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

Isabela Lobo[a], Isabel A. David[a], Ivan Figueira[b], Rafaela R. Campagnoli[c], Eliane Volchan[c], Mirtes G. Pereira[a], Leticia de Oliveira[a,*]

[a] Instituto Biomédico, Universidade Federal Fluminense, Rua Hernani Pires de Mello, 101, Niterói 24210130, Brazil
[b] Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Avenida Venceslau Brás, 71, Rio de Janeiro 22290140, Brazil
[c] Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Avenida Carlos Chagas Filho, 373, Rio de Janeiro 21941902, Brazil

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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

* Corresponding author. Tel.: +55 2126292446.
*E-mail addresses:* isabela@vm.uff.br (I. Lobo), isabeldavid@id.uff.br (I.A. David), ivanfigueira13@gmail.com (I. Figueira), rafacampagnoli@gmail.com (R.R. Campagnoli), evolchan@biof.ufrj.br (E. Volchan), mirtes@vm.uff.br (M.G. Pereira), ldol@vm.uff.br (L. de Oliveira).

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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