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# Changes in absolute theta power in bipolar patients during a saccadic attention task

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ABSTRACT

The present study analyzed absolute theta power (ATP) in brain areas involved with attention in the three phase of BD while the patients performing a saccadic attention task. We hypothesized that patients in depression and mania states show a higher ATP compared to euthymic patients, since a higher ATP is indicative of attention deficit. We analyzed the frontal (F7, F3, Fz, F4 and F8) and central (C3, Cz and C4) areas. Thirty bipolar patients were enrolled in this study. The subjects performed a saccadic attention task while their brain activity pattern was recorded using quantitative electroencephalography (20 channels). Our results showed a main effect for group over C3, C4, Cz, F7, F4, F8 electrodes, and a main effect for moment over Cz, F7, F8 electrodes. These results indicate that both task and groups produce changes in theta activity in distinct cortical areas that participate in the organization of attention. Our results therefore demonstrate that, although it is well established in the literature that theta has a relevant role in the attention process, it is necessary to deepen the investigations to better understand the specifics of theta during visual processing tasks that have a demand for attention.



## 1. Introduction

Bipolar disorder (BD) is a chronic mental illness that is characterized by an alternated occurrence among mania, depression and remission moments (Akiskal et al., 2000; Fleck et al., 2003). This illness is associated with episodes of distress and disruption (Ösby et al., 2001). The main symptoms of mania state are: exceeded grandiosity and paranoid ideas, accelerated and disorganized thought, alterations of perception, increased energy and motor activity, decreased need for sleep, distractibility and impulsive behavior. During the depression state, patients present distortion of thoughts, lower energy and motor activity, feeling of hopelessness and suicidal ideas. In this moment, there is a reduction in cognitive capabilities, such as attention and information processing, as well as slower thought processing.

Neurocognitive dysfunction is associated with the different states of BD (i.e., euthymic, maniac and depressive) (Martínez-Arán et al., 2004;Malhi et al., 2007;Henry et al., 2013), even in the euthymic phase of the illness. Particularly, disruptions in the attention process are suggested to participate of the symptomatology of BD. Murphy et al. (1999) demonstrated impairment in the ability to inhibit behavioral responses and focus attention, while depressed patients demonstrated impairment in the ability

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to shift the focus of attention. Researches also indicated that sustained attention deficit is present in the euthymic state of BD and becomes worse in the states of mania (Clark and Goodwin, 2004). Studies of individuals with bipolar disorder identified deficits in verbal memory, executive functioning and sustained attention in BD patients (Sweeney et al., 2000; Quraishi and Frangou, 2002).

In contrast to the wealth of neuropsychology studies in BD, little is known about electrophysiologic correlates. Recent studies investigated oscillatory responses to the visual oddball paradigm in medication-free bipolar patients, the authors investigated beta activity in manic state (Ozerdem et al., 2008) and gamma coherence in manic and euthymic states (Ozerdem et al., 2010, 2011). On the other hand, recent studies demonstrated that the saccadic movement is an important parameter in the neurological and psychiatric investigations, showing an important role of the frontal cortex and motor cortex in programming saccadic eye movement and visual attention (Corbetta and Shulman, 2002; Mcdowell et al., 2008; Berman et al., 2009). The research conducted by Velasques et al., 2013 observed that the eye saccadic movement task supported the visuospatial processing impairment and a deregulation in cortical inhibitory mechanism in bipolar patients. Although these studies demonstrate alteration in oscillatory activity in the different states of BD, few studies investigated theta activity in this population and no studies related saccadic eye movement with attention, brain oscillations and the BD states.

Several studies have shown overlap between the cortical areas involved in directing attention and preparation of saccades (Ramat et al., 2007). The choice of theta (4–8 Hz) is justified by its relation to cognitive functions, such as sensory information encoding, attention mechanisms, space navigation and communication among different brain regions (Gongora et al., 2014; Tanaka et al., 2014). Studies using electroencephalography (EEG) in bipolar patients have contributed to the verification of numerous rhythmic changes in brain function in depression and mania, leading to important assumptions(Yeap et al., 2009). These studies have a high understanding of how certain biological gears can affect the clinical symptoms of the disease, its progression and treatment responses. The deepening of electrophysiological investigations in bipolar patients is essential to identify the main changes resulting from cognitive impairment, especially of attention. In this context, the aim of this study is to analyze electroencephalographic abnormalities in bipolar patients (i.e., mania, depression and euthymia). The aim of the present study was to assess absolute theta power in the frontal cortex (i.e., the frontal area is involved in the processing of voluntary attention, during a planning and cognitive control task) and central area (i.e., the central line can be influenced by the task and the condition of the patient) during a prosaccade task in the three phase of BD. Although there are other areas involved in attention and saccadic eye movement, such as parietal and occipital cortex, we included the areas that are mainly related to the motor aspects of saccadic eye movement and attention. Therefore, we hypothesized that BD presents an attention impairment, mainly during maniac and depressive phases. This impairment will be represented by an increased absolute theta power in the frontal and central regions for these groups when compared to euthymic phase. (Loo and Makeig, 2012; Poltavski et al., 2012).

## 2. Methods

### 2.1. Subjects

Thirty bipolar patients (14 male), right-handed, age between 25 and 40 years (*mean*: 33.6; S.D.: ±7.06), diagnosed according to the DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition) (American Psychiatric Association, 1994) were enrolled in this study. The patients were recruited from the Psychiatry Institute of the Federal University of Rio de Janeiro and both patients and controls were interviewed using SCID-I (Structured Interview for DSM-IV). All participants had normal or corrected-to normal vision and no sensory, motor, cognitive or attentional deficits that would affect saccadic eye movement. All patients provided written informed consent before entering the study and the experiment was approved by the Ethics Committee of the Psychiatric Institute of Federal University of Rio de Janeiro (IPUB/UFRJ) according to the Declaration of Helsinki. The bipolar patients were divided into 3 major groups (depressive, maniac and euthymic) at the day of the experiment according to their score in the Clinical Global Impression – Bipolar Version (CGI-BP) (Spearing et al., 1997): depressive ($n=10$), maniac ($n=10$) and euthymic ($n=10$).

### 2.2. Tasks and procedures

Subjects were seated on a comfortable chair in a darkened and sound-protected room in order to minimize sensory interference. At the participants' eye level, a bar composed of 30 light emitting diodes (LEDs) was positioned with 15 of these LEDs located on the left side of fixation, and 15 on the right side. The bar had a length of 120 cm. The distance between the participants' eyes and the LED bar was standardized at 100 cm. Computer software controlled the LED bar and determined the presentation of the stimulus. The Brain Mapping and Sensory Motor Integration Lab developed the bar device. Participants were asked to keep their eyes fixed on the center of the bar, and to shift their eyes when they perceived one of the diodes lighting up. Participants were instructed to follow the LEDs with their eyes in such way that their heads remained static. The saccadic eye movement paradigm consisted of a fixed pattern of stimulus presentation where the target-stimulus (target LED) always appeared at a pre-defined position, i.e., LED 12, of either the left or the right side, alternating between left and right. This condition is characterized by predictability, since the stimulus appears at a pre-defined spatial location in the periphery of the visual field. Each LED remained lit for 250 ms, with an inter-LED-time of 2 s. Each participant underwent 12 consecutive blocks, with 20 trials per block. The probability of a light to appear on the left or right side was counterbalanced within and across blocks.

### 2.3. EEG data acquisition

The International 10/20 EEG electrode system (Jasper 1958) was used with a 20-channel EEG system (Braintech-3000, EMSAMedical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivation using the earlobes reference. We used three different sizes of the nylon cap (i.e., S, M and L) according to the subject. Impedance of EEG and EOG electrodes was kept between 5 and 10 kΩ. The data recorded had total amplitude of less than 70 μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between 0.01 Hz (high-pass) and 80 Hz (low-pass), and sampled at 200 Hz. The software Data Acquisition (Delphi 5.0) from the Brain Mapping and Sensory Motor Integration Lab was employed with the digital filter notch (60 Hz).

### 2.4. Saccadic eye movement acquisition

Four additional electrodes of 9 mm in diameter mounted in a bipolar form were used to measure the electrooculogram (EOG). Electrodes were arranged horizontally from the outer canthi of both eyes to determine the horizontal EOG (hEOG) and were positioned vertically above both eyes to determine the vertical EOG (vEOG).

### 2.5. Data processing and analysis

We applied a visual inspection and independent component analysis (ICA) to remove possible sources of artifacts produced by the task (i.e., blink, muscles and saccade-related artifacts). The data were collected using the bi-auricular reference and they were transformed (re-referenced) using the average reference after we conducted the artifact elimination using ICA. We eliminated the components related to eye blink and saccade-related artifacts (mean: 3.2456; S.D.: 0.536). We removed by visual inspection 25 (twenty-five) trials which clearly showed a blink and a saccade-related artifacts "influence", and through ICA we removed the components that showed blink and saccade-related artifacts "contamination". A classic estimator was applied to the Power Spectral Density (PSD), estimated directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB (Matworks, Inc.). Eight hundred ($4\,s \times 200\,Hz$) samples with rectangular windowing were analyzed. We extracted Quantitative EEG parameters within a time frame of 500 ms before the stimulus presentation (moment 1) and 500 ms after the target stimulus (LEDs) (moment 2). The Fourier Transform resolution was 1/4 s–0.25 Hz (FFT). The "Run-test" and "Reverse-Arrangement test" were applied to examine a stationary process, which was accepted for every 1 s (epoch's duration). In this manner, based on artifact-free EEG epochs, the threshold was defined by the mean plus three standard deviations;

epochs which showed a total power higher than this threshold were not included into the analysis. The sampling rate used for all the signals was 200 Hz.

### 2.6. Site localization

We selected the central and frontal areas for analysis because these regions are related to attention process and the control and execution of saccadic movement. The frontal cortex is widely associated with attention, cognition and eye movement generation (Alliket al., 2003; Mcdowell et al., 2008; Lavergne et al., 2008). The central area is responsible for motor ability, eye movement execution, and planning and execution of voluntary movement (Trommershauser et al., 2009; Diniz et al., 2012).

### 2.7. Statistical analysis

Absolute power for the theta frequency band during the fixed saccadic paradigm (i.e., simple light stimulation) was assessed in 30 bipolar patients (i.e., 10 depressive, 10 maniac and 10 euthymic). Groups were compared for the absolute theta power values on frontal (i.e., F7, F3, Fz, F4 and F8) and central (i.e., C3, C4 and Cz) electrodes by means of a repeated measure analysis of variance (ANOVA).

Statistical analysis was performed using SPSS for Windows—version 17.0 (SPSS Inc., Chicago, USA) and absolute theta power was the dependent variables of interest. The statistical analysis was performed using a repeated measures two-way ANOVA with the factors group (3 levels: euthymic, depressive, maniac BD patients) and moment (2 levels: pre and post-stimulus). The group differences were tested using the Scheffé post-hoc test if ANOVA was significant.

## 3. Results

We analyzed the absolute theta power on the following areas: frontal (i.e., F7, F3, Fz, F4, F8 electrodes) and central (i.e., C3, C4 and Cz electrodes) cortex.

### 3.1. Frontal cortex

We found a main effect for group and moment for the electrodes F7 ($F$=102,953; $p<0.001$; $d^a=0.31$; d.f.=2/$F$=33,805; $p<0.001$; $d^a=0.26$; d.f.=1) and F8 electrode ($F$=29,878; $p<0.001$; $d^a=0.42$; d.f.=2/$F$=20,178; $p<0.001$; $d^a=0.23$; d.f.=1)(Figs. 1 and 3 respectively). For the electrode F7 the post-hoc analysis showed that all the groups are different among them; and for the electrode F8 the post-hoc analysis revealed that the depressive group differs from the others, with lower absolute theta power for the depressive group. And we observed a higher beta power for the post-moment. We also found a main effect for group for the F4 ($F$=27.893; $p<0.001$; $d^a=0.52$; d.f.=2) (Fig. 2). For the F4 electrode, the post-hoc analysis showed that the depressive group differs from the euthymic and maniac groups, with a lower absolute theta power for the depressive group.

### 3.2. Central cortex

We found a main effect for group ($F$=11,133; $p<0.001$; $d^a=0.22$; d.f.=2) and moment ($F$=7, 220; $p$=0.007; $d^a=0.47$; d.f.=1) for the electrode Cz (Fig. 5). The post-hoc analysis showed a higher absolute theta power for the depressive group and a lower absolute theta power for maniac group, the groups were different among them. We observed a higher absolute theta power in the post-moment. We also found a main effect for group for the electrodes C3 ($F$=5377; $p$=0.005; $d^a=0.34$; d.f.=2) and C4 ($F$=58,965; $p$=0.000; $d^a=0.37$; d.f.=2) (Fig. 4). For both electrodes the post-hoc analysis showed a difference among all the groups.

## 4. Discussion

This study aimed to observe the patterns of the absolute theta power in frontal and central cortex, while performing an attention task involving saccadic eye movements in subjects with bipolar disorder. In particular, it aimed to observe the theta oscillations in different phases of bipolar disorder, such as depression, mania and euthymia. Therefore, we assessed changes in theta oscillations in the cortical regions involved in the processing of voluntary attention during a task of saccade planning, implementation and cognitive control. The theta activity varies within the range 4–8 Hz and can be seen prominently during sleep, but when the individual is awake there are two types of theta activity (Smith et al., 1999; De Araújo et al., 2002). The first one is related to states of

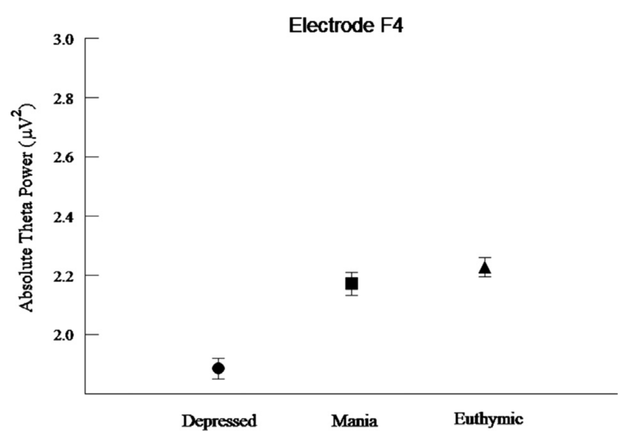


**Fig. 2.** Mean and standard deviation of absolute theta power for electrode F4. The bars represent S.D. A 3 × 2 ANOVA design showed a main effect of group ($p<0.001$).

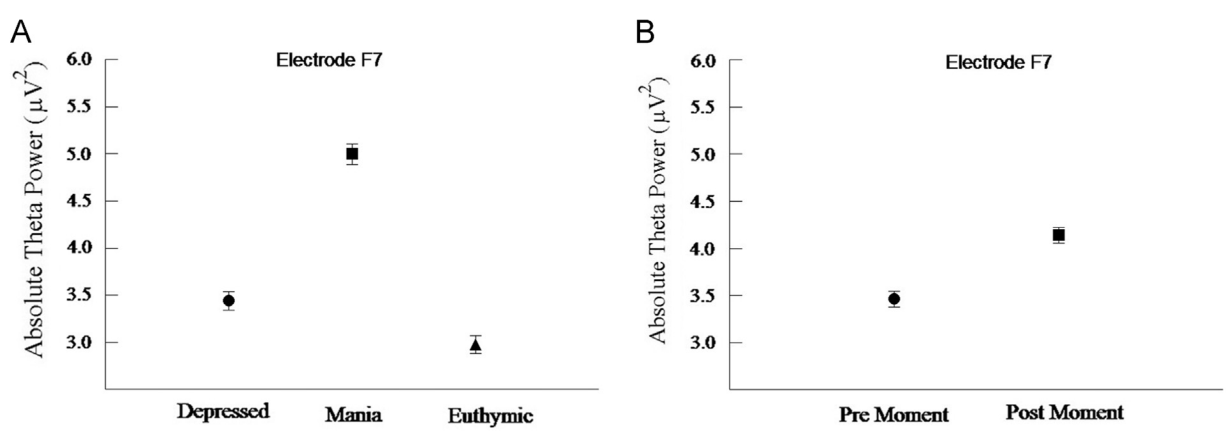


**Fig. 1.** Mean and standard deviation (S.D.) of absolute theta power for electrode F7. The bars represent S.D. A 3 × 2 ANOVA design showed a main effect of group ($p<0.001$) (a) and a main effect of moment ($p<0.001$) (b).

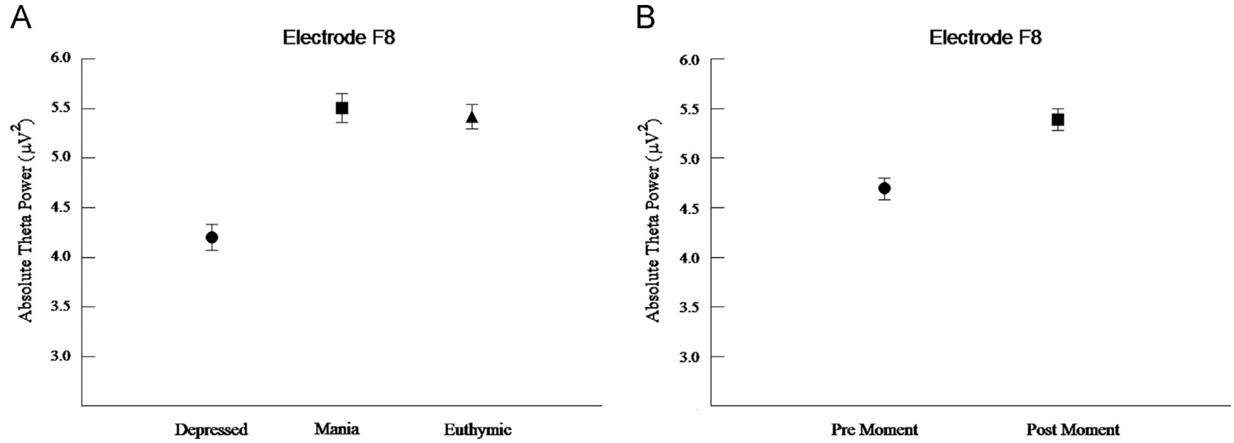


**Fig. 3.** Mean and standard deviation of absolute theta power for electrode F8. The bars represent S.D. The bars represent S.D. A 3 × 2 ANOVA design showed a main effect of group ($p < 0.001$) (a) and a main effect of moment ($p < 0.001$) (b).

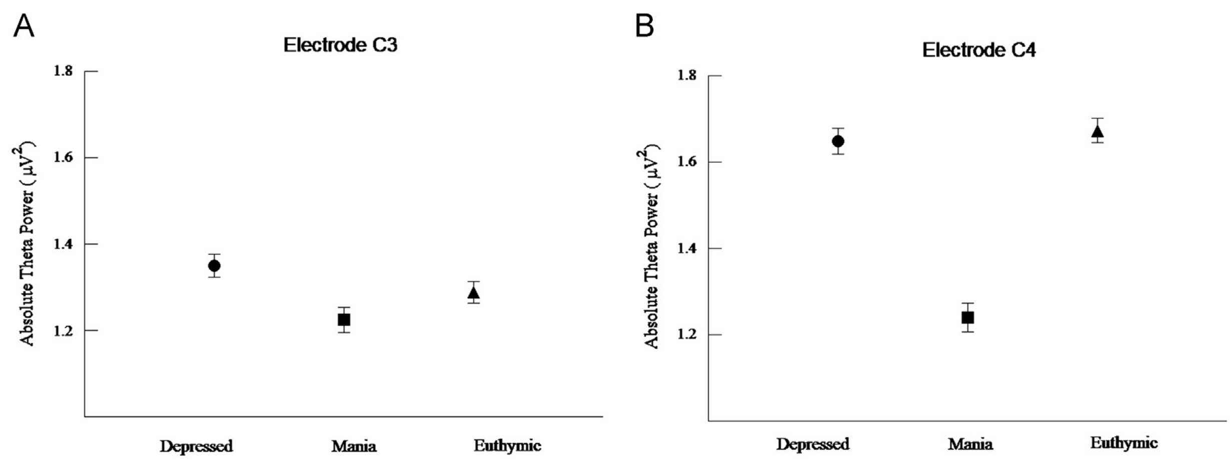


**Fig. 4.** (a) Mean and standard deviation of absolute theta power for electrode C3. The bars represent S.D. A 3 × 2 ANOVA design showed a main effect of group ($p < 0.001$) (b) Mean and standard deviation of absolute theta power for electrode C4. The bars represent S.D. A 3 × 2 ANOVA design showed a main effect of group ($p < 0.001$).

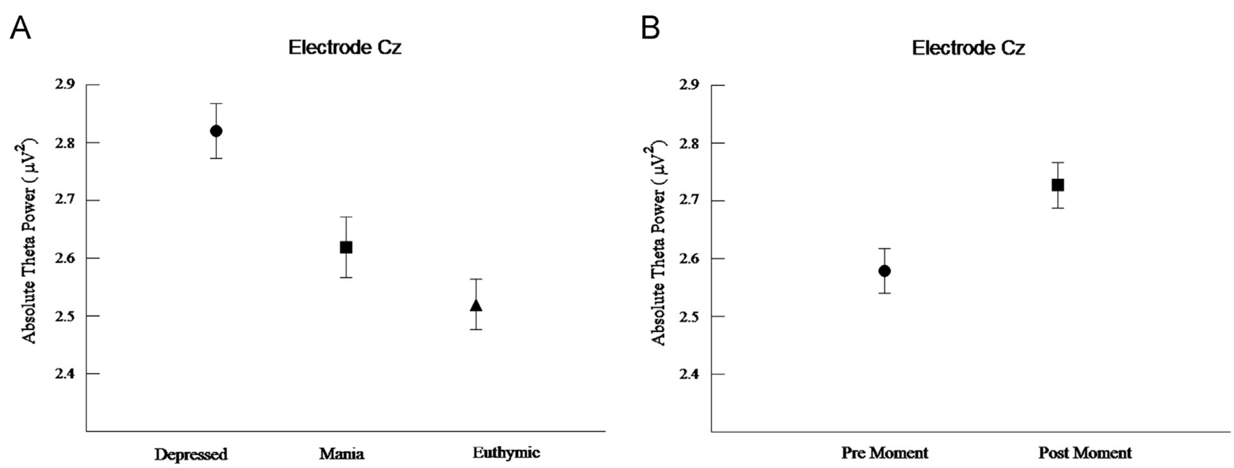


**Fig. 5.** Mean and standard deviation of absolute theta power for electrode Cz. The bars represent S.D.. A 3 × 2 ANOVA design showed a main effect of group ($p < 0.001$) (a) and a main effect of moment ($p < 0.001$) (b).

drowsiness and restricted information processing environment and has a slower characteristic ranging from 4 to 5 Hz (Smith et al., 1999). The second one, with more rapid oscillations, 6–8 Hz, mainly occurs at the front midline of the brain and is associated with focused and voluntary attention, mental effort and efficient processing of environmental stimuli (Smith et al., 1999). From this point of view, affective symptoms such as depression and emotional liability present in BD are associated with excessive theta wave amplitude in frontal lobes (Raine et al., 2000). This same excess in the theta band is related to difficulties in concentration and attention, behavioral change and social adequacy under the cognitive point of view, just as procrastination or the difficulty in taking initiatives are also integrated with symptoms of functional abnormalities in the frontal lobes.

Therefore, our hypothesis is that a lower theta band activity is present in euthymic patients when compared to manic and depressive patients in specific neural networks involved in the attention process, since the theta waves increase in patients with attention deficit (Monastra et al., 1999; Clark et al., 2001, 2002) and patients with depression and mania show changes in attention levels (Clark et al., 2002; Kapczinski et al., 2009). Moreover we expect to find greater theta activity in the right hemisphere during the manic phase and greater theta activity in the left hemisphere during the depression phase. Previous studies agree with our hypothesis. Clark et al. (2002) found a greater activation in frontal and temporal areas in patients during mania and depression. Also, the activation was greater in the right hemisphere during the mania phase, and it was greater in the left hemisphere in depression. These results are associated with specific characteristics of each phase; in depression, we can find reduction of attentive and mnemic activities as well as slow thinking with changes in cognitive processing (Clark et al., 2002); on the other hand, in mania, we observe a disorganized behavior, mental activity acceleration and the presence of psychotic symptoms, with possible greater difficulties to sustain attention, recognize faces and codify information (Kapczinski et al., 2009).

Previous studies demonstrated that an increase in theta power was related to depressive and manic phase of bipolar disorder, therefore the result observed in the present study corroborates with the literature. Regarding the laterality, we did not find a specific relationship between maniac group and theta increase for the right hemisphere; however, we found a theta increase in the left hemisphere for the depressive group.

It is important to highlight that we did not observe lower theta power for euthymic patients when compared to depressive and maniac groups. We verified a theta power increase for the euthymic group in the electrodes localized at the right hemisphere (i.e., F4, F8 and C4 electrodes). This finding suggests that, even in a "mood stability" phase, patients present attention deficit.

Thus, symptomatic bipolar patients suffer changes in sustained attention, inhibitory control and the ability to alternate the attention focus. With regard to our findings, we observed a main effect for the Group independent variable on electrodes C3, C4, Cz, F7, F4, F8, and a main effect for the Moment independent variable on the Cz, F7, F8 electrodes. These results indicate that the task performed as well as the difference between the groups, produces changes in theta activity in distinct cortical areas that participate in the organization of attention. Although our studies were performed in bipolar adults, there are previous studies in children with ADHD which showed an increase in: slow waves, such as theta, correlated with inattention in the central zone, executive problems, hyperactivity and impulsivity, correlated with negativity. Furthermore, Hobbs et al. (2007) investigated EEG abnormalities in adolescents with ADHD showing the increase of the theta band frequency in attention processes. Confronted with evidence of increased theta in a sample of patients with attention deficit, we discuss theta oscillations in relation to BD and its different phases. Therefore, we will divide the discussion of results according to the area investigated and to the main results.

### 4.1. Central cortex

In the central region, we found a main effect for group on electrodes C3, Cz and C4. We found a higher absolute theta power for the Cz and C3 electrodes in the depression group. We identified a higher absolute theta power for C4 in the euthymia group compared to the mania group. Furthermore, we identified a main effect for moment for the Cz electrode with a higher absolute theta power in the post-moment. The central region consists of the supplementary motor area (SMA), the premotor (SMEs) cortex and somatosensory cortex (SMC) (Bastos et al., 2004). The results suggest that the medial central region (i.e., electrode Cz) is influenced by task and by the patient phase. Mean while, the activity of the hemispheres seems to be influenced only by the patient state. Furthermore, for the right central area (electrode C4) we did not find an absolute theta power increase for the depressive group. Power modifications in theta frequency band demonstrate the involvement of these motor areas in processes which involve attention (Slobounov et al., 2000). In a previous study, De Araújo et al. (2002) demonstrated that theta increased after the period of stimulation, between the end of the motor task and the preparation and planning for the next action, and that this increase is more significant in the frontal cortex axis. Our results for the electrode Cz corroborate the findings of De Araújo et al. (2002), who found an increase in theta power after a visuomotor tasks. Another study conducted by Cunha et al. (2004) investigated changes in EEG patterns in healthy subjects during motor task learning. In this research, the pairs of electrodes $C_Z$–$C_3$/$C_Z$–$C_4$ were analyzed in the theta and alpha frequency bands. No variations were found in the absolute theta band power for the moment variable. This finding agrees with the results of the present study. Changes in the theta band observed in the analysis of the hemispheres represent different amounts of allocated attention, and this aspect has a great relationship with the state of the patients (Smith et al., 1999).

### 4.2. Frontal cortex

With respect to the electrodes located in the frontal cortex, we found a higher theta power in the maniac group compared to the other groups (i.e., depression and euthymia) for the F7 electrode located on the left frontal cortex. We also found a higher theta power in the group of depressed patients compared to euthymic patients for the same electrode. As for the F4 and F8 electrodes, which are located on the right frontal cortex, we found a higher theta power in the manic group as compared to the depression group; greater theta power was found in the euthymia group when compared to the depression group.

Previous studies have shown that subjects with attention deficit disorder demonstrate a higher absolute theta power in the frontal area (Machado-Vieira et al., 2005). Moreover, studies also found that bipolar patients in the manic phase and depression have greater attention deficit (Clark et al., 2002). Other studies have demonstrated a poor performance in patients with bipolar disorder compared to controls on measures of attention and working memory (Harkavy-Friedman et al., 2006). Similarly, in recent years, EEG studies in subjects with attention deficit disorder and hyperactivity have shown an increase in the activity of the slow theta waves in frontal areas (Bresnahan and Barry, 2002; Clark et al., 2002; Magee et al., 2005). Therefore, our results are in agreement with these previous findings, since we found greater theta power in manic patients with attention deficit in bipolar disorder.

Our results also showed a significant increase in absolute theta power in the post-stimulus moment, when compared to the pre-stimulus one, in the left (F7) and right (F8) fronto-temporal areas, suggesting that these areas are influenced by the task. This result is associated with attention demand required at the moment before the onset of the stimulus, which requires more attention, so the theta power was lower. Changes in theta have been related to different types and intensities of allocation of attention in a task (Bastos et al., 2004). Therefore, our results are derived from the cognitive demands required by the task.

Many electrophysiological studies corroborate the correlation of increased theta band and their integration with sensory information and their respective motor response in the generation of a voluntary movement, showing that theta oscillations are subordinated to activities in the cortex (Cunha et al., 2004). Therefore, theta band is also related to the implementation of different states of attention and spatial navigation arising from the task.

### 4.3. Conclusion

Our results indicate that group (i.e., euthimyc, depressive, and maniac phases of the bipolar disorder) and moment (i.e., pre and post stimulus) cause significant electrophysiological changes in absolute theta power. Specifically, we verified that prosaccade could be used as an attention evaluation method for identify the different phases of the bipolar disorder. However, it is important to emphasize that we only observed changes in the absolute theta power related to the saccadic task in the electrodes F7, F8 and Cz electrode. According to previous explanation, these findings may result from impairment in the neural substrate (Mechanisms responsible for attention) in individuals with bipolar disorder.

Furthermore, we partially confirmed our hypothesis. We expected to find difference in absolute theta power among the three groups, with a lower absolute theta power for the euthymic group, once the patients in this group have a relative stable mood state. However, we did not find these results for all the electrodes analyzed suggesting the euthymic patients also present attention deficit. Therefore, our results suggest that changes in absolute theta power could be a biomarker of BD. Specifically, we propose that these changes are a permanent characteristic of the disorder; and, depending on the cortical area analyzed, absolute theta power could differentiate among the patients phase.

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