented randomly and to respond to infrequent target tones by using a bottom press. The interstimulus interval was 2 s and the ratio of frequent to rare tones was 4:1. Measurements were obtained using a Keypoint electromyogram machine, and the evoked potential was recorded with silver–silver chloride surface electrodes at frontal (Fz), central (Cz) and parietal (Pz) (according to the10–20 international system). The recording electrodes were referenced to A1+A2 (monopolar electrodes attached to both ear lobes and linked via an electrical jumper). Resistance was lower than 5 kΩ. EEG was segmented into 1000 ms epochs triggered from the stimulus. In order to avoid blink, ocular movement and other artifacts, we fixed an artifact rejection system, so epochs which contained voltage samples exceeding 200 μV at any channel of the register were excluded from further analysis. In addition, and to ensure the constancy and reproducibility of the responses, we repeat the test two consecutives times for each patient (Heinze et al., 1999). Epochs were averaged separately for the infrequent target and frequent not target event related potentials. The acquired signal was filtered through a 0.1 Hz low-frequency filter and a 50 Hz high-frequency filter. The average number of stimuli was 200 (160 infrequent not target stimuli and 40 rare target stimuli) and the maximum permitted error rate for detection of the target stimulus was fixed at 5%. The event-related potential recording obtained at the parietal site was evaluated. P300 was defined as the first large positive (downward deflection) wave after the N100–P200–N200 complex,

Table 1
Comparison between the two groups in demographic characteristics, P300 event-related potential and sustained attention

	Bipolar group	Control group	*P*
Age (mean, SD)	43.9 (11.5)	48.9 (13.2)	NS (0.151)[a]
Sex (% female)	59.1%	37.8%	NS (0.113)[b]
P300 latency (mean, SD)	335. 9 (37.2)	322.5 (31.5)	NS (0.142)[a]
P300 amplitude (mean, SD)	10.1 (3.7)	10.2 (4.5)	NS (0.419)[a]
Attention (mean, SD)	21.1 (6.7)	23.5 (4.1)	NS (0.148)[a]

[a] *U* Mann Whitney.
[b] Chi square.