Journal of Affective Disorders ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Changes in saccadic eye movement (SEM) and quantitative EEG parameter in bipolar patients

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ARTICLE INFO

Article history:
Received 2 April 2012
Accepted 25 April 2012

Keywords:
Bipolar disorder
Gamma coherence
Neurocognitive dysfunction
Quantitative electroencephalography
Information processing

ABSTRACT

Background: There is increasing evidence that neurocognitive dysfunction is associated with the different states in Bipolar Disorder. Gamma coherence is strongly related to cognitive processes and cortico-cortical communication. This paper aims at shedding light on the relationship between cortical gamma coherence within bipolar patients and a control group during a prosaccadic attention task. We hypothesized that gamma coherence oscillations act as a main neural mechanism underlying information processing which changes in bipolar patients.
Method: Thirty-two (12 healthy controls and 20 bipolar patients) subjects were enrolled in this study. The subjects performed a prosaccadic attention task while their brain activity pattern was recorded using quantitative electroencephalography (20 channels).
Results: We observed that the maniac group presented lower saccade latency when compared to depression and control groups. The main finding was a greater gamma coherence for control group in the right hemisphere of both frontal and motor cortices caused by the execution of a prosaccadic attention task.
Limitations: The findings need to be confirmed in larger samples and in bipolar patients before start the pharmacological treatment.
Conclusions: Our findings suggest a disrupted connection of the brain's entire functioning of maniac patients and represent a deregulation in cortical inhibitory mechanism. Thus, our results reinforce our hypothesis that greater gamma coherence in the right and left frontal cortices for the maniac group produces a "noise" during information processing and highlights that gamma coherence might be a biomarker for cognitive dysfunction during the manic state.

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http://dx.doi.org/10.1016/j.jad.2012.04.049

1. Introduction

Bipolar Disorder (BD) is characterized by mood oscillations, with the occurrence of at least one maniac episode (Belmaker and Bersudsky, 2004; Rosa et al., 2010). In addition to these features, some studies observed neurocognitive dysfunction associated with the different states in BD (i.e., depressed, maniac and euthymic). These cognitive alterations are largely related to changes in information processing. Andersson et al. (2008) observed that bipolar patients have an impairment in attention, working memory, executive function, and that these patients present dysfunction in the early stages of information processing. Nonetheless, the authors concluded that impairment in cognitive function could be due to dysfunction in the early stages of information processing.

In this context, the quantitative electroencephalography (qEEG) has been proved a reliable instrument to investigate information processing and neurocognitive features, such as memory and attention (Murray et al., 2011; Porcaro et al., 2011). Specifically, studies showed that gamma band (30–80 Hz) is strongly related to cognitive processes (Herrmann et al., 2010). Gamma band is also widely associated with thalamocortical integration of sensory information and has been interpreted as an index of sensory registration during pre-attentive stages of information processing (Karakas and Basar, 1998; Behrendt and Young, 2004; Deeny et al., 2009). Synchronization of gamma oscillations is associated with cortico-cortical communication of a group of neurons that participate in the cognitive functioning integrated (Rodriguez et al., 1999, Özerdem et al., 2010; Uhlhaas et al., 2010). This phenomenon is known as binding process and contributes to the formation of conscious cognitive processes such as perception, attention and memory (Widmann et al., 2007; Ehm et al., 2010). Previous studies demonstrated that the schizophrenic patients have significant changes in gamma oscillations over the prefrontal cortex when compared to bipolar patients and healthy control group. The results suggest that an alteration in the gamma oscillation may represent important neurophysiologic deficits associated with the spectrum of symptoms commonly found in schizophrenia (Farzan et al., 2010).

Although some studies demonstrate cognitive and electrophysiological alterations in bipolar patients, few authors have focused their investigation on the gamma oscillation. After an extensive bibliographic research, we found only two articles that addressed gamma oscillations: one of them focused on euthymic bipolar patients, and the other one focused on maniac bipolar patients (Özerdem et al., 2010; Özerdem et al., 2011). We did not find a more detailed study comparing gamma coherence between the two different states of BD (mania versus depression) and control subjects during the occurrence of saccadic eye movement. Several researches have shown that saccadic movement is an important parameter in the neurological disease and psychiatric disorder investigation (i.e., Parkinson Disease, Alzheimer Disease, Schizophrenia and Attention Disorder). In such manner, our study aims to investigate gamma coherence differences amongst groups, i.e. depressed, maniac and control groups, on the frontal, central, parietal and occipital cortices during a prosaccade paradigm. We were expecting a reduction in gamma coherence oscillations for depressive patients when compared to healthy controls. Moreover, we formulate the hypothesis that maniac patients would have an increase in gamma coherence, therefore showing a higher communication between electrodes sites, which interferes in the information processing.

2. Methods

2.1. Subjects

Twelve healthy controls subjects (3 male) and twenty bipolar patients (14 male), 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) (First et al., 1996). All participants had normal or corrected-to normal vision and no sensory, motor, cognitive or attentional deficits that would affect saccadic eye movement. Volunteers who proved to have no present or past psychiatric condition and to be medically healthy upon physical examination were enrolled as the control group. 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). The bipolar patients were divided into 2 major groups (depressive and maniac) at the day of the experiment according to their score in the Clinical Global Impression–Bipolar Version (CGI–BP) (Spearing et al., 1997): depressive ($n=10$) and maniac ($n=10$) (Table 1).

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

Table 1
Demographics and clinical characteristics.

	Bipolar patients		**Control ($n=12$) mean (SD)**
	Maniac ($n=10$) mean (SD)	*Depression ($n=10$) mean (SD)*	
Demographic variables			
Gender			
Female	80%	60%	75%
Male	20%	40%	25%
Age	37.5 (7.23)	36.5 (5.55)	26.25 (4.13)
Clinical psychiatry features			
Young score	15.66 (7.00)	4.66 (3.96)	–
CGI-depression	1	3.57 (.53)	–
CGI-mania	3.33 (.81)	1	–
CGI-global	3.33 (.81)	3.57 (.53)	–
Medication at time of assessment			
Antidepressant (%)	–	–	–
Antidepressant (%) + mood stabilizer	100%	57.15%	–
Mood stabilizer (%)	–	42.85%	–

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was standardized at 100 cm. Computer software controlled the LED bar and determined the presentation of the stimulus. 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 LEDs 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 derivations using the earlobes reference. Impedance of EEG and EOG electrodes was kept between 5–10 kΩ. The data recorded had a total amplitude of less than 70 μV. The EEG signal was amplified with a gain of 22,000, analogically filtered between.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 removed by visual inspection all the 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 for the power spectral density (PSD) performed by MATLAB 5.3 (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-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.

2.6. Statistical analysis

Coherence values for the gamma frequency band during the fixed saccadic paradigm (i.e., simple light stimulation) were assessed in 20 bipolar patients (i.e., 10 depressive and 10 maniac) and were compared with 10 healthy controls. Groups were compared for the coherence values on frontal, central, parietal and occipital intra-hemispheric and inter-hemispheric (Fz/F3, Fz/F4, Fz/F7, Fz/F8, F3/F4, F7/F8, P3/Pz, P4/Pz, P3/P4, C3/Cz, Cz/C4, C3/C4, O1/Oz, Oz/O2, O1/O2) electrode pairs 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 saccade latency and gamma coherence (35–80 Hz) were the two dependent variables of interest. We used a semi-automated method to detect the saccade latency; in particular, the saccades were determined at the start of the inflection point of the curve, always recognized from visual inspection. The saccade was separated 500 ms after the stimulus presentation. The highest velocity (first derivate) was detected at the point of deflection. From the moment that the LED lights are given, we define a period of 500 ms to seek the EOG inflection and mark the point that has the highest "acceleration" or the initiation (second derivate) of the EOG signal. Saccades with latencies of less than 100 ms and more than 400 ms were not considered. The statistical analysis of the saccade latency and gamma coherence were performed using a repeated measures one-way ANOVA with the factor group (3 levels: control group, depressed, maniac BD patients). The group differences were tested using Scheffé post hoc test if ANOVA was significant.

3. Results

We analyzed saccade latency and gamma coherence on frontal, central, parietal and occipital cortices. The behavioral measure, saccade latency, demonstrated a statistical difference among maniac group and the others ($F=325{,}953$; $p<0.001$) (Fig. 1). We observed lower saccade latency for maniac group as compared to depression and control groups. We did not find statistical difference between depression and control groups. However, it is important to highlight that the latency mean for the depression group was higher than the control group.

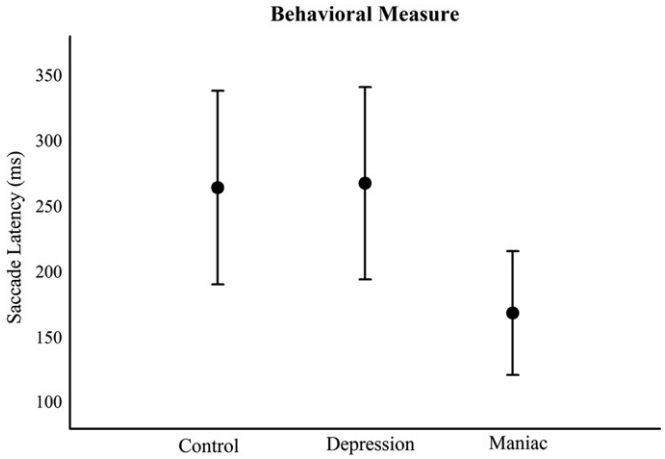

Fig. 1. Saccade latencies (ms) separately shown for each group: control, depression, mania ($p=.000$). Post hoc analysis revealed that group control is different from maniac group.

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Table 2
Mean and standard deviation of behavioral and electrophysiological measures.

	Maniac (n=6) mean (SD)	**Bipolar patients** *Depressed (n=9) mean (SD)*	**Control (n=10) mean (SD)**	***F***	***p***
Saccade latency	168.52 (47.27)***	267.76 (73.49)*	264.44 (73.04)**	325,953	.000
Frontal site					
F7/F3	.278(.205)*	.23(.162)	.227(.139)*	6460	.000
Fz/F4	.265(.135)**	.301(.132)*	.375(.159) ***	26,331	.000
F4/F8	.245(.161)*	.198(.143)*	.142(.108)*	17,059	.000
Central site					
C3/Cz	.284(.159)*	.32 (.186)**	.174(.13)***	35,926	.000
C3/C4	.119(.094) *	.107(.061) **	.08(.046)***	26,195	.000
Cz/C4	.161(.089) *	.185(.097) **	.262(.138)***	31,941	.000
Parietal site					
P3/Pz	.367(.141)*	.433(.14) *	.301(.129)*	31,717	.000
P3/P4	.102(.067)*	.097(.056)	.084(.053) *	3922	.009
Occipital site					
O1/Oz	.556(.193)**	.512(.208) *	.518(.146) ***	5565	.001
Oz/O2	.434(.159)**	.456(.201) *	.6(.16) ***	28,199	.000

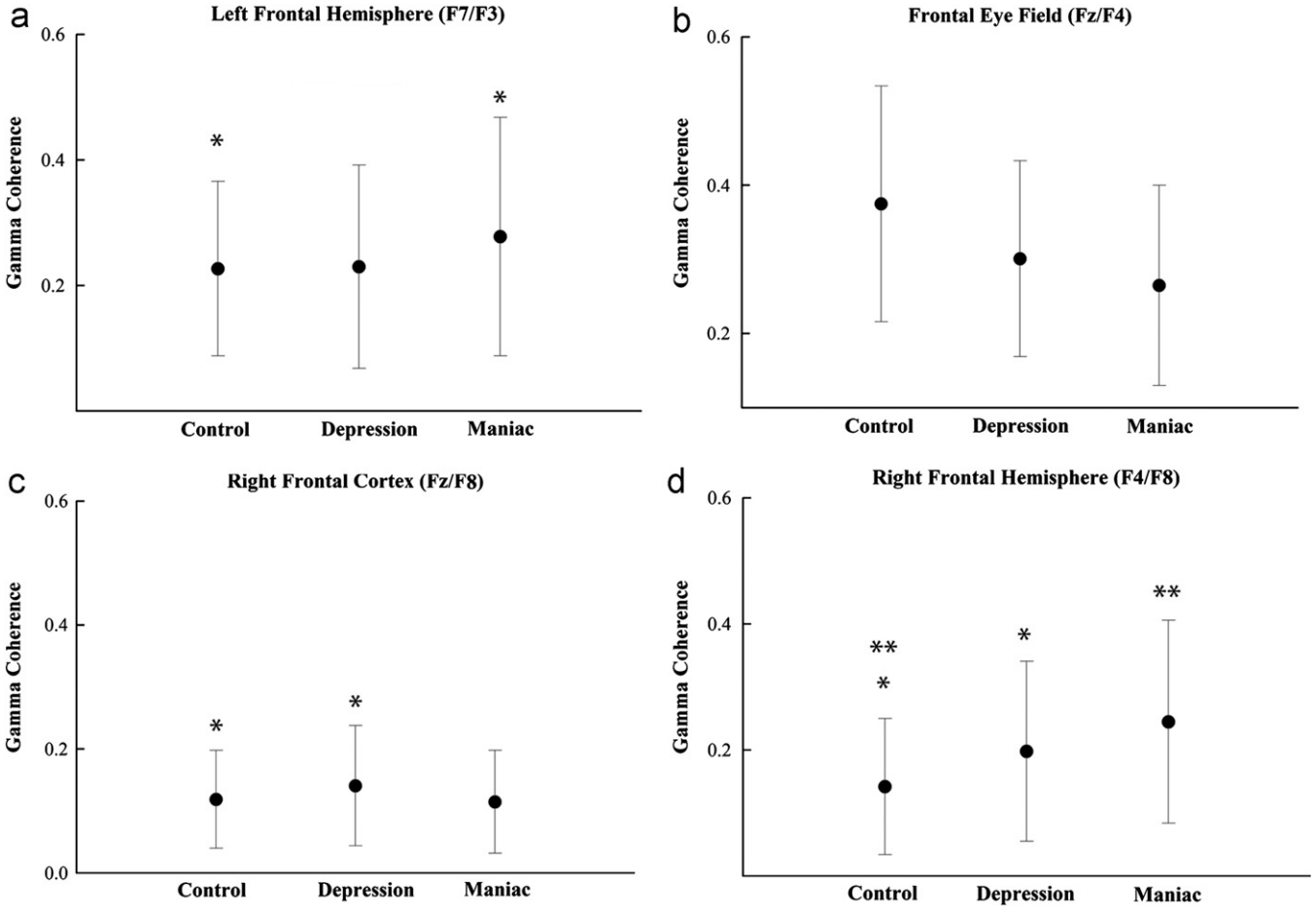

Fig. 2. Mean and standard deviation of gamma coherence over frontal cortex. The figure illustrates the difference among groups for each pair of electrodes located over the frontal cortex. (a) For F7/F3 the statistical analysis revealed that control group differs from maniac group ($p<.001$); (b) for Fz/F4 the statistical analysis revealed that all the groups are different among them ($p=.000$); (c) for Fz/F8 the statistical analysis revealed that control group differs from depression group ($p<.001$); (d) for F4/F8 the statistical analysis revealed that control group differs from maniac and depression groups ($p<.001$).

Gamma coherence measure was statically different among groups for F7/F3, F7/Fz, Fz/F4, Fz/F8, F4/F8, C3/Cz, C3/C4, Cz/C4, P3/Pz, P3/P4, O1/Oz and Oz/O2, pairs of electrodes (Table 2).

3.1. Frontal cortex

For the left frontal cortex we found a higher gamma coherence in maniac BD patients for the electrodes F7/F3 ($F=6460$; $p=.000$),

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as compared with the others groups. The post hoc analysis demonstrated that for F7/F3 electrodes, the maniac group differs from the control group (Fig. 2a). For the right frontal cortex we observed a main difference among the groups for the electrodes Fz/F4 ($p=.000$; $F=26{,}812$), Fz/F8 ($p=.006$; $F=4219$) and F4/F8 ($p=.000$; $F=17{,}059$). However, we did not find a pattern among the groups. For Fz/F4 we demonstrated a higher gamma coherence for the control group, and the post hoc analysis revealed that the control group gamma coherence is different from BD patients (Fig. 2b). For Fz/F8 depressed BD patients have higher gamma coherence when compared to the control group (Fig. 2c), and for F4/F8 we found higher gamma coherence in maniac BD patients when compared to the other groups (Fig. 2d).

3.2. Central cortex

For the central area we observed a difference among the groups for the electrodes C3/C4 ($F=26{,}195$; $p=.000$), C3/Cz ($F=35{,}926$; $p=.000$) and Cz/C4 ($F=31{,}941$; $p=.000$). We found a higher gamma coherence for maniac BD patients at the electrodes C3/C4 (Fig. 3a), for depressed BD patients at C3/Cz (Fig. 3b), and for control group at Cz/C4 electrodes (Fig. 3c). We performed a Scheffé's test as a post hoc to identify the groups' differences. For C3/Cz and for Cz/C4 we found a difference between the control and the other groups. For C3/C4 we identified a difference between control and maniac groups, and control and depression groups.

3.3. Parietal cortex

For the parietal sites we identified a main difference in the factor group for the electrodes P3/Pz ($F=31{,}717$; $p=.000$) and P3/P4 ($F=3922$; $p=.009$). For the left parietal cortex (P3/Pz) we observed a higher gamma coherence for depressed BD patients (Fig. 4a), and for the intra-hemispheric electrodes (P3/P4) we found a higher gamma coherence for maniac BD patients (Fig. 4b). We also observed for both pairs of electrodes a difference among control, maniac and depression groups.

3.4. Occipital cortex

For the occipital sites we found a main difference among the groups for O1/Oz ($F=5565$; $p=.001$) and Oz/O2 ($F=28{,}199$; $p=.000$). We observed a higher gamma coherence for maniac BD patients at O1/Oz (Fig. 4c). For Oz/O2 we found a higher gamma coherence for the control group (Fig. 4d). We also identified a difference between control and depression groups, and control and maniac groups.

4. Discussion

This study aims at shedding light on the relationship between cortical gamma coherence within bipolar patients and a control group. Specifically, we investigated the difference among groups, i.e. depressed, maniac and control, in the frontal, central, parietal and occipital cortices during a prosaccade paradigm. Based on previous electrophysiological findings regarding electrophysiological changes in bipolar patients, we hypothesized that gamma coherence oscillations act as a main neural mechanism underlying information processing which changes in bipolar patients. We expected a reduction in gamma coherence oscillations for bipolar patients, specifically depressive ones, when compared with healthy controls. Moreover, we anticipated that maniac bipolar patients present an enhancement in gamma coherence, which represents higher communication between electrodes sites, and interferes in information processing, when compared to the other groups.

The behavioral measure analysis (i.e., saccade latency) demonstrated a significant difference among the experimental groups. However, the post hoc analysis showed that saccade latency between depression and control groups is not different. We observed that the maniac group presented lower saccade latency when compared to

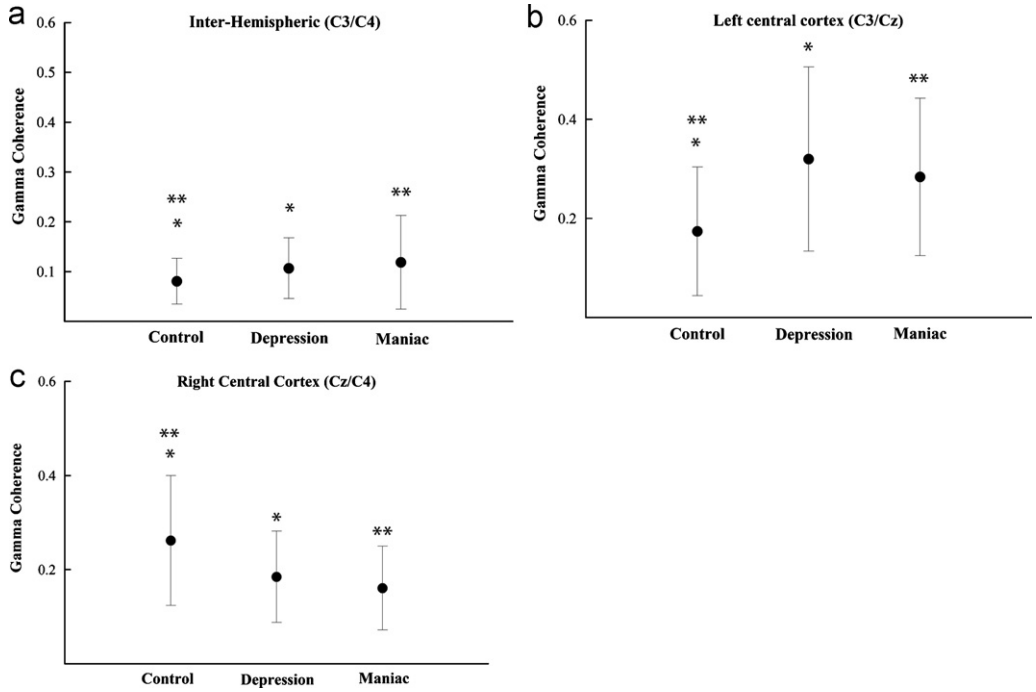

Fig. 3. Mean and standard deviation of gamma coherence over central cortex. The figure illustrates the difference among groups for each pair of electrodes located over the central cortex. (a) For C3/C4 the statistical analysis revealed that control group differs from maniac and depression group ($p<.001$); (b) for C3/Cz the statistical analysis revealed that control group differs from maniac and depression group ($p=.000$); (c) for Cz/C4 the statistical analysis revealed that control group differs from maniac and depression group ($p<.001$).

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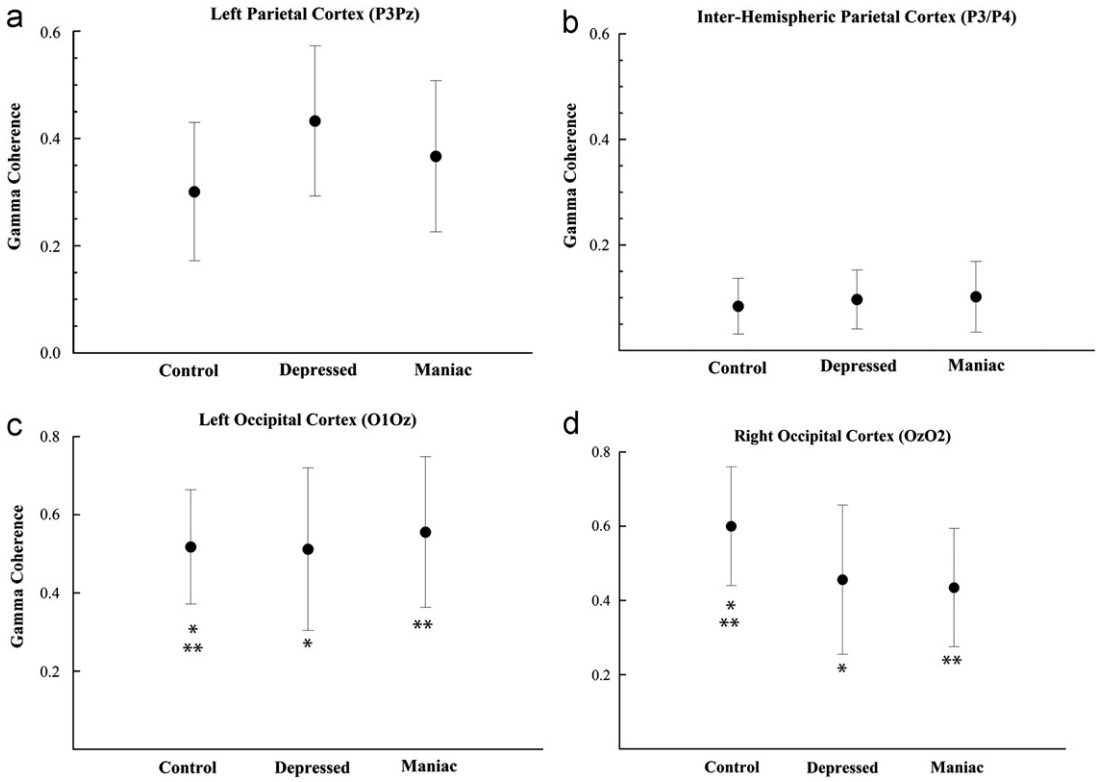

Fig. 4. Mean and standard deviation of gamma coherence over parietal and occipital cortexes. The figure illustrates the difference among groups for each pair of electrodes located over the parietal and occipital cortices. (a) For P3/Pz the statistical analysis revealed difference among the groups ($p=.000$); (b) for P3/P4 the statistical analysis also revealed difference among the groups ($p=.009$); (c) For O1/Oz the statistical analysis revealed that control group differs from maniac and depression groups ($p<.001$); (d) For Oz/O2 the statistical analysis revealed that control group differs from maniac and depression groups ($p=.000$).

depression and control groups. Our data confirms previous results that demonstrate faster reaction for bipolar patients during maniac state; this can be explained by an increase in energy and motor activity for this population (Bearden et al., 2010; Özerdem et al., 2011). Although the behavioral measure did not differentiate the control group from the depression group, the mean latency for depression group was higher than the control group. This tendency also proves a slow processing speed for depressive patients.

A combined assessment of previous studies involving saccade and attention demonstrated 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 main finding was a greater gamma coherence for control group in the right hemisphere of both frontal and motor cortices caused by the execution of a prossacadic task. Specifically, we observed a greater gamma coherence for the control group over Fz/F4, Cz/C4 and right visual cortex (Oz/O2) when compared to maniac and depression groups. For the right parietal cortex (P4/Pz) we did not find a significant difference, however we observed an increase of the gamma coherence mean for the control group. We also observed a decrease in coherence in the left central cortex (C3/Cz) for the control group when compared to maniac; the depression group showed a highest coherence. For the pair of electrodes C3/C4 we verified higher coherence for maniac group when compared to the control group. Contrary to our hypothesis, we found an increased gamma coherence in the maniac group when compared to the other groups (i.e, F7/F3, F4/F8, P3/P4, C3/C4 and O1/Oz). All the findings related to the right hemisphere (i.e., Fz/F4, Cz/C4, Oz/O2) may indicate a deregulation in cortico-cortical synchronization in bipolar group during the execution of a saccadic eye movement.

The pairs of electrodes F3/Fz, Fz/F4, Cz/C4, C3/Cz and C3/C4 represent Broadmann's area 4, 6 and 8. These areas are related to eye movement control, and are known as Frontal Eye Field (FEF). Our results demonstrate that during a specific task (i.e., saccadic attention task) gamma coherence varies according to the group and the area of the cortex observed. Gamma has been associated with attention consciousness perception and it is critical in information processing (Engel et al., 1992; Singer, 1993). Synchronized activity in the gamma range has been hypothesized to integrate neural activity across different cerebral areas (Crick and Kock, 1990; Meador et al., 2002). Our data suggests that may exists a specialization of gamma coherence during the execution of a task involving visuospatial attention. This can be observed when the findings showed higher gamma coherence in the control group when compared to other groups in cortical areas directly related to the task, such as the right FEF (i.e., Fz/F4 and Cz/C4). Some studies have demonstrated a right hemisphere (RH) dysfunction in bipolar patients, supported by reports of relatively greater impairment in visuospatial functioning, lateralization abnormalities, and mania caused by RH lesions (Bearden et al., 2001).

Our experimental task is characterized by a predictability of the location and direction of stimulus presentation. This paradigm allowed an investigation of time reaction, visuospatial functioning and attention processing related to saccadic eye movement. Our results related to the right frontal eye field supported the visuospatial processing impairment in bipolar patients showing the important role played by the right hemisphere. Thus, high frequency communication between cortical areas occurs functionally in agreement with the environment demand (represented by the task). We observed that the gamma coherence behavior also depends on the importance and the functionality of the

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cortical region during the task. In other words, high frequency cortical communication depends on the demand imposed by the environment and it is interpreted according to specific features of the task versus the environment's challenges.

Previous studies reported a decrease in gamma coherence as an electrophysiological marker of cognitive impairment (Ferrarelli et al., 2008; Farzan et al., 2010). Özerdem et al. (2010) reported low gamma coherence in maniac patients for the following pairs of electrodes: F3/F4, C3/C4, T3/T4, T5–T6, P3–P4, O1–O2, F3/P3, F4/P4, F3/T5, F4/T6, F3/O1, F4/O2, C3/O1, C2/O4. However, our results pointed out to greater coherence for F7/F3, F4/F8, P3/P4, O1/Oz and C3/C4 for the maniac patients group when compared to control and depressive patients. Our data revealed that an optimal level of gamma coherence may be important to obtain an appropriate brain functioning during attention. In other words, either increase or decrease in gamma coherence could be associated with an impairment communication between regions. The result highlights an optimum level of coherence between areas to the normal (healthy) processing.

In particular, our findings suggest a disrupted connection of the brain's entire functioning of maniac patients (Chepenik et al., 2010; Palaniyappan and Cousins, 2010; Pompei et al., 2011) and represent a deregulation in cortical inhibitory mechanism. High gamma coherence expresses a higher coupling between electrodes sites, interferes in information processing (Singer, 1993; Gregoriou et al., 2009; Palaniyappan and Cousins, 2010), produces a more intense binding between areas with more sensory information exchange and provokes acceleration in the information processing. Previous studies reported attention and information processing disturbance in bipolar patients during maniac state (Palaniyappan & Cousins, 2010). A high velocity in information processing, and consequently in information exchange is one hypothesis that explains certain bipolar symptoms in the maniac state, such as confused thinking, disturbance in attention measures, complex processing and memory (Quraishi and Frangou, 2002). This hypothesis is confirmed by studies demonstrating that some substances produce symptoms similar the maniac state (e.g., elevate mood and fast thinking), such as caffeine (Durlac et al., 2002; Smith et al., 2005) and nicotine (Gentry et al., 2000; Dar et al., 2007). Thus, our results reinforce our hypothesis that greater gamma coherence in the right and left frontal cortices for the maniac group produces a "noise" during information processing, which can be associated with cognitive dysfunction observed in BD patients during the manic state. Despite our results, these findings need to be confirmed in larger samples and in bipolar patients before start the pharmacological treatment.

Role of funding source
None

Conflict of interest
None

Aknowledgement
None

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Please cite this article as: Velasques, B., et al., Changes in saccadic eye movement (SEM) and quantitative EEG parameter in bipolar patients. Journal of Affective Disorders (2012), http://dx.doi.org/10.1016/j.jad.2012.04.049

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Please cite this article as: Velasques, B., et al., Changes in saccadic eye movement (SEM) and quantitative EEG parameter in bipolar patients. Journal of Affective Disorders (2012), http://dx.doi.org/10.1016/j.jad.2012.04.049