Electrical mapping in bipolar disorder patients during the oddball paradigm

Luiza Wanick Di Giorgio Silva h, *, Consuelo Cartier h, Elie Cheniaux l, Fernanda Novis l, Luciana Angélica Silveira l, Paola Anaquim Cavaco l, Rafael de Assis da Silva l, Washington Adolfo Batista h, Guaraci Ken Tanaka h, Mariana Gongora a, Juliana Bittencourt e, h, Silmar Teixeira l, Luis Fernando Basile f, g, Henning Budde j, k, Mauricio Cagya d, Pedro Ribeiro a, b, c, Bruna Velasques b, c, h

a Brain Mapping and Sensory Motor Integration of the Federal University of Rio de Janeiro (UFRJ), Brazil
b Bioscience Department, School of Physical Education of the Federal University of Rio de Janeiro (EEFD/UFRJ), Rio de Janeiro, Brazil
c Biomedical Engineering Program, COPPE, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
d Institute of Applied Neuroscience (INA), Rio de Janeiro, Brazil
e Laboratory of Physical therapy – Veiga de Almeida University of Rio de Janeiro (UVA/RJ), Rio de Janeiro, Brazil
f Laboratory of Psychophysiology, Faculdade da Saúde, Unesp, São Paulo, Brazil
g Division of Neurosurgery, University of São Paulo Medical School, São Paulo, Brazil
h Neurophysiology and Neuropsychology of Attention, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro – RJ, Brazil
i Brain Mapping and Functionality Laboratory, Federal University of Piaui, Piaui, Brazil
j Faculty of Human Sciences, Medical School Hamburg, Hamburg, Germany
k Sport Science, Reykjavik University, Reykjavik, Iceland
l Anxiety & Depression Laboratory, Institute of Psychiatry of Federal University of Rio de Janeiro (IPUB/UFRJ), Brazil

ABSTRACT

Bipolar disorder (BD) is characterized by an alternated occurrence between acute mania episodes and depression or remission moments. The objective of this study is to analyze the information processing changes in BP (Bipolar Patients) (euthymia, depression and mania) during the oddball paradigm, focusing on the P300 component, an electric potential of the cerebral cortex generated in response to external sensorial stimuli, which involves more complex neurophysiological processes related to stimulus interpretation. Twenty-eight bipolar disorder patients (BP) (17 women and 11 men with average age of 32.5, SD: 9.5) and eleven healthy controls (HC) (7 women and 4 men with average age of 29.78, SD: 6.89) were enrolled in this study. The bipolar patients were divided into 3 major groups (i.e., euthymic, depressive and manic) according to the score on the Clinical Global Impression – Bipolar Version (CGI-BP). The subjects performed the oddball paradigm simultaneously to the EEG record. EEG data were also recorded before and after the execution of the task. A one-way ANOVA was applied to compare the P300 component among the groups. After observing P300 and the subcomponents P3a and P3b, a similarity of amplitude and latency between euthymic and depressive patients was observed, as well as small amplitude in the pre-frontal cortex and reduced P3a response. This can be evidence of impaired information processing, cognitive flexibility, working memory, executive functions and ability to shift the attention and processing to the target and away from distracting stimuli in BD. Such neuropsychological impairments are related to different BD symptoms, which should be known and considered, in order to develop effective clinical treatment strategies.

* Corresponding author. Brain Mapping and Sensory Motor Integration Laboratory, Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB/UFRJ), Av. Venceslau Brás, 71, Botafofo, Rio de Janeiro, 22780-160, Brazil.

E-mail address: luizadigiorgio@gmail.com (L.W. Di Giorgio Silva).

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1. Introduction

Bipolar disorder (BD) and its neurological, cognitive and behavioral bases have been widely investigated. BD is considered to be a relatively frequent and chronic psychiatric condition, causing professional and social difficulties or incapacitation (Akiskal et al., 2000; Fleck et al., 2003; Hisatugo et al., 2009; Kaplan et al., 1997). According to Ozerdem et al. (2008), BD involves various cognitive dysfunctions, even in the euthymic phase of the illness. Emotional deregulation and cognitive deficits in euthymia are indicators of an enduring pathology in BD. Disruptions of the connections among the frontal cortex, amygdala, basal ganglia, thalamus, entorhinal cortex and hippocampus are probable participants in the underlying pathology of BD (Atagün et al., 2013; Dupont et al., 1995; Blumberg et al., 2002; Caliguri et al., 2004; Phillips et al., 2003; Strakowski et al., 2005). These connections are also believed to serve in the modulation of cognition and emotional consonance (Strakowski et al., 2005).

Previous studies have demonstrated cognitive deficits specific for each mood phase of bipolar disorder. Ozerdem et al. (2008) identified manic patients to display signs of dysfunction in attentional measures, complex processing and memory. Having an acute episode of mania or depression is suggested to cause damage to the learning and memory systems (Bearden et al., 2001). Recently, new evidence corroborates the hypothesis of inflammation and neurodegeneration in BD and the relation between number of mood episodes and neurocognitive dysfunction. The understanding of the neurobiology and neuroimaging of BD progression and activity contributes to the establishment of BD biomarkers, which include inflammatory cytokines, neurotrophins, mitochondrial dysfunction, oxidative stress, epigenetic effects, and morphometric and neurostructural abnormalities. These parameters appear to be sensitive to the illness stage, and they are indeed the first biochemical indicators of the staging model in BD (McGorry et al., 2006; Berk et al., 2007; Berk et al., 2011; Roda et al., 2015). This way, we suggest P300 components to be investigated as a BD biomarker, specifically related to information processing and cognitive deficits. According to Purcell et al. (1997), information processing is associated with neurocognitive dysfunctions of BD. Attentional and cognitive alterations are significant in different BD states and they also persist in euthymic phases (Maekawa et al., 2013). Cognitive deficits in response inhibition, verbal memory and attention persist across mood phases but are enhanced during the manic and depressive states (Robinson et al., 2006). These patients present deficits in a broad range of cognitive functions, such as verbal memory, sustained attention, executive function aspects and emotional processing (Andersson et al., 2008; Maekawa et al., 2013). Comparative studies between bipolar disorder patients (BP) and depressive patients showed that, during the manic state, it is harder to maintain attention and inhibit inadequate behaviors, while during depression the problem is shared attention (Murphy et al., 1999).

Electroencephalography (EEG) has been used with BP to verify rhythmic changes in brain functions in both depression and mania states (Atagün et al., 2013; Cole et al., 1993; El-Badri et al., 2001). This kind of electrophysiological research is important to identify resulting changes in cognitive dysfunctions, especially attention. However, most of the studies investigating electrophoretical changes in BP used different methodology and data processing. Maekawa et al. (2013) used electrical mapping to show that BP have deficits in visual information processing, starting from the very early stages all the way to higher-level cognitive functions. The EEG study of Yap et al. (2009) also evidenced that visual processing deficit is apparent in schizophrenic patients and BP. According to Hall et al. (2007, 2012), sensory gating deficit has been proposed as an endophenotype for BD and schizophrenia. Early auditory gamma band response has been used to assess basic brain functions associated with auditory perception and showed that BP and schizophrenic patients featured reduced early evoked gamma band response (Hall et al., 2011; Roach and Mathalon, 2008). Donchin and Coles (1988) used P2 and P3 ERP (event related potential) components to assess higher-order cognitive processes related with attention, working memory and information processing speed. Patients with both disorders showed impaired central P3 ERPs, but P2 ERP deficit has been documented only in schizophrenic patients (O'Donnell et al., 2004). Although Donchin and Coles (1988) observed the P3 component, there is a lack of studies investigating more deeply the P300 component in the BP states, and among BP and healthy subjects. The objective of this study is to analyze the alterations of information processing in BP (euthymia, depression and mania phases) through the observation of the P300 component. We hypothesized BP to present a delay in information processing, represented by a higher P300 latency, mainly in the depressive group. On the other hand, we expect to find lower P300 amplitude for BP.

2. Materials and methods

2.1. Subjects

Eleven healthy controls (7 women and 4 men with average age of 29.78, SD: 6.89) and twenty-eight bipolar patients (17 women and 11 men with average age of 32.5, SD: 9.5) under treatment participated of this study. Patients with a lifetime history of BD and those with only current history of BD were included. They were diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition) (American Psychiatric Association, 1994), and they were asked to suspend medication one day before the exam. Patients with comorbidities were excluded from the study. The subjects were recruited from the Psychiatry Institute of the Federal University of Rio de Janeiro and both patients and controls were interviewed using the SCID-I (Structured Interview for DSM-IV) (First et al., 1996). All participants had normal or corrected-to-normal vision and no sensory, motor, cognitive or attentional deficits. Volunteers who proved to have no present or past psychiatric condition and to be medically healthy upon physical examination were considered for the control group. All patients provided written informed consent before entering the study, according to the Declaration of Helsinki. The experiment was approved by the Ethics Committee of the Psychiatric Institute of the Federal University of Rio de Janeiro (IPUB/UFRJ). According to their score on the Clinical Global Impression – Bipolar Version (CGI-BP) (Spearing et al., 1997) on the day of the experiment, bipolar patients were divided into 3 major groups: euthymic (n = 10), depressive (n = 8) and manic (n = 10).

2.2. Tasks and procedures

The subjects performed the task in a sound and light-attenuated room, in order to minimize sensory interference. The volunteers seated in front of a 15” monitor. First, EEG data was collected at rest for each subject during three minutes. After this, the subjects executed the Oddball Paradigm (explained below) simultaneously to the EEG record, and three more minutes of EEG at rest were recorded. The Oddball paradigm consists of two stimuli presented randomly, with one of them occurring relatively infrequently. The subjects need to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present experiment, target
stimuli corresponded to a square and non-target stimuli to a circle. Subjects were instructed to respond as quickly as possible to the target stimulus by pressing a button on a joystick (Model Quick Shot- Crystal CS4281). Each stimulus lasted 2.5 s, being this the same interval time between stimuli, with the screen turned off. The visual stimulus was presented on the monitor by the event-related potential (ERP) acquisition software, developed in Delphi 5.0 (Inprise Co.). The acquisition software recorded event-related potentials for the F3, Fz, F4, C3, Cz C4, P3, Pz and P4 electrode sites. P300 is the greatest positive-going peak amplitude of the waveform within a time window of 250—500 ms, in relation to a pre-stimulus baseline. The baseline was defined as the mean voltage over 120 ms before the onset of the stimulus. Each subject was submitted to six blocks of 10 trials. In other words, the square was presented 10 times in each block.

2.3. EEG data acquisition

The EEG signal acquisition was recorded using the 20-channel Braintech 3000 (EMS) EEG system, together with the ERP Acquisition program already described. This program was employed to filter the data: Notch (60 Hz), high-pass of 0.3 Hz and low-pass of 25 Hz (order 2 Butterworth). Twenty-one electrodes were arranged on a lyra cap (Eletro Cap Inc., Fairfax, VA) along the scalp on the frontal, temporal, parietal and occipital areas, according to the 10/20 system protocol, and two more electrodes were positioned on the earlobes, set as a reference point, yielding 20 mono-pole derivations to them (using Fpz as ground electrode). The caps were individually adjusted and put on each subject, according to each individual’s circumference and anatomy proportions. The signal corresponding to each EEG derivation resulted from the electric potential difference between each electrode and the pre-established reference (earlobes).

First, the impedance levels of each electrode were calculated, and they were kept below 10 kΩ. The ocular electric activity was estimated by attaching two 9-mm-diameter electrodes in a bipolar montage. The electrodes were positioned, respectively, above and below the right eye orbit, in order to register vertical ocular movements, and on the external corner of the same eye, in order to register horizontal ocular movements. Visual artifacts were a priori inspected through a data visualization program using the Matlab 5.3® (The Mathworks, Inc.).

2.4. Data processing and analysis

The electroencephalographic signals collected during the experiment were processed using methods developed by the Brain Mapping and Sensorimotor Integration Laboratory of the Psychiatry Institute of the Federal University of Rio de Janeiro in a Matlab 5.3® environment. Visual inspection and Independent Component Analysis (ICA) were applied to quantify reference-free data by removing possible sources of task-induced artifacts. Data from individual electrodes exhibiting loss of contact with the scalp or high impedances (>10 kΩ) were deleted, as were data from single-trial epochs that exhibited excessive movement artifact (>100 μV). ICA was then applied to identify and remove any artifacts that remained after the initial visual inspection. ICA is an information maximization algorithm that derives spatial filters by blind source separation of the EEG signals into temporally independent and spatially fixed components. Independent components resembling an eye blink or muscle artifact were removed, and the remaining components were then projected back onto the scalp electrodes by multiplying the input data by the inverse matrix of the spatial filter coefficients derived from ICA, using established procedures. The ICA-filtered data were then re-inspected for residual artifacts, using the rejection criteria described above. Epochs were selected between 0.5 s before and 1.5 s after the stimulus. The total number of epochs used after visual inspection and ICA for each group was as follows: Healthy controls (n = 621); euthymic group (n = 998); depression group (n = 449); and manic group (n = 560).

2.5. Time–frequency analysis

ERPs transform was computed for the Cz and Pz electrodes, since P300 is more prominent for these electrodes. Time-Frequency Analysis was plotted using the EEGLAB toolbox (Delorme and Makeig, 2004) as a qualitative analysis. It was used to visualize and compare low frequencies, such as delta (0.3—4 Hz) and theta (4—8 Hz), related to time arising from the 4 experimental groups (i.e., control, euthymic, depressive, manic).

2.6. Statistical analysis

A one-way ANOVA (SPSS version 18) was applied, in order to investigate the factor group (i.e., HC, euthymic, depressive, and maniac) for P300 and reaction time, separately. Significant difference was set at p < 0.05.

3. Results

3.1. reaction time

The one-way ANOVA demonstrated a main effect for group (p < 0.05). The post-hoc analysis showed no difference between euthymic (average: 451.57 ms, SD: 77.47 ms) and depression (average: 455.94 ms, SD: 81.82 ms) groups. We also observed that the control (average: 414.3109 ms, SD: 79.3314) and manic (average: 433.0641 ms, SD: 81.86123) groups differed from the other groups (Fig. 1).

3.2. Event-related potentials

P300 amplitude and latency were observed, as well as the subcomponents P3a and P3b. Results will be explained and presented according to specific regions: frontal (F3, F4 and Fz), central (C3, C4 and Cz) and parietal (P3, P4 and Pz).

3.2.1. Frontal area

The one-way ANOVA demonstrated a main effect for group for the Fz (Fig. 2b) and F4 (Fig. 3b) electrodes for P300 amplitude and latency (p < 0.05). For the F4 (Fig. 3b) and Fz (Fig. 2a) electrodes, differences were found between the control [(F4 - amp: 0.5733 μV; lat: 335 ms) (Fz - amp: 0.6139 μV; lat: 330 ms)] and manic [(F4 - amp: 0.4434 μV; lat: 350) (Fz - amp: 0.2824 μV; lat: 345)] groups. No difference was found between euthymic [(F4 - amp: 0.4792 μV; lat: 370 ms) (Fz - amp: 0.5396 μV; lat: 360 ms)] and depressive [(F4 - amp: 0.487 μV; lat: 375 ms) (Fz - amp: 0.5419 μV; lat: 355 ms)] groups. When analyzing the F3 electrode, differences were observed among the four groups, i.e., control (amp: 0.31 μV; lat: 330 ms), euthymic (amp: 0.3908 μV; lat: 365 ms), depressive (amp: 0.3393 μV/lat: 365 ms) and manic (amp: 0.08819 μV; lat: 350 ms) (Fig. 3a).

3.2.2. Central area

The one-way ANOVA demonstrated a main effect for group for the Cz and C4 electrodes for P300 amplitude and latency (p < 0.05). P3a and P3b components were observed for the Cz and C4 electrodes in HC. For the Cz electrode (Fig. 2b), no difference was found in the latency among euthymic (amp: 0.4737 μV; lat: 355 ms), depression (amp: 0.4884 μV; lat: 355 ms) and manic groups (amp: 0.4411 μV; lat: 355 ms); however amplitude was higher for the
manic group. The control group (amp: 0.6119 μV; lat: 335 ms) differed from the other groups in amplitude and latency. For the C4 electrode, all groups were different among them: control (amp: 0.5148 μV; lat: 350 ms), euthymic (amp: 0.5811 μV; lat: 365 ms), depressive (amp: 0.5766 μV; lat: 375 ms) and manic (amp: 0.3941 μV; lat: 375 ms) (Fig. 3d). No significant difference was found among the groups for the C3 electrode (p > 0.05).

### 3.2.3. Parietal area

The one-way ANOVA demonstrated a main effect for group for the Pz and P4 electrodes for P300 amplitude and latency (p < 0.05). P3a and P3b components were observed for the Pz electrode in the euthymic and depressive groups. Significant difference was found among all the groups for the Pz electrode: control (amp: 1.107 μV; lat: 480 ms); euthymic (amp: 0.3998 μV; lat: 395 ms); depressive (amp: 0.3674 μV; lat: 410 ms) and manic (amp: 0.6308 μV; lat: 395 ms) (Fig. 2c). For the P4 electrode, difference was found among all groups for the P300 latency; for P300 amplitude, the control group (amp: 0.6119 μV; lat: 470 ms) was different from the others, and no difference was observed among the mood phases of bipolar disorder [euthymic (amp: 0.5234 μV; lat: 390 ms), depressive (amp: 0.4905 μV; lat: 400 ms) and manic (amp: 0.4526 μV; lat: 385 ms)] (Fig. 2d). No significant difference was found among the groups for the P3 electrode (p > 0.05).

### 3.2.4. Time–frequency analysis

Fig. 4 shows Time-Frequency Analysis plots for all the groups investigated in the medial central area (i.e., Cz electrode) (Fig. 4a) and medial parietal area (i.e., Pz electrode) (Fig. 4b). The qualitative data of the Time-Frequency Analysis show changes in the spectral power for all groups, with a more explicit difference between healthy controls and bipolar patients.

### 4. Discussion

The purpose of this study was to investigate neurophysiological differences and similarities between BP and HC, through the P300 analysis. Our main findings were higher P300 amplitude in HC, low P300 amplitude in manic patients, similar amplitude and latency in euthymic and depressive patients and slower reactivity of BP. P300 amplitude and latency in BP during both depressive and euthymic periods did not differ in many areas.

P300 latency indicates stimulus processing time, largely independent of behavioral response selection and execution (Duncan and Donchin, 1982). We observed that BP demonstrated a delay in the information processing, represented by prolonged P300 latency. Before the different phases of information processing (acquisition, primary and secondary analysis, decision and execution), BP have been observed to feature a delay on decision making and execution moments. This result is in agreement with the research by Schulze et al. (2008) that found BP to have P300 latency delays compared to controls at all recording sites, with the most pronounced differences at parietal and central sites. These authors also indicated delayed P300 latency at midline sites to be associated with familial risk for psychotic BD.

Cognitive demands during task processing have an influence on P300 (Muir et al., 1991; Salisbury et al., 1999; Souza et al., 1995; Schulze et al., 2008; O’Donnell, 2004; Pierson et al., 2000). HC presented higher amplitude than BP for the Fz, Cz and Pz electrodes, which are typically responsible electrodes for P300 potential. Lower P300 amplitude for the BD group, when compared to HC, can be associated with neurocognitive dysfunction. We propose lower P300 amplitude to be considered a biomarker for BD that underlies the neurocognitive deficits. Specifically, dysfunctions in attention, memory and executive function are well documented in BD (Azorin et al., 1995; Bearden et al., 2001; Clark et al., 2002, 2005). However, most of these studies did not observe the event related potentials (ERPs). Previous studies observing P300 amplitude in healthy subjects related lower P300 amplitude with reduced attention allocation during a task. More symptomatic samples may be more likely to demonstrate amplitude deficits (Schulze et al., 2008). P300 amplitude reduction in BP is in agreement with previous paper results (Salisbury et al., 1999; O’Donnell et al., 2004). The manic group showed small P300 amplitude, mainly for the frontal electrodes (F3, Fz and F4), which reflect the activity of Brodmann cortical area 8. This region is located just before the pre-motor cortex and it participates in executive control and behavior, inductive reasoning, planning, memory processes and working memory (Trans Cranial Technologies, 2012).

According to Gordeev (2008), P300 amplitude is significantly
influenced by the complexity of a stimulus, while P300 latency is directly related to the speed at which the task is executed. Several researchers correlate changes in P300 amplitude with changes in the level of attention, pointing it as being directly proportional to the level of attention in the execution of a task (Gordeev, 2008). The pre-frontal cortex is related to executive functions, cognitive flexibility, working memory (De Carvalho et al., 2010), behavioral planning and complex thoughts, such as decision making, attention control (Bechara et al., 1997; Damasio, 1994), behavior modulation (Windmann et al., 2002; Waltz et al., 1999), and emotional regulation (Windmann et al., 2002; Lobo et al., 2011).

This small amplitude can be related to an impairment of these cognitive functions in BP during the manic state. This fact is in agreement with the mania symptoms, since they include superficial attention, disorganized thought, quantitative alterations of perception, distractibility, impulsive behavior, among others (Clark et al., 2002; Thompson et al., 2005; Goldberg, 2010).

El-Badri et al. (2001) showed young euthymic patients with bipolar affective disorder to feature significant EEG abnormalities and cognitive impairments, as well as disturbed EEG activity at rest, when compared with control subjects of similar age. This reduction in P300 amplitude can also be seen in schizophrenic patients (SP). According to Bestelmeyer (2012), BP and SP could not be differentiated based on their ERPs. If the P300 amplitude reflects attentional resource allocation, SP allocate more resources to the distracting task-irrelevant stimuli than to the task-relevant stimuli (Grillon et al., 1990). Previous research has shown that BP show some attentional deficits, which are, however, not as severe as the ones found in schizophrenia (Bozmak et al., 2005).

Results also identified euthymic and depressive patients to present marked P3a and P3b components in the parietal area. In the central area, these elements (i.e., P3a and P3b) were seen only in the HC group, whose amplitude was higher than for BP. Grillon et al. (1990) demonstrated SP to show smaller P3a and P3b amplitudes compared to HC. These authors suggested HC and patients with schizophrenia to process target and distracting stimuli differently. The reduced P3a response in the patients with bipolar disorder suggests an impaired covert orienting response or an inability to shift the attention to meaningful auditory stimuli (Friedman et al., 2001). Bestelmeyer (2012) compared the P300 of BP, SP and HC and found P3a to be slightly greater than P3b in all groups. According to the research conducted by Jahshan (2012), BP exhibited large P3a reductions for Fz, compared to the HC group, and medium reductions compared to the schizophrenia group. This finding suggests that both groups of patients may have problems detecting changes in their auditory environment.

The behavioral analysis of reaction time confirmed the electrophysiological findings already described, showing that BP have impaired information processing, which is slower, when compared to HC. Euthymic and depressive patients presented slower reactivity to the stimuli, as was also shown by other studies (Kertzman et al., 2010; Lampe et al., 2004; Pier et al., 2004), which highlight a slower response of BP during reaction time tasks that can be related to a dysfunction of information processing during the depressive state (Azorin et al., 1995; Rose and Ebmeier, 2006).

Fig. 3. Comparison among control, euthymic, depression and manic groups for P300 component (p < 0.05). (a) A one-way ANOVA showed significant difference among all groups for P300 latency and amplitude for the F3 electrode. (b) A one-way ANOVA showed significant difference between control and manic groups for P300 latency and amplitude for the F4 electrode. (c) A one-way ANOVA showed significant difference among all groups for P300 latency and amplitude for the C4 electrode. (d) A one-way ANOVA showed significant difference among all groups for P300 latency and difference between control group and bipolar patient group for P300 amplitude for the P4 electrode.
5. Conclusion

The main findings of this study were: higher P300 amplitude in HC, low P300 amplitude in manic patients and similar amplitude and latency in euthymic and depressive patients. The manic group showed the smallest P300 amplitude, mainly for the frontal electrodes, which can be related to manic state symptoms. This study provided some evidence of cognitive deficits in BP, like a delay in information processing and reduced attention allocation, which is in agreement with previous studies about BD cognitive aspects. Such finding is clinically relevant, since these neuropsychological impairments are related to different BD symptoms, which should be known and considered, in order to improve treatment strategies.

The novelty of this research is the electrophysiological analysis of P300, in order to differentiate ERP aspects at different moments of BD. The small amplitude for the pre-frontal area electrodes can be related to an impairment of cognitive flexibility, executive functions, working memory and other cognitive functions. The reduced P3a response suggests an impaired ability to shift the attention and processing to the target and away from the distracting stimuli in BP. As future directions, we suggest the execution of more studies using the same methodology of P300 components. This methodological pattern could contribute to strengthen our results and reinforce the importance of P300 as a biomarker for BD. We also propose that new studies comparing the EEG parameters across groups depending on the number of experienced mood episodes should be implemented, in order to relate more closely the electrocortical changes in BD using the new inflammation and neuroprogression theories in BD.

Conflicts of interest

The authors and the represented institutions confirm that the content of the present article has no conflict of interest.

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