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Research report

# Frontal cortex absolute beta power measurement in Panic Disorder with Agoraphobia patients

Marcele Regine de Carvalho [a,b,c,d,*], Bruna Brandão Velasques [c,e,h], Rafael C. Freire [a,b], Maurício Cagy [c,f], Juliana Bittencourt Marques [c], Silmar Teixeira [c,i,j], Rafael Thomaz [a,b], Bernard P. Rangé [d], Roberto Piedade [c], Hagop Souren Akiskal [k], Antonio Egidio Nardi [a,b], Pedro Ribeiro [c,e,g]

[a] Laboratory of Panic and Respiration, Institute of Psychiatry of Federal University of Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro, Brazil
[b] National Institute of Translational Medicine (INCT-TM), Rio de Janeiro, Brazil
[c] Brain Mapping and Sensory Motor Integration, Institute of Psychiatry of Federal University of Rio de Janeiro (IPUB/UFRJ), Rio de Janeiro, Brazil
[d] Institute of Psychology of Federal University of Rio de Janeiro (IP/UFRJ), Rio de Janeiro, Brazil
[e] Institute of Applied Neuroscience (INA), Rio de Janeiro, Brazil
[f] Division of Epidemiology and Biostatistics, Institute of Community Health, Federal Fluminense University (UFF), Rio de Janeiro, Brazil
[g] Bioscience Department (EEFD/ UFRJ), School of Physical Education, Rio de Janeiro, Brazil
[h] Neuromuscular Research Laboratory, National Institute of Traumatology and Orthopedics (NITO), Rio de Janeiro, Brazil
[i] Physiotherapy Department – Piquet Carneiro Policlinic – State University of Rio de Janeiro, Brazil
[j] Laboratory of Physical Therapy, Veiga de Almeida University, Rio de Janeiro, Brazil
[k] International Mood Center, University of California, San Diego, La Jolla, USA

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ABSTRACT

Panic disorder patients are hypervigilant to danger cues and highly sensitive to unpredictable aversive events, what leads to anticipatory anxiety, that is one key component of the disorder maintenance. Prefrontal cortex seems to be involved in these processes and beta band activity may be related to the involvement of top-down processing, whose function is supposed to be disrupted in pathological anxiety. The objective of this study was to measure frontal absolute beta-power (ABP) with qEEG in panic disorder and agoraphobia (PDA) patients compared to healthy controls. *Methods*: qEEG data were acquired while participants (24 PDA patients and 21 controls) watched a computer simulation (CS), consisting of moments classified as "high anxiety" (HAM) and "low anxiety" (LAM). qEEG data were also acquired during two rest conditions, before and after the computer simulation display. The statistical analysis was performed by means of a repeated measure analysis of variance (two-way ANOVA) and ABP was the dependent variable of interest. The main hypothesis was that a higher ABP in PDA patients would be found related to controls. Moreover, in HAM the ABP would be different than in LAM. *Results*: the main finding was an interaction between the moment and group for the electrodes F7, F8, Fp1 and Fp2. We observed a higher ABP in PDA patients when compared to controls while watching the CS. The higher beta-power in the frontal cortex for the PDA group may reflect a state of high excitability, together with anticipatory anxiety and maintenance of hypervigilant cognitive state. *Conclusions*: our results suggest a possible deficiency in top-down processing reflected by a higher ABP in the PDA group while watching the CS and they highlight the recruitment of prefrontal regions during the exposure to anxiogenic stimuli. *Limitations*: the small sample, the wide age range of participants and the use of psychotropic medications by most of the PDA patients.



## 1. Introduction

Panic disorder (PD) is a multidimensional anxiety disorder that involves the activation of a complex brain circuitry (Dresler et al., 2013) and is characterized by abrupt and intense physiological sensations, accompanied by fear of its consequences (APA, 2000).

* Corresponding author at: Av. das Américas, 500. Bloco 21. Sala 232. Barra. Zip Code: 22640-100. Rio de Janeiro - RJ – Brazil Tel.: +55 21 2436 8202; mob.: +55 21 99658 7080; fax: +55 21 25236839.
*E-mail address:* marcelecarvalho@gmail.com (M.R. de Carvalho).

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It is associated with impaired quality of life, and is also related to psychiatric comorbidities (Goodwin and Gotlib, 2004). Agoraphobia is one of those, and is related to increased morbidity of PD (Kessler et al., 2006). Panic Disorder with Agoraphobia (PDA) patients tend to be hypersensitive even for lower anxiety stimulus, exhibiting hyperarousal responses, as they are hypervigilant to danger cues (Beck et al., 1992). Because PD patients experience unexpected panic attacks, they tend to be concerned about having more panic attacks, being highly sensitive to unpredictable aversive events what, over time, may lead to anticipatory anxiety, which contributes to the maintenance of the disorder (Grillon et al., 2008).

The current neuroanatomical models of PD suggest that the neuropathological process underlying panic symptoms may be heterogeneous; involving limbic, cortical and subcortical regions. Electroencephalogram (EEG) can collect neuroelectric data from cortical structures and it is also able to reflect the activation of subcortical structures on the cerebral cortex in real time. In PD, quantitative EEG (qEEG) power indices may be more reflective of brainstem modulation of cortical excitation (Malmivuo and Plonsey, 1995; Knott et al., 1996; Niedermeyer and da Silva, 2005). The most commonly electrophysiological changes observed in PD patients, either in studies with quantitative EEG (Hanaoka, 2005; Locatelli et al., 1993) as well as in conventional EEG examinations (Bystritsky et al., 1999; Dantendorfer, 1996), are attributed to frontal and temporal cortex activation.

Despite the few studies, the alpha band decreased activity and the beta band increased activity have been a pattern for PD patients (Wiedemann et al., 1998; Gordeev, 2008; Wise et al., 2011). The alpha band (8–13 Hz) reflects top-down, inhibitory control processes. Thereby, an absolute alpha-power decrease in the frontal cortex in PD may reflect a dysfunction in thalamic–cortical circuits, that is associated with incapacity to inhibit irrelevant information, role played especially by the prefrontal cortex (PFC) (Klimesch et al., 2007; de Carvalho et al., 2013). The beta-band (13–30 Hz) activity seems to be related to the maintenance of the current cognitive state. Thereafter, it is hypothesized that excessive enhancement of beta-band activity may result in an abnormal persistence of the current state and a deterioration of flexible behavioral and cognitive control (Engel and Fries, 2010).

The aim of this study is to observe absolute beta-power in the scalp frontal region as a whole (F3, F7, Fz, F4, F8, Fp1, and Fp2 electrodes) in PDA patients compared to healthy controls while watching an anxiogenic computer simulation (Freire et al., 2010) comprised of high anxiety moments (HAM) and low anxiety moments (LAM). We were expecting a higher absolute beta-power in PDA patients on all electrodes when compared to healthy controls, due to a possible deterioration of flexible behavioral and cognitive control that exists in anxiety. Moreover, we formulated the hypothesis that, in high anxiogenic moments, absolute beta power might be different than in low anxiety moments. Both moments are characterized by potentially fearful stimuli for the PDA patients, but the low anxiety situations refer to the situations where the difficulty of exposure to anxiogenic events tends to be smaller (although it still exists), that is, they refer to those moments when the patient will be about to leave the situations of greater discomfort and, for this reason, might experience less anxiety.

## 2. Methods

### 2.1. Participants

We selected a convenience sample of 24 PDA patients (8 male and 16 female; ages varying between 25 and 61 years old, mean: 38.75, SD: ± 10.09), who were in psychopharmacological treatment at the Laboratory of Panic and Respiration at the Institute of Psychiatry, and were evaluated in the Department of Applied Psychology at the Institute of Psychology before treatment; both institutes are located at the Federal University of Rio de Janeiro (UFRJ). The subjects' recruitment was done through posters with information about the research that were pasted on the walls of the outpatient sector of the Institutes of Psychiatry and Psychology at UFRJ. All patients that met the study inclusion criteria were invited to participate. The patients were interviewed with the
M.I.N.I. 5.0 (Sheehan et al., 1998; Amorim, 2000) and fulfilled DSM-IV [1] criteria for PDA. Another inclusion criterion was the occurrence of at least two panic attacks in a 30-day period before the visit. Patients with comorbid dysthymia ($n=1$), generalized anxiety disorder ($n=2$), social phobia ($n=1$) or depression ($n=3$) were included only when PDA was judged to be the primary diagnosis (Table 1). Some of them began the treatment unmedicated ($n=7$), while others were already taking antidepressants ($n=3$), benzodiazepines ($n=5$) or both antidepressants and benzodiazepines ($n=9$) (Table 2). The patients performed three self-evaluation questionnaires to measure the severity of anxiety, depression and PDA symptoms: Beck Anxiety Inventory (BAI) (Beck et al., 1988) (mean score: 22.68 and SD: ± 14.17; which means moderate anxiety); Beck Depression Inventory (BDI) (Beck et al., 1961) (mean score: 16.37 and SD: ± 10.99; which means mild depression) and Panic and Agoraphobia Scale (PAS) (Bandelow, 1995) (mean score: 23.82 and SD: ± 9.96; which means moderate PDA symptoms).

There was also a control group with 21 healthy participants (4 male and 17 female; ages from 23 to 61 years old, mean: 40.52, SD: ± 12.47), who were screened with the M.I.N.I. 5.0 (Sheehan et al., 1998; Amorim, 2000) and did not fulfill criteria for any psychiatric disorder. Subjects with other psychiatric disorders, neurological, cardiologic or respiratory diseases were not included in this study, neither in the patient nor in the control group. Patient and control group did not differ from each other in age ($p=0.848$). Our local Ethics Committee (Comitê de Ética em Pesquisa do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro-CEP-IPUB/UFRJ) approved the protocol, which complied with the principles of the Declaration of Helsinki. After the experiment was fully explained, the subjects signed a voluntary written consent.

**Table 1**
PDA patients' comorbidities.

| Disorder | *n* | % |
|---|---|---|
| Dysthymia | 1 | 4.17 |
| Generalized anxiety disorder | 2 | 8.33 |
| Social phobia | 1 | 4.17 |
| Major depression | 3 | 12.50 |
| None | 17 | 70.83 |
| **Total** | **24** | **100** |

**Table 2**
PDA patients on medication.

| Medication | *n* | % |
|---|---|---|
| Antidepressants | 3 | 12.50 |
| Benzodiazepines | 5 | 20.83 |
| Antidepressants and benzodiazepines | 9 | 37.50 |
| Unmedicated | 7 | 29.17 |
| **Total** | **24** | **100** |

### 2.2. Computer simulation

The simulation consisted of a 4-min three-dimensional computer animation developed by Triptyque LAB (www.triptyquelab.com). Two 30-s periods in which a gray screen was displayed, one before and the other after the animation per se, were included in this animation. The animation was in a first person perspective (a graphical perspective rendered from the viewpoint of observer of the computer simulation) and there was a camera movement as if the subject was walking inside/outside a bus and looking at different directions during a bus ride. The animation starts at a bus stop: the bus arrives, the subject gets on the bus and sits down, the bus moves through city streets, it stops again and is filled by many people, it moves through the streets, goes in a tunnel, stops inside the tunnel because of traffic, it starts moving again, gets out of the tunnel, stops at a bus stop, and the subject gets off the bus and watches the bus leave. The simulation included sound, which consisted of ordinary street noises associated with the images (Freire et al., 2010). In a previous study, this computer simulation demonstrated to be a useful method to induce anxiety and somatic symptoms in PDA patients. Compared to health controls, they had higher scores in anxiety self-evaluation scales and had higher skin conductance level, electrodermal response magnitude, respiratory rate, tidal volume, and respiratory rate irregularities. Two of ten patients had PA when watching the simulation. The heart rate means were higher for PDA patients who had PA (Freire et al., 2010).

The computer simulation consisted of situations classified as "high anxiety" and "low anxiety". They were classified as being "high" or "low anxiety" by patients that participated in the cited previous study (Freire et al., 2010). The high anxiety situations were when the bus gets filled with people, when the bus gets in a tunnel and when it stops inside the tunnel because of traffic. And the low anxiety situations were those when the camera just moves around and the subject sees the bus, when the bus moves through the streets but is not filled with people, when the bus leaves the tunnel and there is no traffic and when the subject gets off the bus and watches the bus go away. These low anxiety situations refer to the situations where the difficulty of exposure to anxiogenic events tends to be smaller (but it still exists), that is, moments when the patient is about to leave the situations of greater discomfort and, for this reason, may experience less anxiety. All these situations were connected with EEG recordings through computer software designed by the Brain Mapping and Sensory Motor Integration Laboratory of the Psychiatry Institute of the Federal University of Rio de Janeiro.

### 2.3. Experimental procedures

The experiment was fully explained to the subjects and they signed a voluntary written consent. Patients with PDA filled out the BAI, BDI and PAS scales. Subjects were seated on a comfortable chair in a darkened and sound-protected room in order to minimize sensory interference. The subjects were positioned in front of a 32-in. monitor and the distance between the participants and the monitor was 30 cm. Speakers were positioned around the room and the experiment was divided into three stages: (1) rest condition 1 (RC1): 4 min of open eyes rest qEEG recording; (2) computer simulation (low anxiety and high anxiety situations) – the participants watched the movie, and concomitant signal qEEG was recorded; (3) rest condition 2 (RC2): 4 min of open eyes rest qEEG recording. All qEEG recordings, for both patients and healthy controls, were made in the afternoon, from 1 PM to 4 PM. Subjects were oriented to have at least 8 h of sleep before recordings.

### 2.4. EEG data acquisition recording

The International 10/20 EEG electrode system (Jasper, 1958) was used with a 20-channel EEG system (Braintech-3000, EMSA Medical Instruments, Brazil). The 20 electrodes were arranged on a nylon cap (ElectroCap Inc., Fairfax, VA, USA) yielding monopolar derivation using the earlobes reference. 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).

### 2.5. 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., blinking and muscle-related artifacts) (Onton et al., 2006). 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. Through visual inspection, we removed all the trials which clearly showed blinking and a muscle-related artifacts "influence", and through ICA we removed the components that showed blinking and muscle-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 × 200 Hz) samples with rectangular windowing were analyzed. For the computer simulation, we extracted qEEG parameters within a time frame of 1 s before and 2 s after each situation. As the anxiogenic events do not have an instantaneous beginning, rather, they are gradual, the gap of 1 s prior to labeling served as a guarantee that we did not lose snippets of information signal due to a failure in marking the exact start of events. Therefore, the situations were classified according to their characteristics and they were grouped into two different moments: low anxiety moments (LAM) and high anxiety moments (HAM). LAM and HAM moments were 3 s length periods spread along the computerized simulation. Six moments were marked during the computer simulation (a total of 9 s of LAM and 9 s of HAM). 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.

### 2.6. Statistics analysis

Statistical analysis was performed using SPSS for Windows – version 17.0 (SPSS Inc., Chicago, USA) and absolute beta power (13–30 Hz) was the dependent variable of interest. Absolute beta power values during the computer simulation presentation were assessed in 24 PDA patients and were compared with 21 healthy controls. Groups were compared for the absolute beta power values on all frontal electrodes (i.e., F7, F3, Fz, F8 and F4) by means of a repeated measure analysis of variance (ANOVA). The statistical analysis was performed using a repeated measures two-way ANOVA with the factors group (2 levels: patients and control group) and moment (4 levels: RC1, NAM, AM, and R2). The moment differences were tested using Scheffé post hoc test if ANOVA was significant. We also performed *a t*-Test between LAM and HAM for each group at each electrode separately.

## 3. Results

We analyzed absolute beta power on frontal cortex. The two-way repeated measures ANOVA revealed an interaction between the factors group and moment for the F7 [$F(3, 2868)=7008$; $p<0.001$; $\eta_p^2 = 0.007$] (Fig. 1a), F8 [$F(3, 2868)=2911$; $p=0.033$; $\eta_p^2 = 0.003$] (Fig. 1b), Fp1 [$F(3, 2868)=10.328$; $p=0.000$; $\eta_p^2 = 0.011$] (Fig. 1c) and Fp2 [$F(3, 2868)=2863$; $p=0.035$; $\eta_p^2 = 0.003$] (Fig. 1d) electrodes. In order to examine the interaction, we performed *a t*-Test between the groups for each moment separately for each electrode. For RC1 we found that the groups differed from each other for the Fp1 and Fp2 electrodes. For LAM and HAM the groups differed only for the Fp1 electrode. For RC2 the groups differed from each other only in F7, F8, Fp1 and Fp2 electrodes.

## 4. Discussion

This study investigated the absolute beta-power difference between the PDA and the control group on the frontal cortex while watching a computer simulation with HAM and LAM. Based on previous electrophysiological findings in PDA patients, we hypothesized that this group would present a higher absolute beta-power for all frontal electrodes. We also expected that frontal regions would react differently between the HAM and LAM.

Our main result was the interaction between group and moment for the electrodes F7, F8, Fp1 and Fp2. This interaction demonstrates that power fluctuation is a function of the two independent variables, group versus moment. That is, the main effects for group alone and for moment alone cannot fully explain the oscillation of the dependent variable absolute beta-power. For this reason, the aim of this study is to focus on and discuss this data.

Examining the interactions, we found that the two groups differed at RC1on FP1 and FP2 electrodes, with a greater absolute beta-power for PDA patients when compared to the healthy subjects. Observing the left prefrontal cortex (Fp1) we also verified that the groups were different at LAM and HAM. The LAM and HAM are characterized by potentially fearful stimuli for the PDA patients, and such stimuli produce anxiety states in these individuals. We found higher beta power in PDA patients at HAM when compared to healthy controls. Furthermore, we also found that the two groups differed at RC2 for all four electrodes (F7, F8, Fp1, and Fp2), with a greater absolute beta-power for patients when compared to the healthy subjects. We observed that prefrontal areas were recruited all over the experiment, but at RC2 the frontal areas next to temporal cortex were recruited likewise.

Our results are in agreement with previous studies that report a high absolute beta-power in PD patients (Sviderskaya et al., 2001; Gordeev, 2007; Pavlenko et al., 2009). The increase of beta activity has been associated with cortical activation (Bekisz and Wróbel, 1993; Gola et al., 2011). It is hypothesize that the beta-band activity is related to the maintenance of the current sensorimotor/cognitive state. If the maintenance of the current state is intended or predicted, beta oscillations and/or coupling in the beta-band are expressed more strongly. If changes in the stimulus are expected, gamma-band activity may predominate (Engell and Fries, 2010). In addition, the pathological enhancement of

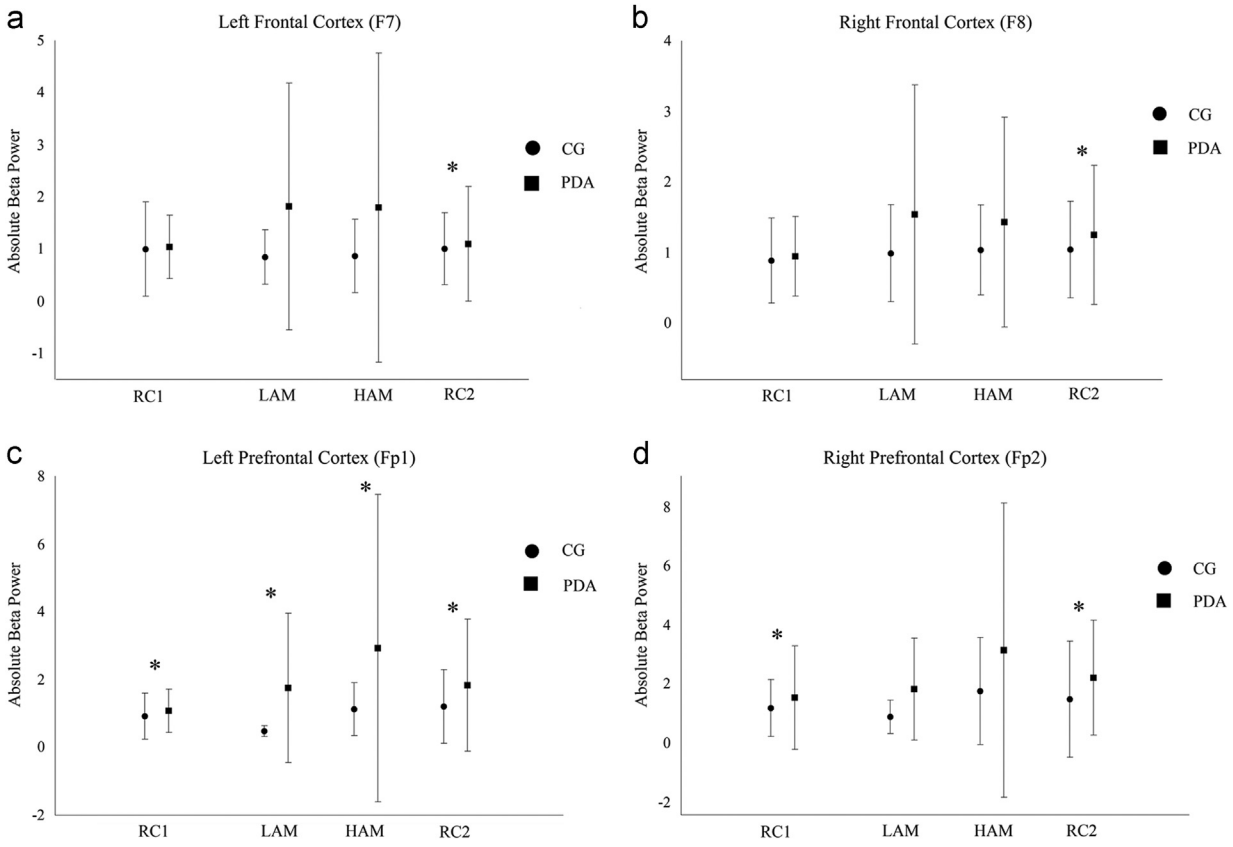


**Fig. 1.** Mean and standard deviation of absolute alpha power on the frontal (F7, F8) and prefrontal (Fp1, Fp2) cortexes. (a) For F7 the statistical analysis revealed an interaction between group and moment ($p=0.001$); (b) for F8 the statistical analysis revealed an interaction between group and moment ($p=0.033$); (c) for Fp1 the statistical analysis revealed an interaction between group and moment ($p=0.000$); (d) for Fp2 the statistical analysis revealed an interaction between group and moment ($p=0.035$). The (*) demonstrates the difference between groups (i.e., control and PDA groups).

beta-band activity is likely to result in an abnormal persistence of the status quo and in a deterioration of flexible behavioral and cognitive control (Engell and Fries, 2010).

Beta band activity may be related to the involvement of top-down processing. High beta band activity is related to tasks involving a strong endogenous, top-down component, whereas a decrease of beta activity is related to tasks where the behavioral response is fundamentally determined by bottom-up factors (Engell and Fries, 2010). Studies have shown that endogenous top-down attention is associated with communication in lower frequency bands (Buschman and Miller, 2007', 2009). Studies have also related beta activity to target stimulus processing in the attentional blink paradigm. In this paradigm, the saliency of the target stimulus to be detected is intentionally kept low (Gross et al., 2004, 2006; Kranczioch et al., 2007). Following these data, Engell and Fries (2010) proposed that the enhancement or decrease of beta band activity may related to top-down processing and also to the contents of the top-down signal: beta activity may be enhanced if the current status is given priority over new signals that are considered distractive.

The current literature has provided evidence that anxious individuals show increased attentional capture by danger cues and are more likely to interpret emotionally ambiguous stimuli as threatened. These cognitive biases must be implicated in the maintenance of anxiety (Bishop, 2008). The responses to threat-related stimuli are more constantly attributed to the interaction of associative and attentional processes and also to associative and interpretative processes. Recent studies support that amygdala–prefrontal circuitry is involved in enabling both representations of stimulus emotional salience and top-down control mechanisms to influence associative, attentional and interpretative processes. However, this circuitry may be disrupted in anxiety, what leads to alterations in associative, attentional and interpretative processes that sustain threat-related processing bias; probably by impaired recruitment of prefrontal control mechanisms and hyper-responsivity to threat of the amygdala (Bouton, 2002; Van Damme et al., 2006; Bishop, 2008). Given this information, we can hypothesize that the maintenance of this processing bias, thus the maintenance of the status quo, as described above, may be involved in the recruitment of the prefrontal electrodes and the electrodes closer to the temporal cortex at RC2, even when anxiety stimuli were not presented anymore.

In addition, at the anxiety moments (LAM and HAM) significant activity of beta band was only observed over the left prefrontal cortex. Prefrontal cortex activity over the left hemisphere in anxiety was also found on Dresler et al. (2012) study: activation in the left prefrontal cortex was found in the PD group when processing disorder-specific versus neutral words. According to the authors, increased left activation may indicate altered processing of emotional stimulus material; that is, the neural pattern in the PD group could be explained by verbal memory processes, semantic control processes and attention-related processes (Dresler et al., 2012). It is known that emotional lateralization may depend on diverse factors (Wager et al., 2003). It has been hypothesized that the left and right anterior regions of the brain are important components of an affective regulatory system that mediates approach and avoidance behavior: Jackson et al. (2000) found that relative left-sided baseline frontal activation was associated with ability to voluntarily suppress negative emotion. Thus, left hemisphere activation has been associated with approach, response to reward, and positive affect. As opposed, the right hemisphere activation has been associated with avoidance, withdrawal from aversive stimuli, and negative affect (Davidson, 1993). Wager et al. (2003), in recent meta-analyses, tested some of the accepted hypotheses about valence, gender and lateralization in emotion. Their findings may help clarify our findings. Wager et al. (2003) found no significant lateralization for valence (positive/negative) or approach/withdrawal across brain regions; that is, they found no support for that the right hemisphere is more likely to process emotional material than the left hemisphere. They also reported nominally more activation peaks for emotional activation in the left hemisphere than the right, but the difference was not statistically significant. They tested valence lateralization specifically for the frontal cortex and they found no significant frontal lateralization based on positive/negative valence, and these results were similar to those for approach/withdrawal. According to their overall findings, they emphasized that withdrawal/negative emotion-related activity was predominantly left-lateralized in the limbic system (Wager et al., 2003).

Lastly, the observed beta band activity at prefrontal areas (Fp1 and Fp2), just before the computer simulation display (RC1), may be related to anticipatory anxiety. Adaptation in part depends on one's ability to anticipate aversive events in order to deal with or to prevent unpleasant outcomes, besides, anticipating future circumstances can become extreme and may contribute to excessive worry and anxiety, hyper attention to specific threat signs and behavioral withdrawal (Nitschke et al., 2005). The prefrontal cortex is related to this capacity to foresee futures events and also to respond to potential threats and to coordinate defensive reactions through connections to the amygdala, hypothalamus and periaqueductal gray region (Canterasa and Graeff, 2014). Gray et al. (2003) recorded electroencephalographic Steady State Visually Evoked Potentials (SSVEP) among right-handed males while relaxed and during the anticipation of an electric shock (anticipatory anxiety condition) and they found support for the involvement of frontal, anterior temporal and occipital cortical regions during anticipatory anxiety. Nitschke et al. (2005) assessed the neural patterns of anticipating and being exposed to aversive pictures, within functional magnetic resonance imaging (fMRI) among healthy volunteers, and found out that the anticipatory processes were associated with activations in rostral ACC, right dorsolateral prefrontal cortex and medial bilateral orbitofrontal cortex. Following this rationality, Grillon et al. (2008) recruited individuals with panic disorder and, relative to healthy controls, they had increased startle magnitude in the context of an unpredictable condition. According to Grupe and Nitschke (2013), feelings about threat under conditions of uncertainty are related to ventromedial prefrontal cortex and anterior insula dysfunction; the consequence of the deficient ventromedial prefrontal cortex inhibition of amygdala may be amygdala hyperactivity, what contributes to increased vigilance towards potential threat, as already cited above.

Our results confirm our hypothesis that the PDA patients might present a higher absolute beta power in the frontal cortex when compared to healthy controls. During HAM, absolute beta power tended to be higher than during LAM. The data also confirmed the PDA patients' tendency to present anticipatory anxiety by anticipating future aversive circumstances. Anticipatory anxiety tends to keep a hypervigilant state to threat cues and a lack of cognitive flexibility to appraise new events. All these characteristics may be related to an imbalance of top down mechanisms involving prefrontal cortex inhibition of the amygdala. The limitations of this study were the small sample, the wide age range of participants, the gender of participants was not balanced in the samples and the use of psychotropic medications by most of the PDA patients.

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**Conflict of interest**

None to declare.

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