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Title: Visual Evoked Potential in Bipolar Disorder Patients during the Oddball Paradigm

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Keywords: Bipolar disorder; EEG; Information Processing; Neurobiology; P300.

Abstract: Bipolar disorder (BD) is characterized by an alternated occurrence between acute mania episodes and depression or remission moments. The electroencephalography (EEG) has been used with bipolar disorder patients (BP) to verify rhythmic changes in brain functions in the depression and mania states. The objective of this study is to analyze the alterations of information processing in BP (euthymia, depression and mania) during an attention and movement saccadic task, focusing on the P300 component, which is an electric potential of the cerebral cortex generated in response to external sensorial stimuli and which involves more complex neurophysiological processes related to stimulus interpretation. After observing P300 plus 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 an 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 BP.

Cover letter

Reviewers,

This research is original and has been done in order to analyze the alterations of information processing in bipolar patients (euthymia, depression and mania phases) through the observation of the P300 component. We hypothesized bipolar patients would present a delay in the information processing, represented by a higher P300 latency, mainly in depressive group. On the other hand, we expected to find slower P300 amplitude for bipolar patients.

We enrolled in this study eleven healthy controls (HC) and twenty-eight bipolar patients (17 women and 11 men). 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. The Ethics Committee of the Psychiatric Institute of Federal University of Rio de Janeiro (IPUB/UFRJ) approved the experiment. According to their score on the Clinical Global Impression – Bipolar Version (CGI-BP) (Spearing et al., 1997) on the day of the experiment, we divided the bipolar patients into 3 major groups: euthymic (n=10), depressive (n=8) and manic (n=10).

Our main findings 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 a delay in the information processing and reduced attention allocation, which is in agreement with previous studies that showed cognitive aspects of BP.

The **novelty** of this research is the electrophysiological analysis of P300 in order to differentiate ERP aspects in 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.

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CONFLICT 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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Visual Evoked Potential in Bipolar Disorder Patients during the Oddball Paradigm

INTRODUCTION

Bipolar disorder (BD) and its neurological, cognitive and behavioral bases have been investigated widely. BD is considered a relatively frequent and chronic psychiatric condition, causing professional and social difficulties or incapacitation. It is characterized by an alternated occurrence between acute mania episodes and depression or remission moments (Akiskal et al., 2000; Fleck et al., 2003; Hisatugo, 2008; Kaplan et al., 1997), or by the occurrence of mixed episodes featuring the characteristics of both states. The BD symptoms can appear at any age, but they most commonly emerge between the second or third life decades. This illness is associated with episodes of distress and disruption, and with a relatively high risk of suicide (Ösby et al., 2001).

The etiology of BD is not known yet, but many researches cite the existence of complex dysfunctions, including alterations of the receptors and post-receptors of neurotransmitters. In this context, the GABA (gamma-aminobutyric acid) neurotransmitter, which is the core component of cortico-limbic circuitry, is found to be defective in the cerebral cortex of bipolar patients (Başar & Güntekin, 2008; Benes & Berretta, 2001). Dysfunction in GABA/glutamatergic systems and neural circuits that regulate cognitive processing seems to be involved in the underlying pathology (Başar & Güntekin, 2008). Cortical inhibitory deficits were thought to provide neurophysiological evidence for an association between bipolar disorder and disrupted cortical GABA related inhibitory neurotransmission (Başar & Güntekin, 2008; Levinson et al., 2007).

According to Özerdem 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, 2013; Dupont et al.1995; Blumberg et al. 2002; Caligiuri 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).

During the manic state, cognitive changes occur, such as: exceeded optimism, grandiosity and paranoid ideas, accelerated and disorganized thought, quantitative alterations of perception, increased energy and motor activity, decreased need for sleep, distractibility, pleasure seeking and impulsive behavior. In addition, other cognitive distortions happen and provoke inadequate behavior: the patients' idea that, since they feel good, they do not need the medicaments anymore; the patients' belief that they are the only ones who are right, overestimating their own opinions and disregarding other people's opinions; the focus on the present; the overestimation of their capacities, among others. Manic patients also display signs of dysfunction in attentional measures, complex processing and memory (Özerdem et al., 2008).

During the depression state, the distortion of thoughts, rules and beliefs can cause hopelessness and suicidal ideas. Some of the most common distortions are: the patients' belief that their difficulties are definitive and insoluble obstacles; the belief that they have lost, irreversibly, the capacity to rejoice or feel

pleasure in life; the feeling of guilt; the idea that only death can relieve their distress; the feeling of anger against people. Furthermore, there is a reduction in cognitive capabilities, such as attention and information processing, as well as slower thought processing.

It is suggested that having an acute episode of mania or depression can cause damage to the learning and memory systems (Bearden et al., 2001). According to Purcell et al. (1997), information processing is associated with neurocognitive dysfunctions of BD. Attentional and cognitive alterations are significant in different states of BD. 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 in depression the problem is the shared attention (Murphy et al., 1995).

The electroencephalography (EEG) has been used with BP to verify rhythmic changes in brain functions in both depression and mania states (Atagün, 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. 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 will present a delay in the information processing, represented by a higher P300 latency, mainly in depressive group. On the other hand, we expect to find slower P300 amplitude for BP.

MATERIALS AND METHODS

Subjects

We enrolled in this study eleven healthy controls (HC) and twenty-eight bipolar patients (17 women and 11 men with average age of 32.5, SD: 9.5). The patients were diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition) (American Psychiatric Association, 1994). We recruited the patients 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. The Ethics Committee of the Psychiatric Institute of Federal University of Rio de Janeiro (IPUB/UFRJ) approved the experiment. According to their score on the Clinical Global Impression – Bipolar Version (CGI-BP) (Spearing et al., 1997) on the day of the experiment, we divided the bipolar patients into 3 major groups: euthymic (n=10), depressive (n=8) and manic (n=10).

Tasks and Procedures

The subjects performed the task in a sound and light-attenuated room, to minimize sensory interference. The volunteer sited in front of a 15” monitor. First, we collected the EEG data at rest for each subject during three minutes. After this, the subject executed the Oddball Paradigm (explained below) simultaneously to the EEG record; and we registered more three minutes of EEG at rest. Oddball

paradigm consists of two stimuli presented randomly, with one occurring relatively infrequently. The subjects need to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present experiment, target stimuli correspond to a square and non-target stimuli to a circle. We instructed the subjects to respond as quickly as possible to the target stimulus by pressing a button in a joystick (Model Quick Shot- Crystal CS4281). Each stimulus lasted 2.5 seconds, 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. The 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. We defined the baseline 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.

EEG data acquisition

The EEG signal acquisition was recorded using the 20-channel Braintech 3000 (EMSA) 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 lycra 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 correspondent 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.).

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.

Statistical Analysis

We applied a one-way ANOVA (SPSS version 18) to investigate the factor group (i.e., HC, euthymic, depressive and maniac) for the P300 and the reaction time separately. We considered significant differences for $p<0.05$.

RESULTS

Reaction Time

The behavioral analysis of the reaction time showed that all groups were different, with the exception of the euthymic and depressive groups, which were similar to each other. The control group reaction time (414.3109 ms) was the lowest one, while the manic group (433.0641 ms) showed a faster reaction time, when compared to the euthymic (451.5718 ms) and depressive (455.942 ms) groups (Figure 1)

Eveten-Related Potentials

We observed P300 amplitude and latency as well as the subcomponents P3a and P3b. We will present and explain the results according to the specific regions: frontal (F3, F4 and Fz), central (C3, C4 and Cz) and parietal (P3, P4 and PZ).

Frontal area

We did not observe the typical conformation of P3a and P3b for the F3, F4 and Fz electrodes. Analyzing the F3 electrode, we observed a greater P300 amplitude and a large P300 latency in the euthymic (amp: 0.3908µV; lat: 365ms) and depressive groups (amp: 0.3393µV/lat: 365ms) when compared to the HC group (amp: 0.31µV; lat: 330ms). We also observed a smaller P300 amplitude for the manic patients (amp: 0.08819µV; lat: 350ms) when compared to the others (Figure 2). For the F4 (Figure 3) and Fz (Figure 4) electrodes we found a greater amplitude and a smaller latency in HC [(F4 - amp: 0.5733µV; lat: 335ms) (Fz - amp: 0.6139µV; lat: 330ms)]; and a smaller amplitude and a greater latency for manic group [(F4 - amp: 0.1443µV; lat: 350) (Fz - amp: 0.2824 µV; lat: 345). We did not find difference between euthymic [(F4 - amp: 0.4792µV; lat: 370ms) (Fz - amp: 0.5396µV; lat: 360ms)] and depressive [(F4 - amp: 0.487µV; lat: 375ms) (Fz - amp: 0.5419 µV; lat: 355ms) groups, however these groups differs from the others.

Central area

We only observed the P3a and P3b components for the C4 and Cz electrodes in HC. For C3, the P300 amplitude and latency were very similar among the euthymic (amp: 0.2274µV/lat: 335ms), depressive (amp: 0.2112µV/lat: 335ms) and manic (amp: 0.2351µV/lat: 360ms) groups, while latency was smaller in

HC (amp: 0.224µV/lat: 335ms) (Figure 5). For the C4 electrode, the same highest P300 amplitude and latency were presented by the euthymic (amp: 0.581 µV; lat: 365ms) and depressive groups (amp: 0.5766 µV; lat: 375ms). HC presented smaller amplitude and latency (amp: 0.5148µV; lat: 350ms) and the manic group showed smaller amplitude (amp: 0.3941 µV; lat: 375ms) (Figure 6). For the Cz electrode, the amplitude in the control group (amp: 0.6119 µV; lat: 335ms) was greater and the latency smaller than the amplitude and latency found in the other groups. We did not observe difference among the latency in the euthymic (amp: 0.4737µV; lat: 355ms), depression (amp: 0.4884µV; lat: 355ms) and manic groups (amp: 0.4411µV; lat: 355ms), however the amplitude was higher for manic group (Figure 7).

Parietal area

We observed the P3a and P3b component only for the Pz electrode in the euthymic and depressive groups. No significant difference was found for P3, so this electrode was discarded (Figure 8). For the P4 electrode, we find the greatest P300 amplitude and latency in the control group (amp: 0.6326µV; lat: 470ms). The latency in the euthymic (amp: 0.5234µV; lat: 390ms), depressive (amp: 0.4905µV; lat: 400ms) and manic (amp: 0.4526µV; lat: 385ms) groups were similar, but they presented differences in their amplitudes (Figure 9). For Pz, the control group (amp: 1.107µV; lat: 480ms) amplitude and latency were discrepantly higher than in the others. The manic group showed great amplitude (amp: 0.6308µV; lat: 395ms), higher than the euthymic (amp: 0.3998µV; lat: 395ms) and depressive (amp: 0.3674µV; lat: 410ms) groups (Figure 10).

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 and similar amplitude and latency in euthymic and depressive patients. The P300 amplitude and latency in BP during both depressive and euthymic periods did not differ in many areas.

We observed that BP demonstrated a delay in the information processing, represented by a prolonged P300 latency. Before the different phases of information processing (acquisition, primary and secondary analysis, decision and execution), has been observed that BP has a delay on decision making and execution moments. Lower P300 amplitude for the BD group, when compared to HC, is associated with a reduced attention allocation, as it is well described in the literature that P300 amplitude is related to the amount of attentional resources engaged during a task. In other words, cognitive demands during task processing influence P300 (Muir et al., 1991; Salisbury, 1999; Souza, 1995; Schulze et al., 2008; O´Donnell, 2004; Pierson et al., 2000).

The manic group showed small P300 amplitude, mainly for the frontal electrodes (F3, Fz and F4), which reflect the activity of eighth Brodmann cortical area. This region is situated just anterior the premotor cortex and participates of executive control and behavior, inductive reasoning, planning, memory processes and working memory (Trans Cranial Technologies, 2012).

According to Gordeev (2008), the amplitude of P300 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 the 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 JF, 2010). Özerdem et al. (2008) pointed out that manic patients also display signs of dysfunction in attentional measures, complex processing and memory. Clark et al. (2005) concluded that BP present a deficit in sustained attention during the acute manic crisis. The frontal reductions in BP may reflect abnormalities in a hypothetical frontal generator, consonant with reports about altered frontal lobe functioning in mania (Salisbury, 1999).

El-Badri et al. (2001) showed that young euthymic patients with bipolar affective disorder 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 the 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, but not as severe as the ones found in schizophrenia (Bozikas et al., 2005).

We also identified that euthymic and depressive patients present a marked P3a and P3b components in the parietal area. In the central area, these conformations (i.e., P3a and P3b) were seen only in the HC group, whose amplitude was higher than in BP. Grillon et al. (1990) demonstrated that SP showed smaller P3a and P3b amplitudes compared to HC. These authors suggested that HC and patients with schizophrenia processed 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., 2000), 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 & Ebmeier, 2006).

CONCLUSION

Our main findings 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 a delay in the information processing and reduced attention allocation, which is in agreement with previous studies that showed cognitive aspects of BP. The novelty of this research is the electrophysiological analysis of P300 in order to differentiate ERP aspects in 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.

LIST OF ABBREVIATIONS

BD: Bipolar Disorder

BP: Bipolar Disorder Patients

EEG: Electroencephalogram

ERP: Event-related potential

GABA: Gamma-aminobutyric acid

HC: Healthy controls

ICA: Independent Component Analysis

SP: Schizophrenic patients

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Figure(s)

Graphs:

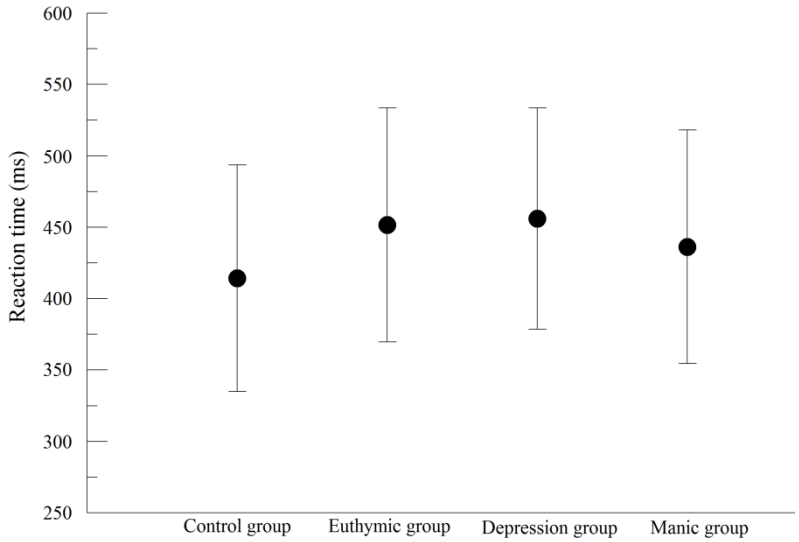

Figure 1: An one-way ANOVA design showed a reaction time difference between all groups of the oddball paradigm with the exception of the euthymic (■) and depressive (▲) groups ($p<0.05$).

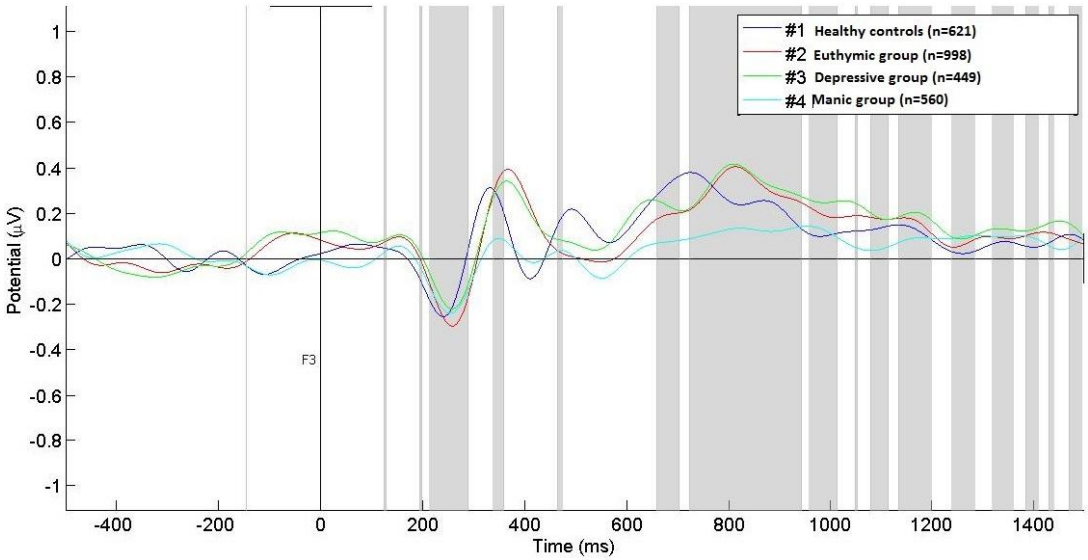

Figure 2: Grand average P300 waveforms recorded from F3 electrode plotted on Matlab 5.3®.

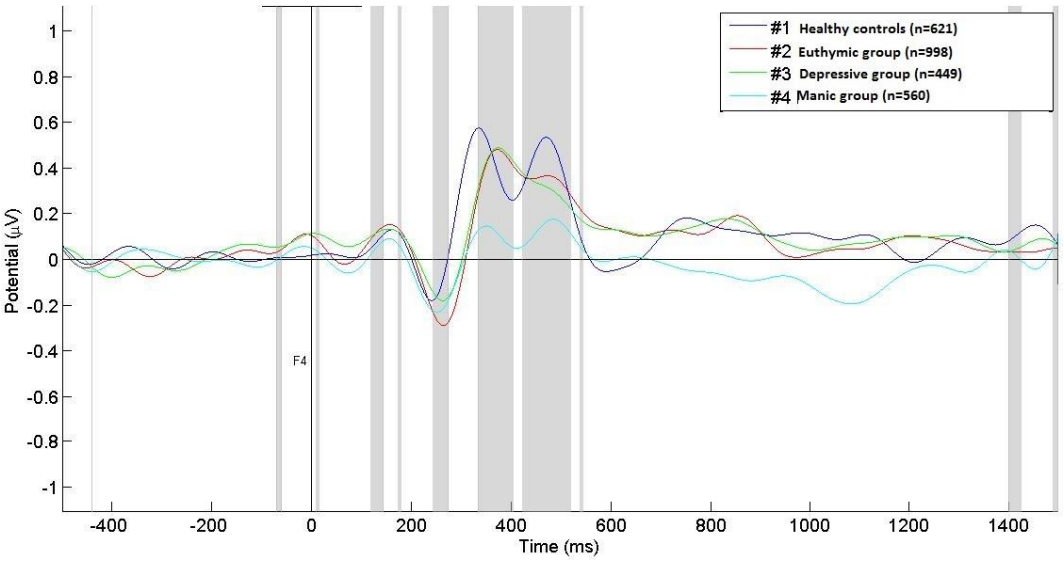

Figure 3: Grand average P300 waveforms recorded from F4 electrode plotted on Matlab 5.3®.

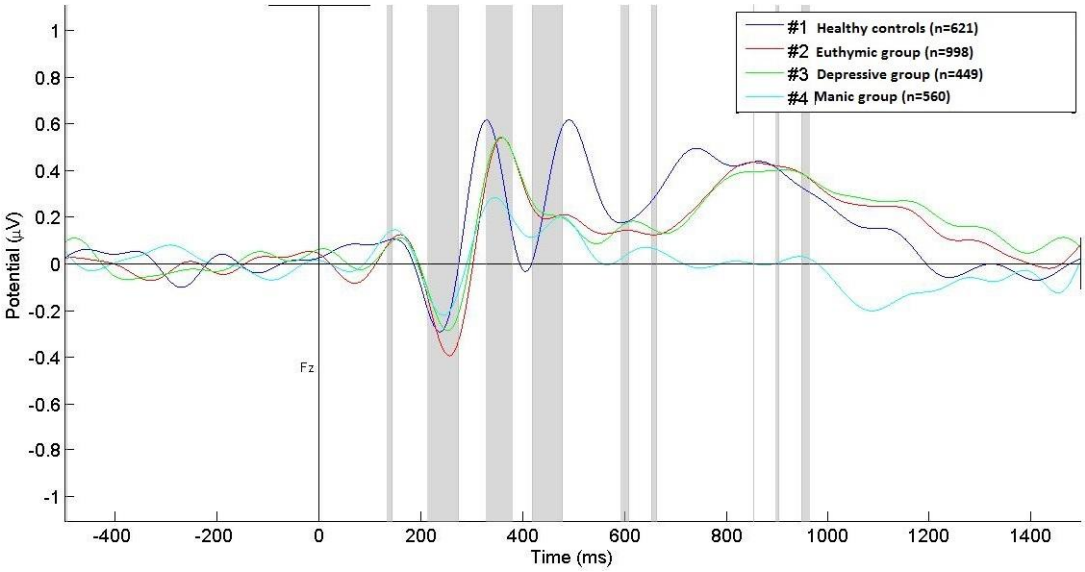

Figure 4: Grand average P300 waveforms recorded from Fz electrode plotted on Matlab 5.3®.

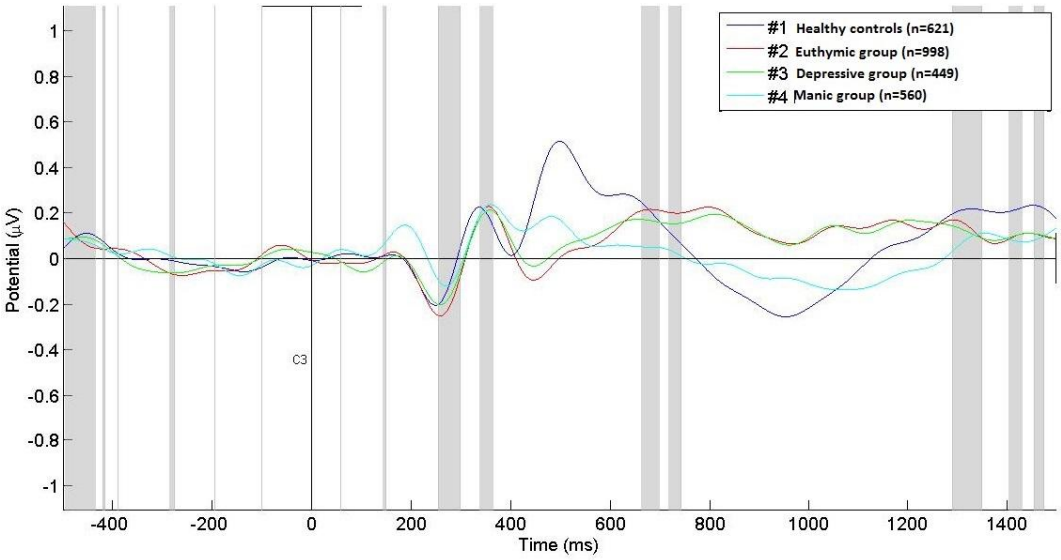

Figure 5: Grand average P300 waveforms recorded from C3 electrode plotted on Matlab 5.3®.

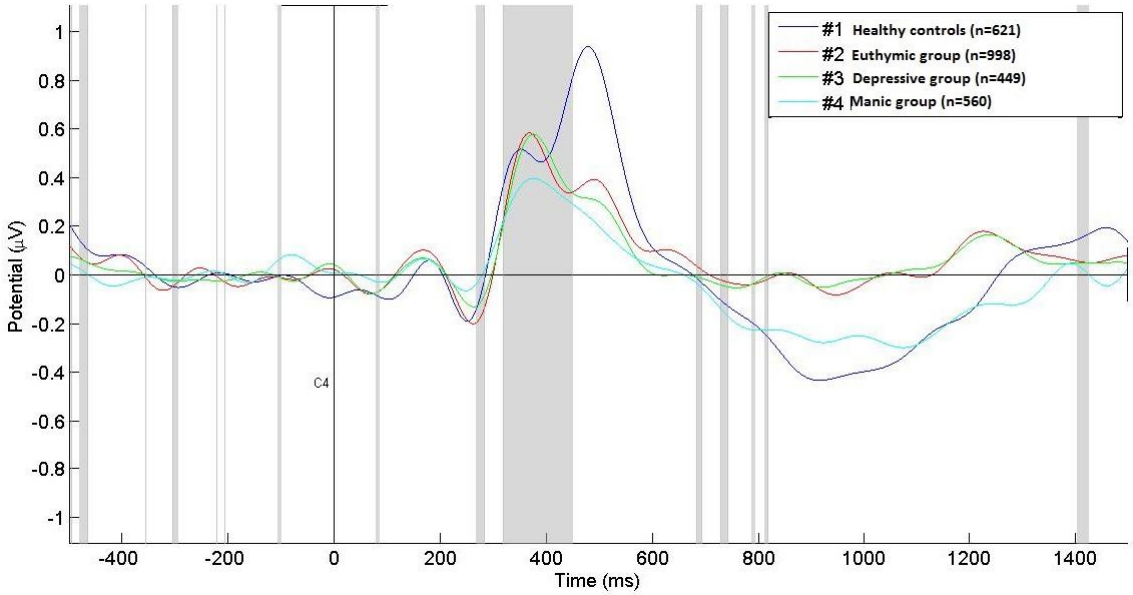

Figure 6: Grand average P300 waveforms recorded from C4 electrode plotted on Matlab 5.3®.

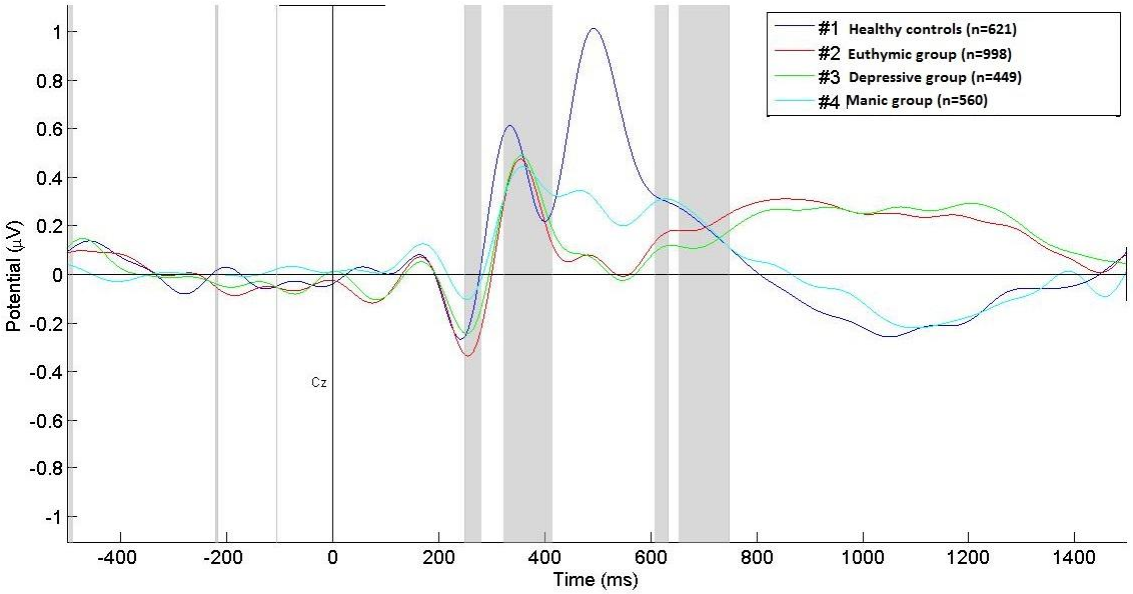

Figure 7: Grand average P300 waveforms recorded from Cz electrode plotted on Matlab 5.3®.

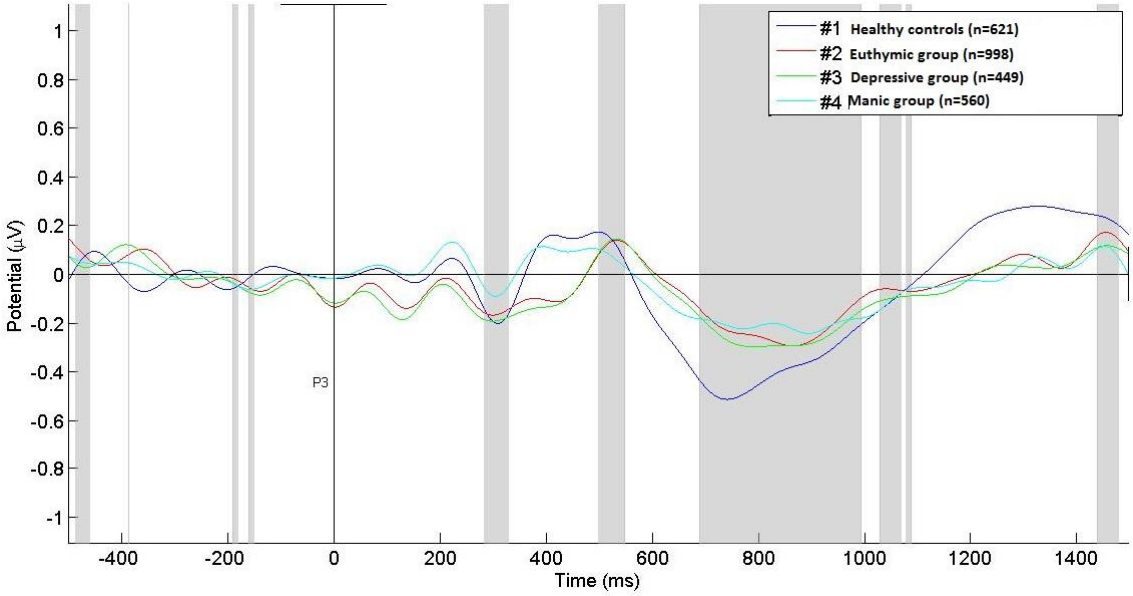

Figure 8: Grand average P300 waveforms recorded from P3 electrode plotted on Matlab 5.3®.

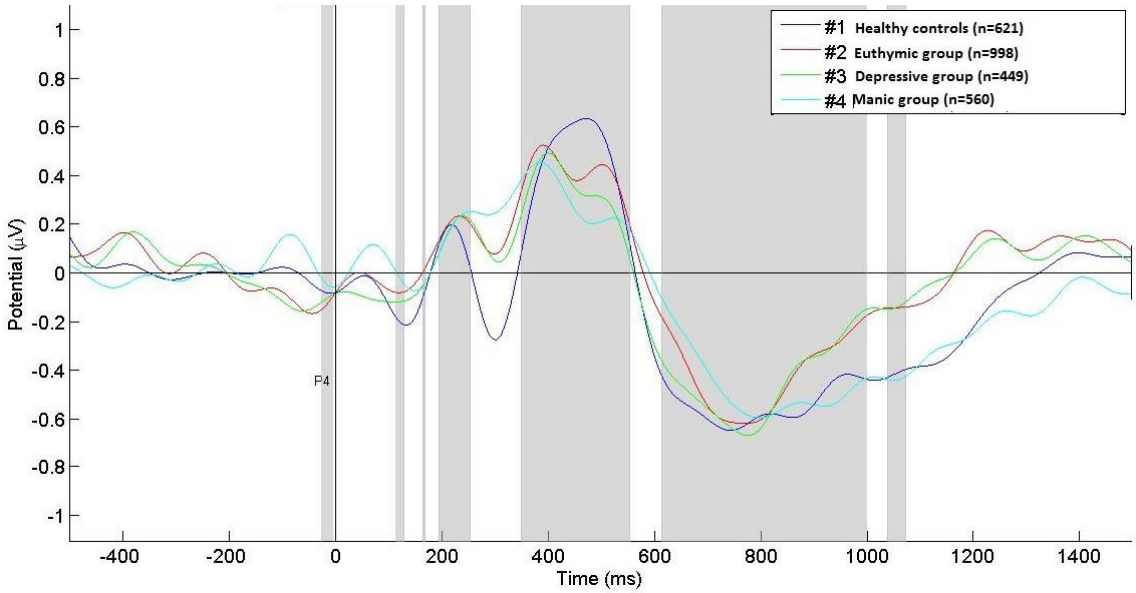

Figure 9: Grand average P300 waveforms recorded from P4 electrode plotted on Matlab 5.3®.

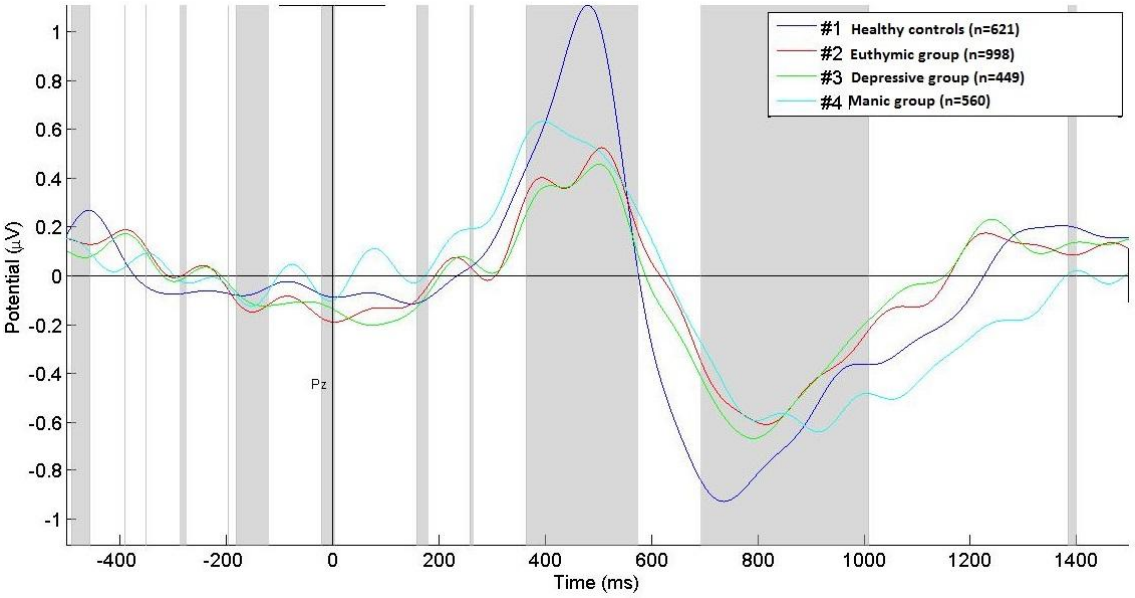

Figure 10: Grand average P300 waveforms recorded from Pz electrode plotted on Matlab 5.3®.

Highlights:

- Higher P300 amplitude in healthy controls, low P300 amplitude in manic patients.
- Similar P300 amplitude and latency in euthymic and depressive patients.
- Manic group showed the smallest P300 amplitude, mainly for the frontal electrodes.
- Small P300 amplitude for the pre-frontal area electrodes can be related to an impairment of cognitive flexibility, executive functions and working memory.
- This study provided some evidence of a delay in the information processing and reduced attention allocation of bipolar patients.