Biological Psychology 103 (2014) 233–241

Contents lists available at ScienceDirect

Biological Psychology

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

Brain reactivity to unpleasant stimuli is associated with severity of posttraumatic stress symptoms.

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ARTICLE INFO

Article history:
Received 25 February 2014
Accepted 7 September 2014
Available online 27 September 2014

Keywords:
Posttraumatic stress symptoms
PTSD
Trauma
Emotion
Emotional reactivity
ERP
PCA
LPP

ABSTRACT

Despite the impressive progress in the biological research of posttraumatic stress disorder (PTSD), little is known about the neurobiological correlates of emotional reactions in healthy people with posttraumatic stress symptoms (PTSS). The present study investigated whether PTSS are related to the electrocortical processing of unpleasant pictures in a sample of undergraduate students. Participants were instructed to judge whether images were unpleasant or neutral while an EEG was taken. The late positive potential (LPP) to unpleasant relative to neutral was more positive for people with high PTSS than with low PTSS. Additionally, a temporospatial principal components analysis (PCA) for the whole sample identified positivities that were directly correlated with PTSS. These results provide evidence that brain reactivity to unpleasant cues would predict PTSS intensity and thus be a biomarker of PTSS severity.

1. Introduction

The ability to detect and respond to emotional signals from the environment is essential for survival. Many studies have suggested that the brain prioritizes the processing of emotion-laden stimuli (Öhman, Flykt, & Esteves, 2001; Pereira et al., 2006, 2010; Phelps, Ling, & Carrasco, 2006; Vuilleumier, Armony, Driver, & Dolan, 2001). For example, compared with neutral stimuli, unpleasant stimuli evoke increased brain activity in several regions (Carretié, Albert, López-Martín, & Tapia, 2009; Phan, Wager, Taylor, & Liberzon, 2002), suggesting that enhanced perception could be important for selecting an appropriate response (see also Keil et al., 2010). However, an exaggerated emotional response, especially to unpleasant stimuli, may be deleterious to mental health. For instance, anxiety disorders have been associated with an overreaction to emotional cues (Cisler & Koster, 2010; Etkin & Wager, 2007; Hofmann, Ellard, & Siegle, 2012).

Posttraumatic stress disorder (PTSD) is an anxiety disorder that has been linked to an overreaction to and a failure to recover from unpleasant events (Foa, Feske, Murdock, & Kozak, 1991; Orr et al., 2000; Shin et al., 2005; Volchan et al., 2011; Wessa & Flor, 2007; Yehuda & LeDoux, 2007). For example, Foa et al. (1991) found that rape victims with PTSD presented longer response latencies for naming the color of rape-related words than other target-word types compared with non-PTSD victims and non-victim control subjects. Vythilingam et al. (2007) showed that patients with PTSD present increased interference for unpleasant distracters on an affective Stroop task compared with trauma controls and non-traumatized healthy participants. Studies using script-driven imagery paradigms have also found intense reactions to trauma-related stimuli in PTSD subjects (see Lobo et al., 2011, for a review). Volchan et al. (2011) investigated posturography and electrocardiography in response to script-driven imagery. They found that the immobility reported after symptom provocation was associated with a restricted area of body sway and correlated with an accelerated heart rate and a diminished heart rate variability, which indicates that PTSD subjects preserve an involuntary defensive strategy in response to trauma cues. After a symptom provocation, PTSD patients sustained an increased heart rate, whereas trauma controls recovered to basal levels (Norte et al., 2013). Furthermore, fear conditioning paradigms show that PTSD patients have higher

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http://dx.doi.org/10.1016/j.biopsycho.2014.09.002
0301-0511/

sympathetic nervous system arousal during conditioning and have enhanced conditioned responses to trauma reminders (Orr et al., 2000; Wessa & Flor, 2007).

Increased emotional reactions can even occur in response to non-trauma related stimuli. Using fearful, neutral, and happy faces, Shin et al. (2005) studied firemen and war veterans with and without PTSD. The PTSD participants exhibited increased activity in the amygdala and decreased activity in the medial prefrontal cortex (mPFC) in response to fearful faces compared to happy faces. Additionally, a negative correlation was found between amygdala and mPFC activity, which suggests a failure of amygdala activity regulation in PTSD. Taken together, these and other studies (e.g., Liberzon et al., 1999; Mueller-Pfeiffer et al., 2010) support the idea that PTSD involves a hyper-responsiveness to unpleasant cues.

On the other hand, a possible hyper-responsiveness to unpleasant cues in people exposed to traumatic events but who did not develop clinical PTSD, (i.e., subsyndromal PTSD), has been less explored. Although these people do not have a PTSD diagnosis, there is evidence suggesting that "partial" or subsyndromal PTSD is associated with significant functional disability in the general population (Mylle & Maes, 2004; Pietrzak, Goldstein, Malley, Johnson, & Southwick, 2009; Zlotnick, Franklin, & Zimmerman, 2002) especially in women (Stein, Walker, Hazen, & Forde, 1997). For instance, in a sample of breast cancer survivors, both PTSD and subsyndromal PTSD were associated with employment absenteeism and the seeking of mental health services (Shelby, Golden-Kreutz, & Andersen, 2008). Partial PTSD was also associated with elevated lifetime rates of anxiety, heavy drinking and drug use, substance use disorders, emotional problems, and suicide attempts (Berger et al., 2007; Pietrzak et al., 2009; Read et al., 2012).

Thus, the study of traumatized individuals who preserve posttraumatic stress symptoms (PTSS) may be helpful in elucidating the factors that determine resilience or potential vulnerability to PTSD. In fact, the NIMH launched the research domain criteria (RDoC) project in 2009 to create a framework for research on pathophysiology, especially for genomics and neuroscience, in order to provide a framework for classifying mental disorders based on empirical data (Insel et al., 2010). The RDoC is explicitly dimensional in its approach; the biological and clinical variables examined in a research project can be measured on a spectrum spanning the range from normal to abnormal (Simmons & Quinn, 2013). Therefore, determining the full range of variation from normal to abnormal is important for improving our understanding of what is typical versus pathological. Taking the RDoC framework into consideration, it is probable that posttraumatic responses also exist in a continuum rather than in a traditional dichotomous model of health and disease. In the present study, we investigated whether increased brain reactivity to unpleasant cues is associated with high levels of PTSS in a sample of undergraduate students. This relatively healthy sample minimizes confounding factors such as comorbidities and medication use and might represent a good approach for studying PTSS as a continuum. We hypothesized that brain reactivity to unpleasant cues would predict PTSS intensity and thus be a possible biomarker of PTSS severity.

The electroencephalography technique known as event-related potentials (ERPs) is a powerful tool to investigate brain reactivity to emotional content because it can assess the time course of emotional reactions. Specifically, the positivities at approximately 300 ms of the ERP (the P3 family, such as P300 and the late positive potential) have been used to study processes related to attention and emotion (Johnson, 1986; Magliero, Bashore, Coles, & Donchin, 1984). Compared with neutral stimuli, emotional (pleasant or unpleasant) stimuli elicit a slow and sustained positive ERP that has a centro-posterior midline scalp distribution and is commonly called the late positive potential (LPP). The LPP differs substantially between emotional and neutral stimuli, reflecting the stages of processing that follow stimulus identification and are modulated by task manipulations (Hajcak, MacNamara, & Olvet, 2010; Kok, 1997, 2001; Mocaiber et al., 2010). Thus, the late positive potential has been considered an index of emotional reactivity because it is highly sensitive to the emotional intensity of the stimuli and indexes selective attention toward motivationally salient content (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Keil et al., 2002; Schupp et al., 2000; Schupp, Junghöfer, Weike, & Hamm, 2003).

The aim of the present study was to investigate brain reactivity to unpleasant stimuli in a non-clinical sample of undergraduate students with PTSS after exposure to traumatic events. Specifically, we evaluated whether PTSS severity was associated with electrocortical reactivity to unpleasant pictures during an emotional judgment task. Our hypothesis was that people with more severe PTSS would react more strongly to unpleasant pictures than to neutral images, even in a non-clinical sample. Evidence for this suggests the possibility for hyper-responsiveness in the EEG signal to act as a potential biomarker of PTSS severity.

2. Methods

2.1. Participants

Forty-eight undergraduate students at the Fluminense Federal University (42 women) volunteered for the experiment. They were selected using a purposive sampling technique, which targets a particular group of people. In the present study, the participants were selected according to their exposure to a potentially traumatic event. This event was assessed by a specific question at the beginning of the "Post-traumatic Stress Disorder Checklist-Civilian Version" scale (PCL-C, Weathers, Litz, Herman, Huska, & Keane, 1993), which was translated and adapted to Portuguese (Berger, Mendlowicz, Souza, & Figueira, 2004). In the pre-experimental phase, the participants completed this checklist and were informed that they might be invited to participate in the next step. For the next step (the EEG study), we invited volunteers with various scores on the PCL-C scale who reported having experienced, witnessed, or confronted an event that involved death, serious injury or a threat to the physical integrity of themselves or others (the A1 criterion of the DSM IV). On the day of the EEG experiment, the participants completed the PCL-C again. Thus, each of the participants in the sample experienced at least one traumatic event that fits the A1 criterion of the DSM IV and had some degree of PTSS.

Four of the participants were excluded due to poor EEG data. One participant was excluded because of the use of a medication with central nervous system action. The final sample consisted of 43 volunteers (38 women) between 18 and 28 years of age (mean (M) = 20 ± 1.96). All of the participants had normal or corrected-to-normal visual acuity. The final sample reported no psychiatric or neurological problems and was not under medication with central nervous system action. The participants were naive to the purpose of the experiment. All of the procedures were approved by the Research Ethics Committee of the Fluminense Federal University, and all participants gave informed consent before data collection.

2.2. Stimuli

All of the images used in the experiment were taken from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008) or from the World Wide Web. The neutral pictures consisted of photographs of people in daily life, and the unpleasant images consisted of photographs of mutilated bodies. We matched the unpleasant and neutral stimuli in terms of both color content and complexity (e.g., number of faces, number of body parts, etc.). Following the protocol developed by Bradley and Lang (1994), all of the images were assessed on a scale of 1–9 in terms of valence (from unpleasant to positive) and arousal (from low to high) by a separate group of graduate students (n = 20) with ages similar to the current subjects (M = 22.3, SD = 1.81). The unpleasant and neutral images differed significantly from each other in their IAPS normative valence (M = 2.09 and 5.12, respectively, t = −41.8, p < 0.001) and arousal (M = 6.74 and 3.29, respectively, t = 40.08, p < 0.001) ratings.

2.3. Procedure

The experiment was conducted in a room with dim ambient light and sound attenuation. The participants sat in front of an LCD monitor with their head resting on a forehead/chin supporter approximately 57 cm from the screen. A microcomputer running E-Prime v1.2 (Psychological Software Tools Inc.) timed the presentation of the stimuli, delivered the triggers, and recorded the key presses. The participants gave their informed consent and were seated and connected to the electroencephalograph sensors (EEG).

The participants performed an emotional judgment task in which they had to decide whether the presented picture was neutral or unpleasant by pressing one

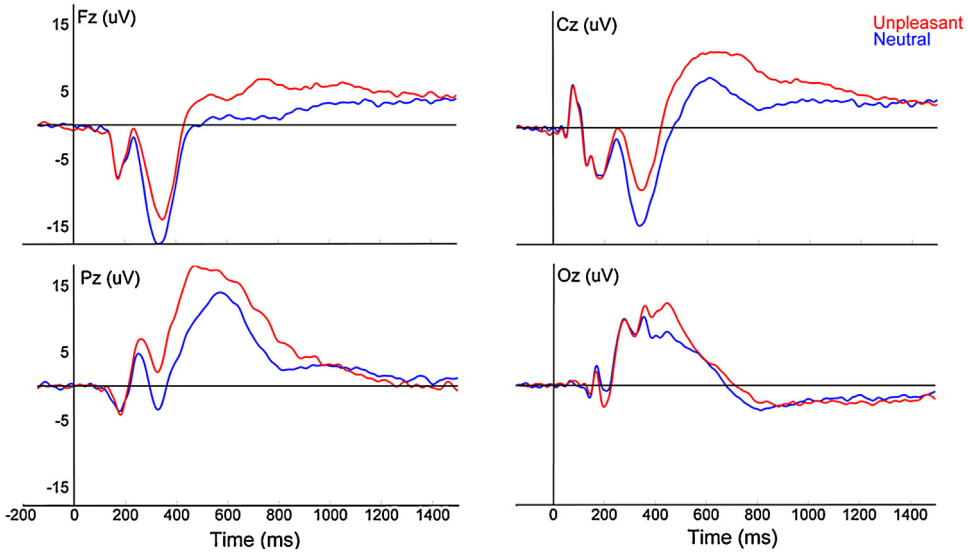

Fig. 1. Grand average waveforms for selected midline frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) electrodes for the unpleasant and neutral trials.

of two buttons ("1" or "Z" on the keyboard). Each trial started with a blank screen (100 ms) followed by a fixation cross shown for 800 to 1200 ms. A central picture ($9^\circ \times 12^\circ$) and two peripheral white bars ($0.3^\circ \times 3.0^\circ$) were then simultaneously shown for 200 ms, followed by a 2000 ms inter-trial interval (ITI) (the fixation cross remained during both the picture and the ITI). The participants were instructed to ignore the task-irrelevant peripheral bars and to respond as quickly and accurately as possible to indicate whether the central image was neutral or unpleasant. The peripheral bars were a part of another experimental condition that will not be described in this paper.[1] The buttons (right or left finger) corresponding to the neutral/unpleasant pictures were counterbalanced across subjects. Each test contained an equal number of neutral and unpleasant trials ($n = 80$ per condition). The order of the picture presentation was pseudo-randomized, i.e., no more than three consecutive images with the same valence appeared. Therefore, the experimental session consisted of one block of 160 photos.

The subjects performed a practice block before performing the experimental block. An additional set of 15 neutral pictures of household objects from the IAPS (Lang et al., 2008) was selected for the practice block. This training block was not included in the analyzes.

2.4. Posttraumatic Stress Disorder Checklist-Civilian Version (PCL-C)

The PCL is one of the most widely used self-report instruments for measuring PTSD symptoms (Elhai, Gray, Kashdan, & Franklin, 2005). Developed at the National Center for PTSD, the PCL-C is a 17-item self-report measure of posttraumatic stress symptoms related to the severity of intrusive, avoidance, and hyperarousal symptoms experienced in response to a stressful life event. Using a 5-point Likert scale (1 = not at all, 5 = extremely), the participants rated the extent to which each symptom has bothered them in the past month. Previous studies have demonstrated the appropriateness of the PCL-C in assessing PTSS in samples of undergraduate students exposed to potentially traumatic events (Blanchard et al., 2004; Ruggiero, Del Ben, Scotti, & Rabalais, 2003; Terhakopian, Sinaii, Engel, Schnurr, & Hoge, 2008; Tull, Barrett, McMillan, & Roemer, 2007).

On the day of the experiment, the PCL-C scale was again completed (after the EEG recording) by each participant. This second PCL-C score was the one used for the analyzes described in this study. In addition, the volunteers described the index trauma to which the symptoms on the PCL-C scale were related. The participants answered the question "What was the most severe traumatic event in your life?" The index traumas reported by the participants were: "death/loss of someone close to you" ($n = 16$), "violent crime" ($n = 12$), "medical causes" ($n = 8$), "vehicle accident" ($n = 2$), "child abuse" ($n = 2$), "domestic violence" ($n = 1$), and "other" ($n = 2$).

In our sample, the PTSS scores ranged from 17 to 77 ($M = 40.44$, SD = 15.34). Twenty of the participants (46.5%) scored 44 or above on the PCL-C scale, indicating that they met the criteria for possible PTSD according to the cutoff score provided by Blanchard, Jones-Alexander, Buckley, and Forneris (1996) for civilians (see Ruggiero et al., 2003, for further evidence supporting the use of the 44 cutoff score in undergraduate student samples). The final sample population consisted of a high PTSS group (that scored 44 or above on PCL-C; $M = 54$; $n = 20$), and a low PTSS group (that scored below 44; $M = 29$; $n = 23$).

2.5. Behavioral data analysis

Reaction time (RT) < 150 ms (anticipation), slow responses (RT > 1500 ms), and incorrect key-press responses were excluded from the RT and EEG analyzes. We calculated each subject's median RT for the unpleasant and neutral trials. We then applied a two-tailed paired Student's *t*-test to compare the mean of the unpleasant and neutral trials. To create an emotional modulation index, we subtracted the median response time for the pictures in the neutral trials from that for the unpleasant trials for each volunteer. Positive values in this index indicate slower RTs to the unpleasant than to the neutral pictures, and negative values indicate faster RTs to the unpleasant than to the neutral pictures. After calculating the RT emotional modulation index, we performed Pearson correlations between the RT emotional index and the PCL-C scores. The alpha level adopted for statistical significance was $\alpha = 0.05$.

2.6. Event-related brain potential recording and analysis

We recorded the EEGs using a BrainNet BNT-36 (EMSA Equipamentos Médicos Ltd., Rio de Janeiro, Brazil) recording system with 23 electrodes positioned according to the electrode sites from the 10–20 system: FPz, FP1, FP2, Fz, F7, F3, F4, F8, Cz, C3, C4, T7, T8, Pz, P3, P7, P4, P8, Oz, O1, O2, M1, and M2. All of the electrodes were referenced to Cz during the recording session and re-referenced to the averaged mastoids offline. The sample rate was 400 Hz during data acquisition, and the impedance was kept below 5 kΩ for all of the electrodes. The data were filtered offline using 0.1 Hz high-pass and 30 Hz low-pass digital filters. The offline analysis of the data was performed using the EEGLAB v5.03 toolbox (Delorme & Makeig, 2004) with MatLab v7.9 (MathWorks, Natick, MA). Eye movement artifacts were removed from the data using an independent component analysis (ICA) available in EEGLAB. ICA algorithms have been shown to be effective in isolating the components that correspond to eye blinks (Jung et al., 2000). These components were excluded from the data only after a visual inspection of the topographical maps demonstrated their proximity to the ocular area and established waveform characteristics. The EEG data were epoched from a 200 ms pre-stimulus onset to a 1500 ms post-stimulus onset. The event-related potentials (ERPs) associated with correct "neutral" and "unpleasant" responses were averaged for each condition. The original grand average waveforms for each condition and the topographical maps are presented in Fig. 1. The baseline corresponded to the 200 ms period preceding the stimulus onset. Epochs containing deviations larger than 100 μV relative to the baseline for any of the electrodes were rejected. The epoch rejection rate did not exceed 20% per subject.

The LPP analysis included central (C3, C4, and Cz), parietal (P3, P4, and Pz), and occipital sites (O1, O2, and Oz). The mean peak amplitudes were quantified between 300 and 600 ms following each picture onset, which has been commonly described for LPP (Olofsson, Nordin, Sequeira, & Polich, 2008). These data were submitted to a repeated measures analysis of variance (ANOVA; using the Greenhouse–Geisser correction) for factors of Anterior-posterior (3 levels: central, parietal, and occipital), laterality (3 levels: left, right, and midline), valence (2 levels: neutral and unpleasant), and PTSS as a between factor (2 levels: high PTSS and low PTSS).

[1] In the "judge bars" condition, the volunteers were instructed to ignore the central image and judge whether the peripheral bars were in the same or different orientations. Each condition (judge bars or judge picture) was blocked with a total duration of 10 min per block. In addition, there was an interval between the blocks of about 5 min in which the experimenter entered the experimental room. The order of the blocks was counterbalanced between subjects.

After conducting the ANOVA, the Newman–Keuls procedure was used to test for significant post hoc comparisons at $\alpha = 0.05$.

To improve the data exploration, we applied a temporospatial principal component analysis (PCA) to the data. The PCA promotes data reduction through a statistical decomposition of the ERPs, which simplifies the description and analysis of the data (Dien & Frischkoff, 2005). The PCA was conducted using the ERP PCA Toolbox (Dien, 2010) for MatLab (MathWorks Inc., Natick, MA) using the covariance matrix and Kaiser normalization (as suggested by Dien, Beal, & Berg, 2005). The analysis was performed in two steps, beginning with the temporal and followed by the spatial PCA, as previously described (Foti, Hajcak, & Dien, 2009; MacNamara, Foti, & Hajcak, 2009). For the temporal PCA, all of the time points in each trial were used as variables, and the observations included all 43 of the subjects, the 23 channels, and the two conditions. The promax rotation was applied for this initial temporal PCA step (Dien, Khoe, & Mangun, 2007). Thereafter, a spatial PCA was performed using the recording sites (electrodes) as variables and all of the participants, conditions, and temporal factor scores as observations. The infomax rotation was used for the spatial PCA step (Dien et al., 2007). The temporal PCA yielded 12 factors, and two spatial factors were extracted for each temporal factor. This yielded a total of 24 temporospatial factor combinations. Of these, 16 factors each accounted for >1% of the variance and were retained for further examination. The obtained PCA scores correspond to the voltage accounted for the peak channel and the peak time point for each factor.

We chose factors for statistical analysis according to a priori knowledge about the ERP components relevant to the experimental design (Dien et al., 2005). Although earlier ERP components (i.e., early posterior negativity (EPN) have been shown to be sensitive to emotional content (Foti et al., 2009; Junghöfer, Bradley, Elbert, & Lang, 2001; Olofsson et al., 2008), other influences such as picture complexity have been implicated in the modulation of these earlier ERP components (Bradley, Hamby, Löw, & Lang, 2007). Taking that into account, we selected 12 PCA factor scores that encompass components from 300 ms and beyond for further statistical analysis.

Following this criteria, we compared the PCA factor scores obtained for unpleasant and neutral conditions using a two-tailed, paired Student's *t* test. To investigate the extent to which emotional modulation in the PCA varied with PTSS, we calculated an emotional modulation index. This index was created by subtracting the PCA factor scores of the neutral condition from those of the unpleasant condition for each subject.

In order to evaluate if the PCA factor scores were associated with PTSS (dependent variable), we performed a sequence of bivariate analyzes including the PCA factor scores that were modulated by emotion and the PCL-C scores (initial simple regression analysis). Those variables presenting *p*-values <0.20 in this step of the analysis were then selected for inclusion in a controlled forward stepwise multiple regression model (Mickey & Greenland, 1989). As the objective was to identify factors associated with PTSS, the models were adjusted for this variable. The first variables included were those with lower p values. The variables that increased the significance of the model, increased R^2, and did not present collinearity with other variables were maintained. To evaluate the existence of collinearity between variables and whether the inclusion of a new variable produced an increase in the standard error of the other variables of the model, we conducted Pearson correlations. The final model retained the PCA factor scores that best explained the variance in combination, being the PCA factor scores that were more important in predicting PTSS. The alpha level adopted for statistical significance was $\alpha = 0.05$.

3. Results

3.1. Behavioral data

The participants were faster to judge the unpleasant images than the neutral images (M unpleasant = 592.64, SD = 102.53; M neutral = 619.31, SD = 98.7, $t = 4.08$, $p < 0.001$). Additionally, there was no significant correlation between the reaction time latency or the number of errors and PTSS (assessed by PCL-C) ($p > 0.05$ for all comparisons).

3.2. Electrophysiological data

3.2.1. Grand averages and 300–600 ms time window analysis

To illustrate the general effects related to emotion, the grand average waveforms and the spatial distribution of the voltage (scalp topographies) prior to the PCA analysis are shown. Fig. 1 exhibits brain activity (unpleasant and neutral) for all of the subjects. There is a noticeable sustained positivity increasing from the frontal to the parietal sites following picture presentation. It can also be observed that unpleasant pictures elicited a greater positivity than did the neutral pictures.

Table 1
Description for each PCA factor score with the mean unpleasant minus neutral (emotional modulation index), and *t*-test for unpleasant versus neutral.

PCA factor score	Mean unpleasant minus neutral (and SD) in μV	*t* test unpleasant versus neutral
353Oz	4.14 (3.63)	7.46**
353Cz	4.62 (3.60)	8.41**
468C4	0.33 (0.82)	2.66*
553Pz	3.00 (2.68)	7.33**
553F8	0.66 (1.52)	2.87*
770Fz	3.21 (3.39)	6.21**

* $p < 0.05$.
** $p < 0.0001$.

The ANOVA of the LPP mean peak amplitudes revealed a significant interaction between Antero-posterior and valence $F(2,82) = 41.06$, $p < 0.00001$ $\varepsilon = 0.80$, with the emotional effect (i.e., the increase of LPP to unpleasant relative to neutral pictures) being higher in parietal and central compared to occipital. Interestingly, the interaction between PTSS and Valence was also significant $F(1,41) = 6.22$, $p < 0.05$, with the emotional effect for unpleasant related to neutral being significantly higher in the high PTSS group than in the low PTSS group (Fig. 2). In addition, post hoc analysis showed that there were no differential effects between the neutral pictures across the groups ($p = 0.34$, n.s.). There was also a significant interaction between Antero-posterior and Laterality $F(4,164) = 8.07$, $p < 0.01$, $\varepsilon = 0.85$, with the differences between right, midline, and left being significant, except in the parietal sites, and between midline and right for the occipital sites ($p < 0.001$ for all other comparisons).

3.2.2. PCA

The ERP components of interest were quantified using a temporospatial PCA, and all of the following data presentation and analysis were based on this approach. Similar to MacNamara et al. (2010), we adopted the name of the factor using the relevant temporal (i.e., peak latency) and spatial (i.e., peak channel) information. For example, factor '400Oz' refers to a factor that peaked 400ms after picture onset and was maximal at the midline occipital recording site. Of the 12 PCA factor scores initially selected (see Section 2), six were sensitive to emotional content (with unpleasant PCA factor scores more positive than the neutral scores). Two early positivities (occipital and central) peaking at 353 ms, a middle central positivity peaking at 468 ms, two other middle positivities (frontal and parietal) peaking at 553 ms, and a late frontal positivity peaking at 770 ms showed significantly higher values for the unpleasant images than for the neutral images ($p < 0.05$ for all comparisons, see Table 1). These six PCA factor scores were consistently found in previous studies that investigated the effects of emotional modulation on ERPs and are consistent with the time course and scalp distribution of the LPP (Foti et al., 2009; MacNamara et al., 2009; MacNamara, Ochsner, & Hajcak, 2010).

As stated previously, only the PCA factor scores that were modulated by emotion were used to investigate the association between PTSS and emotional brain reactivity. The emotional modulation index was created by subtracting the PCA factor score of the unpleasant pictures from that of the neutral pictures and was correlated with the PTSS level of each subject. Positive values in this PCA emotional modulation index indicate an increased reaction to the unpleasant stimuli compared with the neutral stimuli. Bivariate analyzes were performed including the PCA factor scores that were modulated by emotion and the PTSS (dependent variable). Significant associations ($p < 0.05$) were found between four PCA factor scores and PTSS: 353Cz ($\beta = 0.34$); 353Oz ($\beta = 0.36$); 468C4 ($\beta = 0.35$); and 770Fz ($\beta = 0.31$). A marginal association was found between 553Pz and PTSS ($\beta = 0.29$, $p = 0.06$). A controlled forward

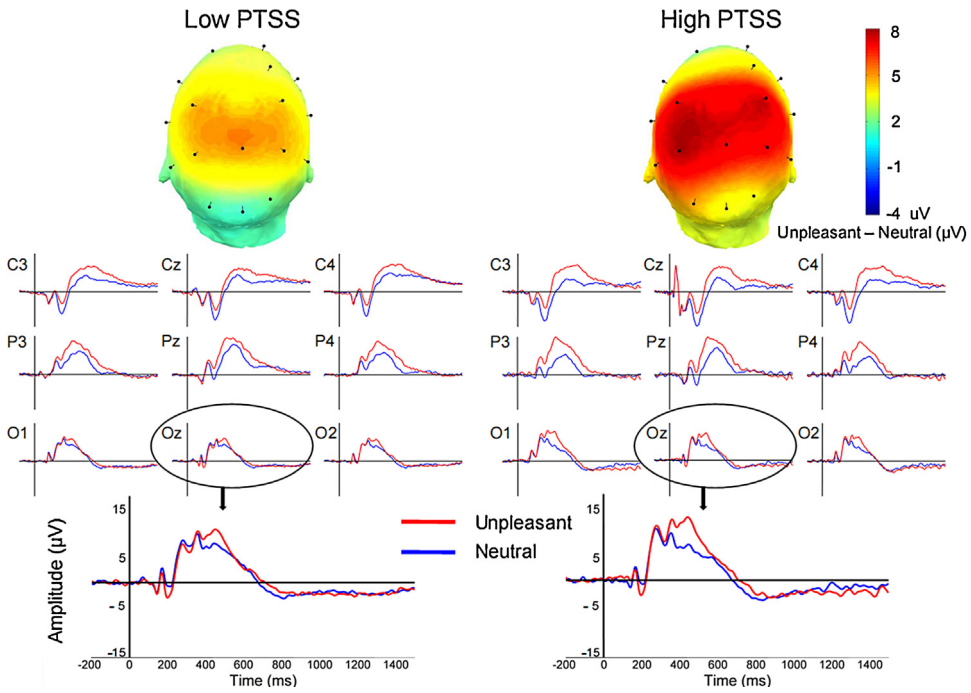

Fig. 2. *Top*: Topographical maps of the LPP averaged in the 300–600 ms time window for unpleasant minus neutral (μV) in low PTSS severity (left) and high PTSS severity (right). *Middle*: Grand averages for selected central (C3, Cz, and C4), parietal (P3, Pz, and P4), and occipital (O1, Oz, and O2) electrodes for unpleasant (red) and neutral (blue) conditions for low PTSS (left) and high PTSS (right). *Bottom*: The ERP waveforms obtained for the Oz electrode in both unpleasant and neutral conditions for low PTSS (left) and high PTSS (right) are represented as full-size traces to facilitate visualization. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Regression parameters for the association between PCA factor scores (unpleasant minus neutral values as the independent variable) and PTSS (PCL-C as the dependent variable) scores, $n = 43$.

Step	β	Standard error	p-Value
(1) 353Oz	0.314	0.14	0.031
(2) 468C4	0.310	0.14	0.033

stepwise multiple regression analysis with PTSS as the dependent variable and the five PCA factor scores as predictors was performed in attempt to find the most important variables for predicting PTSS. The initial models comprised of each of the PCA factor scores, following the order of statistical significance (higher to lower). The final model retained two PCA factor scores, the 353Oz and the 468C4, that together were the best solution to explain the variance in PTSS ($R = 0.47$, $R^2 = 0.22$, $p < 0.01$, see Table 2). In other words, larger emotional modulation indexes in these two PCA factor scores were associated with increased PTSS.

Additionally, only for illustration purposes, we selected a particular PCA factor score (353Oz) that revealed a significant association between the PCA emotional modulation index and PTSS in order to show an example waveform and topographical map for individuals with high and low PTSS (Fig. 3). The emotional modulation produced by the unpleasant pictures is enhanced in the participants with high levels of PTSS compared with the participants with low levels of PTSS.

4. Discussion

Our findings provide evidence for an association between the severity of PTSS in undergraduate students and brain reactivity to unpleasant stimuli. We found that people with high levels of PTSS have a more pronounced emotional effect (LPP to unpleasant relative to neutral) than people with low levels of PTSS. We also found a significant positive correlation between PTSS and the PCA factor scores, such that greater PTSS were associated with larger PCA factor scores for unpleasant versus neutral stimuli. In the behavioral data, we found that reaction times to the unpleasant pictures were faster than to the neutral pictures. While, this facilitation was not associated with PTSS, it is consisted with other studies that have shown that when the emotional information of the image is important for the execution of a task (e.g., to judge picture valence), there is a reduction in the manual reaction time for emotional pictures relative to neutral pictures (Calvo & Avero, 2009; Huang & Luo, 2006).

The EEG results of the present study corroborate the strong body of research that has found that unpleasant pictures elicit greater ERP positivity than do neutral pictures (Codispoti, Ferrari, & Bradley, 2007; Cuthbert et al., 2000; Hajcak, Dunning, & Foti, 2009; Hajcak et al., 2010; Hajcak & Olvet, 2008; Keil et al., 2002; Schupp et al., 2000). Moreover, the PCA factor scores found in the present study are compatible with the time course, scalp distribution, and emotional sensitivity of the LPP (Hajcak et al., 2010; Olofsson et al., 2008). Interestingly, in our study, this emotional effect (unpleasant minus neutral) seemed to be more pronounced in students with more severe PTSS, indicating that these people are more reactive to unpleasant content than are people with less severe PTSS. This evidence is consistent with a study which found that, compared with healthy control subjects, traumatized groups (with and without PTSD) displayed increased P300 and late positive complex amplitudes to trauma-specific questions, indicative of enhanced emotional processing of these stimuli (Wessa, Jatzko, & Flor, 2006). Taken together, these findings corroborate the idea that the increased brain reactivity to unpleasant stimuli indexed by P300 family ERPs may occur in people without a PTSD diagnosis but with PTSS. Furthermore, in the present study, by using the PCA for the EEG data and a multiple regression analysis with the PCL-C, we obtained two major advantages. First, we could observe the association between emotional reactivity without the prior choice of an

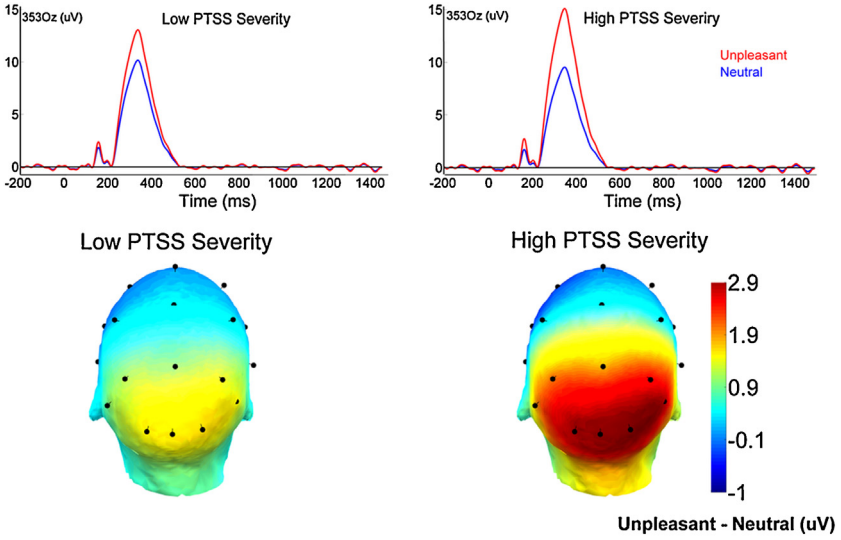

Fig. 3. *Top*: Waveforms for unpleasant minus neutral stimuli for the PCA factor score 353Oz in participants with low PTSS severity (left) and high PTSS severity (right). *Bottom*: Topographical maps of the 353Oz factor in subjects with low PTSS severity (left) and high PTSS severity (right).

analysis time window of interest. Second, the multiple regression analysis allowed us to observe the association between emotional effect and the severity of PTSS while considering the sample as a whole, without establishing cutoff points for PCL-C that separate the population into high and low. These advantages provide us with stronger evidence for the relationship between the severity of PTSS and emotional reactivity, as indexed by the LPP.

Despite this evidence, the EEG hyper-responsiveness to emotional stimuli in subjects with PTSD and PTSS is still a matter of debate. For example, a recent study (Grasso & Simons, 2012) of children and youth with PTSD found no LPP differences in response to images of attacks between the PTSD and control groups (non-trauma exposed youth) (see also Javanbakht, Liberzon, Amirsadri, Gjini, & Boutros, 2011; Johnson, Allana, Medlin, Harris, & Karl, 2013; Wessa, Karl, & Flor, 2005). These contrasting results in the literature might be related to the diversity of tasks, differences in the psychometric measures used to access symptom severity, the types of stimuli used, or to a lack of consistency in aspects of the EEG methodology (e.g., filters, time window analysis, and different channel references). In our study, we used a traditional LPP analysis and as well as the PCA technique. One of the great advantages of using this technique for EEG analysis is that it is not necessary to determine a time window, thus it can provide new insights into the time course associated with the phenomena under investigation.

It is interesting to note that people with PTSS, even those without a PTSD diagnosis, actually present impairments in daily life situations. Psychometric studies of students with PTSS are in agreement with this fact. For instance, a study from Grasso et al. (2012) found that students with probable PTSD reported fewer personal resources (i.e., perceived social support, self-esteem, and optimism) than did students with a lower probability of PTSD and non-trauma exposed students. There is also an association between peritraumatic tonic immobility, a defensive reaction, and PTSS, which suggests a vulnerability for psychopathological outcomes following a traumatic event (Portugal et al., 2012). Furthermore, there is psychometric evidence that PTSS severity is related to difficulties in emotion regulation (Cloitre, Miranda, Stovall-McClough, & Han, 2005; Ehring & Quack, 2010; Tull et al., 2007).

In addition to daily impairments, some studies have also shown significant brain alterations in PTSS individuals. For example, activation for emotional versus neutral stimuli in ventral frontolimbic regions such as the ventromedial prefrontal cortex was highly positively correlated with PTSS in war veterans (Morey, Petty, Cooper, Labar, & McCarthy, 2008). The same study found that the activation for an executive task was negatively correlated with PTSS in areas of the dorsal executive network, such as the middle frontal gyrus. Another fMRI experiment revealed that veterans with high PTSS severity who were engaged in an emotional oddball task showed enhanced neural activity in ventral-limbic and dorsal regions for emotional stimuli and attenuated activity in dorsolateral prefrontal and parietal regions for attention targets compared with a group of veterans with low PTSS (Hayes, Labar, Petty, Mccarthy, & Morey, 2009).

Peripheral data in PTSS samples also shows an altered pattern. Badour and Feldner (2013) found a positive correlation between the severity of PTSS and skin conductance reactivity to script-driven imagery in a non-clinical sample of women with a history of interpersonal assault. Another study that used a fear conditioning task for U.S. military service members identified higher heart rate responses to both danger and safety cues for the high PTSS group relative to the low PTSS group (Roy et al., 2013). Curiously, in PTSD patients, there is evidence that most symptomatic patients with histories of cumulative traumatization show discordant physiological hyporeactivity, perhaps due to sustained stress that may ultimately impair defensive responses (McTeague et al., 2010). Future studies should address the specific role of chronicity, and the duration of posttraumatic stress symptoms in non-clinical samples as well. Taken together, these findings highlight the importance of studying non-clinical populations with PTSS. Considering that posttraumatic responses most likely exist on a continuum, questions regarding resilience, vulnerability, and development of PTSD can be clarified with a better understanding of posttraumatic stress symptomatology. Moreover, studies of non-clinical student populations have other advantages. The relatively healthy sample minimizes confounding factors such as comorbidities and medication, and studying undergraduate students also has the advantage of yielding samples with similar age and education levels.

This study has some limitations. First, caution is needed to extrapolate the results to clinical populations. Our subjects were attending university and volunteered for the experiment, which suggests that the functional impairment of the participants was low or nonexistent. Second, the lack of a control group without trauma exposure could be considered a limitation, but it was difficult to find this profile in college students in a place with high levels of

urban violence such as the metropolitan region of Rio de Janeiro. However, the PTSD literature includes a number of important studies without a non-PTSS/PTSD group (i.e., Badour & Feldner, 2013; Berger et al., 2007; Hayes et al., 2009; Morey et al., 2008; Moser, Hajcak, Simons, & Foa, 2007). Finally, we did not find any significant association between PTSS and the behavioral data, i.e., there was no correlation between reaction time latency and the number of errors with PTSS. One possible explanation for this finding is that the sample size was too small to capture this association.

In summary, we demonstrated that mutilation pictures are useful for evaluating brain hyper-responsiveness that is associated with the severity of PTSS. Although mutilation is not a trauma related image to all traumatized subjects, it causes intense emotional reactions in the general population (Azevedo et al., 2005; Bradley, Codispoti, Cuthbert, & Lang, 2001). The present study was able to demonstrate a significant association between the P3 family (e.g., LPP) amplitude to mutilation pictures and severity of PTSS, which suggests that the P3 family can be used in the future as a potential biomarker for evaluating PTSD severity. There is already evidence that P3 family ERPs can be used as a potential biomarker for PTSD (Johnson et al., 2013). For instance, using the Fisher Linear Discrimination Method, P300 measures correctly classified 90% of PTSD patients and 85% of controls (Attias, Bleich, Furman, & Zinger, 1996). Considering the RDoC project perspective (Insel et al., 2010), our results support the idea that studying mental disorders as a continuum may allow for a better understanding of the transition from the normal or typical to the pathological.

Acknowledgments

The authors wish to thank Dr. Joseph Dien for his assistance on the PCA analysis. We also thank Gabriel C. Motta-Ribeiro for technical support and Dr. Evandro Coutinho for assistance with the multiple regression analysis. This work was supported by funds from federal and state Brazilian research agencies (CNPq, CAPES, and FAPERJ).

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