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Early automatic hyperarousal in response to neutral novel auditory stimuli among trauma-exposed individuals with and without PTSD: An ERP study

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Running Head: Early hypervigilance after trauma

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Abstract

Event Related Potential (ERP) studies have associated Posttraumatic Stress Disorder (PTSD) with enhanced P3 amplitudes in response to trauma-related stimuli, along with reduced amplitudes in the context of neutral (trauma-unrelated) stimuli. Additionally, a bias towards trauma-related stimuli is also observed among trauma-exposed participants not meeting criteria for PTSD, suggesting that trauma exposure itself, and not only the severity of posttraumatic stress (PTS), is a critical factor in information processing changes. However, previous examination of the response of trauma-exposed (PTSD and non-PTSD) participants to novel, neutral stimuli has produced conflicting findings. The current study examined ERPs in response to a novelty oddball paradigm comprised of neutral distractor sounds. Participants were 16 individuals with PTSD, 21 trauma-exposed individuals without PTSD, and 12 non-traumatized controls. Detailed trauma histories and PTS symptoms were collected. A significant effect of group on early ERPs was observed, showing an increase in the N1–P2 complex peak amplitude among the PTSD group, relative to controls. Among the entire sample, significant positive correlations were observed between PTS symptom severity, as well as trauma history, and early N1–P2 complex peak amplitudes, in response to novel stimuli. Furthermore, trauma-exposed participants with no PTS symptoms exhibited larger N1 amplitudes compared to participants with no trauma history. No trauma-related alterations in later ERP components were observed. These results suggest that trauma exposure may lead to hyperarousal at early processing levels, even in response to neutral novel stimuli. The findings concur with the neurocircuitry model that associates PTSD with hyperresponsivity of the amygdala.
Keywords: Posttraumatic Stress Disorder, event related potentials, N1–P2 complex, novelty auditory oddball paradigm, early hyperarousal
Early automatic hyperarousal in response to neutral novel auditory stimuli among trauma-exposed individuals with and without PTSD: An ERP study

1 INTRODUCTION

Exposure to a traumatic, life-threatening event is often followed by distressing symptoms such as intrusive memories, negative cognitive and mood alteration, hyperarousal, and a constant effort to avoid trauma-related stimuli. In some cases, the symptoms will meet threshold for a clinical diagnosis of posttraumatic stress disorder (PTSD; DSM 5, APA, 2013). PTSD prevalence rates are estimated to be between 3% and 12% of the U.S. adult population (Kessler, Sonnega, Bromet, Hughes & Nelson, 1995; Pietrzak, Goldstein, Southwick & Grant, 2011). In other cases, the level of reported posttraumatic symptoms may meet some, but not all, criteria for the disorder (Cukor, Wyka, Jayasinghe, & Difede, 2010).

PTSD is usually associated with specific clinical features that include intrusive thoughts and imagery, concentration difficulties (DSM 5, APA, 2013; Block & Liberzon, 2016), and deficits in working memory and attention (Karl, Malta, & Maercker, 2006). Research findings in PTSD have found an attentional bias to trauma-related stimuli (i.e. stimuli associated with traumatic event exposure) (Beck, Freeman, Shipherd, Hamblen, & Lackner, 2001; Buckley, Blanchard, & Neill, 2000; Pineles, Sipherd, Mostoufi, Abramovitz, & Yovel, 2009) along with decreased attention to neutral (non-threatening) stimuli (Ehlers & Clark, 2000). This evidence is in accord with the “resource allocation” model of PTSD that theorizes an attentional bias to trauma-related threat stimuli at the expense of attention to neutral information (Ehlers & Clark, 2000; Foa, Steketee, & Olasov-Rothbaum, 1989). Some PTSD research studies using behavioral experimental procedures such as the Emotional Stroop (Cisler et al., 2011) and dot probe (Fani et al., 2012) tasks, provide evidence supporting the model, while studies that used other behavioral measures report no PTSD-related effects (Kimble, Frueh & Marks, 2009; Hauschildt, Wittekind, Moritz, Keller & Jelinek, 2013; Wittekind, Muhtz, Jelinek & Moritz, 2015). The resource allocation model concurs with neuro-cognitive conceptualizations of PTSD, such as the neurocircuitry model. Like the resource allocation model, the neurocircuitry model associates PTSD with hypersensitivity to trauma-related stimuli as a result of information processing changes due to impaired...
prefrontal cortex (PFC) top-down regulation of hyperresponsivity within the amygdala (Rauch, Shin, & Phelps, 2006).

Event related potentials (ERPs) are formed by averaging the electro-encephalographic (EEG) measurements of brain responses to repeated presentation of stimuli. These event related potentials are characterized by excellent time resolution, especially suitable for examining rapid processing of potentially threatening stimuli (LeDoux, 2000). Previous ERP studies have employed a three-stimulus oddball distractor paradigm in which the participants are requested to respond to a low frequency “target” stimulus presented amongst high frequency, repetitive “standard” stimuli and low frequency salient “distractors” that they must ignore (see Javanbakht, Liberzon, Amirsadri, Gjini, & Boutros, 2011, for review; see also Johnson, Allana, Medlin, Harris, & Karl, 2013). When individuals with PTSD are presented with an oddball paradigm involving trauma-related distractors, the most commonly observed finding is elevated P3 amplitude in response to both targets (referred to as P3b) and distractors (referred to as P3a); in the context of neutral (trauma-unrelated) distractors, their P3 amplitude in response to both targets and distractors is reduced (Javanbakht et al., 2011; Karl, Malta, & Maercker, 2006). These findings have been interpreted as support for the previously described models of PTSD (resource allocation, neurocircuitry) and seem to indicate a specific attentional bias to trauma-related stimuli in PTSD, rather than evidence of general hyperarousal (Karl, Malta, & Maercker, 2006).

However, this pattern of cerebral function has not always been observed in PTSD. One study reported no significant differences in P3a amplitude between trauma-related and trauma-unrelated distractors among trauma-exposed individuals (Tillman et al., 2012), another study found no P3a amplitude differences between PTSD and non-PTSD participants (Johnson et al., 2013), and a final study found PTSD-related increases in P3b amplitude in response to neutral stimuli (Metzger et al., 2002).

Though previous ERP research has indicated robust effects of trauma exposure on P3 amplitude, the findings regarding P3 latency are less consistent. P3 latency, the time interval from stimulus onset to peak amplitude, is considered to reflect stimulus classification speed and depth of stimulus processing (Donchin, 1981; Polich, 1987). Previous ERP research has indicated no statistically significant effects of trauma exposure on P3b latencies elicited by neutral targets among neutral distractors, and inconclusive findings regarding trauma’s effect on P3a in response to neutral distractors.
(Karl et al., 2006; Johnson et al., 2013). However, one study reported a positive association between either P3a and P3b latency and PTS symptom severity among participants with PTSD in response to neutral stimuli (Shucard, McCabe & Szymanski, 2008). The existing research literature, therefore, leaves gaps in our understanding of the contribution of trauma to P3 latency.

Though ERP studies have clearly indicated PTSD-related alterations in response to trauma-related stimuli, the effects of trauma exposure on the response to neutral, trauma-unrelated stimuli are not clear. The cerebral response of trauma-exposed participants to a novelty paradigm (an oddball paradigm in which distractor stimuli are novel, unique, and rare), in which the distractors are unrelated to trauma, has rarely been tested and has resulted in conflicting findings (Kimble, Kaloupek, Kaufman, & Deldin, 2000; Kimble, Fleming, Bandy, & Zambetti, 2010; Neylan et al., 2005). The conclusions of two relevant meta-analyses in the literature indicated that traumatic event exposure does not affect either P3b or P3a amplitude in a novelty paradigm (Johnson et al., 2013; Karl, Malta, & Maercker, 2006); these findings were considered further support for a specific attentional bias to trauma-related stimuli in PTSD (Ehlers & Clark, 2000; Rauch et al., 2006). However, this hypothesis of specific attentional bias in PTSD is weakened by the fact that PTSD symptoms frequently include general hypervigilance and an exaggerated startle response (DSM 5, APA, 2013), along with enhanced cerebral activation to a wide variety of innocuous stimuli beyond the specific stimuli related to the original trauma (Brunetti et al., 2015; Rauch et al., 2000).

PTSD-associated attentional alterations identified in the presence of trauma-related stimuli have been primarily observed in relatively late latency components such as N2 (a negative component peaking around 200–350 ms) and P3 (a positive component peaking after 300 ms). Both N2 and P3 have been typically associated with response categorization and working memory updating (Galletly, McFarlane, & Clark, 2008; Kimble et al., 2000; Luck, 2014). However, a few studies have demonstrated PTSD-associated attentional effects on earlier components such as N1 and P2 (peaking approximately 80–100 ms and 175–200 ms after stimulus onset respectively; Muller-Gass & Campbell, 2002), suggesting that traumatic event exposure may affect earlier, automatic processes related to perceptual processing (Attias, Bleich, Furman, & Zinger, 1996; Ehlers et al., 2006; Felmingham, Bryant, & Gordon, 2003; Huang & Luo, 2006; Klimova, Bryant, Williams, & Felmingham, 2013). Determining the nature of traumatic
exposure effects on the various stages of information processing would allow better conceptualization of PTSD.

The conflicting findings regarding the PTSD-related information processing in response to novelty may have also been affected by the type of participant samples. Previous PTSD studies employing the novelty paradigm almost exclusively compared trauma-exposed war veterans with and without PTSD (Kimble et al., 2000; Neylan et al., 2005). Since attentional alterations as well as structural brain changes have also been reported in non-PTSD samples (those exposed to trauma with either no posttraumatic symptoms or symptoms not meeting criteria for diagnosis of PTSD) (Karl, et al., 2006; Thomas, Goegan, Newmar, Arndt, & Sears, 2013), it is possible that participants “without PTSD” within the novelty paradigm studies were also affected by their trauma exposure, leading to the lack of significant differences between the PTSD and the non-PTSD groups. In order to better conceptualize the basis of PTSD, a more nuanced research approach appears necessary. Therefore, it is important to more carefully examine the cerebral response to novelty by comparing participants with PTSD to trauma-exposed participants without PTSD (non-PTSD), and to control participants with no previous traumatic experience. Moreover, according to some authors, the degree of traumatic event exposure (trauma history), not the presence of PTS symptoms, may be the critical factor affecting cerebral information processing (Kimble et al., 2010). This postulation is supported by ERP study findings of changes in P3 and N1 components, as well as structural brain changes (reduced hippocampal volume, in particular), among trauma-exposed participants without PTSD (Covey, Shucard, Violanti, Lee, & Shucard, 2013; Gjini et al., 2013; Kimble et al., 2010). Accordingly, it is crucial to evaluate the relative contribution of mere exposure to traumatic events on alterations in information processing.

The current study was designed to examine information processing of novel, unique, and neutral (unrelated to trauma) stimuli, among individuals with PTSD, trauma-exposed individuals without PTSD, and trauma-unexposed controls. We measured participant trauma in two ways: both as a categorical and a continuous variable. We measured it via a detailed trauma history, which established the presence or absence of exposure to trauma, as well as the number of traumatic experiences. We also measured posttraumatic symptom severity by using a PTSD symptom severity questionnaire. Additionally, we designed the study to examine whether trauma exposure and/or PTS symptom severity have different
effects on early automatic processes (i.e. N1 and P2 components) than on late information processes, such as voluntary attention allocation and stimulus classification (i.e., N2 and P3 component).

Based on previous research findings suggesting that trauma leads to a hypervigilant style of information processing (Kimble, Fleming, & Bennion, 2013), we hypothesized that trauma exposure would be followed by increased cerebral activation. Specifically, we hypothesized that: (1) compared to non-traumatized controls, both trauma-exposed groups (PTSD and non-PTSD) would exhibit increased activation in response in a novelty paradigm, as expressed by larger ERP component amplitude; (2) ERP peak amplitudes would positively correlate with the quantitative magnitude of previous traumatic history and level of PTS symptom severity; (3) no P3 latency alterations among trauma-exposed participants and (4) information processing changes, as well as correlations with trauma indices, would be evident at both early (N1, P2) and late (N2, P3) ERP components.

2 METHOD

2.1 Participants

Trauma-exposed participants were recruited through local university advertisement boards, and through flyers posted at a university student counseling center and various local medical centers, requesting participation of individuals who have experienced severe negative life events. Thirty-seven participants (25 females) reported a previous traumatic history that included at least one traumatic event that met both DSM-IV “criterion A” (APA, 1994) as well as DSM-5 “criterion A” for PTSD diagnosis (APA, 2013). These participants were divided into two groups. The first group, the “PTSD” group, consisted of 16 participants (13 females) who had scores of at least 15 or greater on the Posttraumatic Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997); a cut-off point of 15 (or higher) on the PDS indicates significant PTSD severity that corresponds to PTSD diagnosis (Daie-Gabai, Aderka, Allon-Schindel, Foa, & Gilboa-Schechtman, 2011; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999). The second group, the “non-PTSD” group, included 21 participants (12 females) that had been exposed to one or more trauma-related events but scored 14 or lower on the PDS at the time of testing. The control group consisted of 12 university students (11 females) recruited through local university advertisements, with no previous traumatic history. Overall, the total sample consisted of 49 participants. Normal hearing
was verified using audiometric screening (pure tone thresholds of 20 dB HL at 500–4000 Hz, in both ears). Participants were requested to report any medical problems, being in psychological or psychiatric treatment, or the use of any medication; no participants reported meeting any of those criteria. All participants provided signed informed consent and were compensated for their time. The study was approved by the University Ethics Committee.

2.2 Measures and Procedures

2.2.1 Clinical Interview. Participants underwent a short interview with a licensed clinical psychologist (trained to evaluate PTSD symptoms), in order to establish that participants in the trauma-exposed groups (PTSD, non-PTSD) were exposed to least one traumatic event that met both DSM-IV “criterion A” (APA, 1994) as well as DSM-5 “criterion A” for PTSD diagnosis (APA, 2013).

2.2.2 Posttraumatic Diagnostic Scale (PDS). A 49-item self-rating scale developed to assess PTSD diagnosis according to DSM-IV criteria (Foa, 1995). The first section of the questionnaire includes a short checklist that identifies potentially traumatizing events experienced by the respondent. Next, in the case of more than one traumatic experience, the participant is asked to choose one single traumatic experience “that currently bothers you the most” (major event). With regard to the major event, the participant is asked to use a 4-point scale to rate the frequency with which he or she has experienced each one of 17 PTSD symptoms over the previous 30 days; the 17 items measure thought intrusion (re-experiencing), avoidance, and arousal symptoms. A PTSD symptom severity score is calculated by summing the 17 items’ ratings. In the current study, a PDS score of 15 or more was used as a dimensional symptom index that allowed differentiation between the PTSD and non-PTSD groups, a method considered quite acceptable in the literature (Winters et al., 2014). Previous research findings have demonstrated high internal consistency and test-retest reliability as well as a satisfactory agreement with PTSD-related diagnostic interviews such as the Structural Clinical Interview for DSM Disorders - SCID (Foa et al., 1997).

2.2.3 Trauma History Questionnaire (THQ). A 24-item self-report questionnaire developed to measure exposure to potentially traumatic events included in the “A1 criteria” of DSM-IV for PTSD and acute stress disorder (Hooper, Stockton, Krupnick, & Green, 2011). The events may include crime-
related events (e.g. robbery, mugging), general disaster and trauma (e.g. injury, natural disaster, witnessing death), and unwanted physical and sexual experiences. The THQ has been widely used to measure previous traumatic history among clinical (PTSD) and non-clinical (non-PTSD) populations. Moderate to high test-retest reliability and validity have been reported (Hooper et al., 2011). In the current study, a trauma history score was calculated by adding the number of different types of traumatic events reported by the participant, with scores ranging from 0 to 24. Thus, a higher score indicates a higher rate of different kinds of traumatic event exposure. One participant did not complete the THQ; thus, data relating to trauma history were available for only 48 of the 49 participants.

2.3 Auditory Novelty Oddball Task

All participants’ brain activity was recorded via EEG while performing an auditory novelty oddball task based on the random sequence of three types of stimuli consisting of a target (2000 Hz, 180 ms, pure tone, 60 db SPL, 1 ms rise and fall time, p = 0.2, n = 50), novel (p = 0.20, n = 51), and standard (1000 Hz, 180 ms, pure tone, 60 db SPL, 1 ms rise and fall time, p = 0.6, n = 150) sounds. The novel sounds consisted of primarily computer-generated whistles and buzzes as well as unidentifiable sounds (clunks, pings, buzzes, etc.) with varying duration times (355–1100 ms), with an intensity of 60 db SPL. We used 17 different novel sounds that were randomly repeated 3 times. For the entire task, 251 stimuli were presented binaurally through earphones (Sony, MDR-V700). Inter-stimulus intervals were 2201 ms.

Participants were seated in a comfortable armchair, told they would hear all kinds of sounds through the earphones, and were asked to press a button on a joystick when they identify the target sound.

2.4 Electrophysiological Testing and Measures

The EEG was recorded in a room free of noise and electromagnetic fields. Continuous EEG was recorded using Micromed SD 64 channels system and a Neuroscan 64 channel elastic cap with electrode locations based on the 10/20 system. All electrodes were referenced to an electrode located at the tip of the nose. A ground electrode was placed on the right mastoid. A vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. The impedance measure
for each electrode was always below 5 kΩ. Raw data were continuously recorded with 16 bit A/D, a band pass filter of 0.15 Hz-463 Hz, and a sampling rate of 1024 Hz. All data were analyzed using BPM software. EEG Recordings were segmented into time intervals time-locked to the stimuli, and extended from 200 ms pre-stimulus to 2000 ms post-stimulus. An eye movement correction procedure was performed offline using an eye movement correction algorithm (Henkin, Kishon-Rabin, Gadoth, & Pratt, 2002). The algorithm detects an epoch with ocular artifacts by comparing the signals recorded from above and below the eye. In a second step, a correction is performed for each record and each channel separately. Additionally, after correction of the algorithm, EEG signals were visually scored on a high resolution computer monitor, and portions of the data containing eye movement that were not corrected by the algorithm, muscle movement, or other sources of artifact, were removed. Baseline correction for each trial was performed using the 200 ms prior to stimulus onset for each channel separately. Amplitude rejection was applied to the data prior to averaging. Records with amplitude higher than 250 microvolts (even in a single channel) were excluded. For each participant, all trials were averaged per stimulus type (target, novel and standard). In the final stage of averaging, the data were filtered using a 6 Hz low-pass filter.

Figure 1 presents the Global Field Power (GFP) that was calculated across all 12 electrodes (see the statistical analysis section for specifications) and groups (PTSD, non-PTSD, control) for each trial type (target, novel, standard). The GFP was calculated by the root mean square (RMS) of the grand averaged waveform (Murry, Brunet, & Michel, 2008), thus obtaining positive components that indicate the strength of the potential being recorded. The GFP provides a reference-independent measure of response strength (Murry et al., 2008). The GFP, derived from the mean square, produced positive values for either positive or negative components. Figure 1 presents the GFP with four components that were identified in their initial (either negative or positive) format. These components were: (1) a negative component between 30–120 ms that was identified as N1; (2) a positive component between 110–210 ms that was identified as P2; (3) a negative component between 160–250 ms that was identified as N2; and (4) a positive component between 250–450 ms that was identified as P3. For each of these components, ERPs were quantified in terms of peak amplitudes (maximum positive or negative
amplitude from baseline in microvolts within the specified time window) and latency (time interval from stimulus onset to peak amplitude in milliseconds).

**INSERT FIGURE 1**

### 2.5 Statistical Analysis

Analyses were conducted using SPSS version 24 (Arkmonk, N.Y.; IBM Corp., 2013). For comparison of behavioral assessment measures (PDS, THQ) a multivariate analysis of variance (MANOVA) with group (PTSD, non-PTSD, control) as an independent variable was used. A one-way ANOVA was conducted to assess group differences in age. A non-parametric chi-square test was conducted to compare gender differences among the three groups.

ERP component (i.e., N1, P2, N2, P3) amplitude and latency comparisons between the study groups were conducted by a repeated measure analysis of variance (ANOVA) with Group (PTSD, non-PTSD, control) as a between-factor and Trial Type (target, novel, standard) X Electrode Midline Site (prefrontal, frontal, central, parietal) X Electrode Side Site (left, midline, right) as within-factors. We also examined the amplitudes of the N1-P2 complex that were derived by subtracting the amplitudes of P2 from N1, thus obtaining the amplitude difference from the peak of the N1 wave to the peak of the P2 wave (Graham, Langley, Bradshaw, & Szabadi, 2001; Mauguière, Cooper, Holder, Luxon, & Murray, 1995; Morris, Steinmetzger, & Tøndering, 2016). For all these ERP components, an additional, similar ANOVA was conducted only for participants reporting no PTS symptoms on the PDS; this allowed comparison between participants with previous trauma exposure and no symptoms (group 1, consisting of 7 participants out of the non-PTSD group who reported previous trauma exposure but no PTS symptoms) to those without any history of trauma (group 2, consisting of the 12 control participants). In the ANOVAs, Greenhouse-Geisser corrections were applied as necessary for violations of sphericity, and partial eta squared ($\eta^2_p$) served as an estimate for effect sizes. In all the ANOVAs, Bonferroni post hoc tests were used to examine group differences. Independent t tests were used to probe some of the interactions when needed for ERP component analyses. Data were obtained from 12...
electrodes (PF1, PFz, PF2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) that were divided between two location factors. Given that the P3 response of different locations may represent divergent cognitive processes (Katayama & Polich, 1998), we assigned each electrode to a four level midline site factor denoting prefrontal (PF1, PFZ, PF2), frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) sites. Electrodes were also divided into a three-level side site factor denoting left (PF1, F3, C3, P3), middle (PFz, Fz, Cz, Pz) and right (PF2, F4, C4, P4) sites. This categorization of the electrodes into two factors is in accordance with previous research (Kimble et al., 2000).

Pearson correlation coefficients were calculated between the PDS total severity score, THQ trauma history score, and the N1–P2 complex amplitude, as well as P3 peak amplitudes and latencies. For both components, correlations were obtained for target, novel and standard trials. For the correlation analysis, amplitudes as well as latencies were calculated by averaging electrodes in the Left, Middle and Right for each midline site, thus denoting average amplitudes or latencies for prefrontal, frontal, central and parietal sites. Correlations were calculated between PTSD measures and ERP components at midline sites that exhibited the highest peak amplitude (i.e. central site for the N1-P2 complex, parietal site for the P3 component).

3 RESULTS

3.1 Participant Characteristics

On the PDS, the majority of the participants in trauma-exposed groups (PTSD and non-PTSD) reported motor vehicle accidents (22, 59.5%) as their major traumatic experience. Most participants described a history of multiple types of trauma. The trauma type distribution of the “main traumatic event” is presented in Table 1. No significant statistical differences were found in the distribution of the main trauma type between the PTSD and non-PTSD groups, $\chi^2(5, N = 37) = 5.26, p > .05$.

Demographic and trauma-related variables are presented in Table 2. No significant gender differences were found between groups, $\chi^2(2, N = 49) = 5.47, p > .05$, despite female predominance. No significant group differences in age were found. As expected, a significant effect of group on trauma measures (PDS, THQ) was observed [Hotelling’s Trace; $F(4, 84) = 43.65, p < .00, \eta^2_p = .67$]. Univariate
ANOVA revealed a significant effect of group on the level of PTS symptoms, as indicated by the PDS score: participants in the PTSD and non-PTSD groups reported "moderate to severe" and "mild" levels of PTS, respectively, according to PDS norms (McCarthy, 2008). Post hoc tests indicated significantly higher levels of PTS among the PTSD group compared to the non-PTSD ($p < .00$) group, and, as would be anticipated, among both trauma-exposed groups ($p < .01$) compared to the asymptomatic control group. Finally, as would also be expected, a significant effect of group on THQ scores was also observed, indicating significantly higher rates of previous traumatic exposure in the trauma-exposed groups compared to the Controls.

**TABLE 2 ABOUT HERE**

### 3.2 ERP Component Analysis

#### 3.2.1 ERP component amplitude and latency.

The grand averages of the ERP waveforms among the study groups can be seen in Figure 2 for ERP elicited at target, novel and standard stimuli for Fz, Cz and Pz electrodes. The results of the analysis of the various ERP component amplitudes and latencies are provided below.

**INSERT FIGURE 2**

#### 3.2.1.1 ERP component amplitude.

**ANOVA analysis.**

Five separate repeated measures ANOVAs with Group (PTSD, non-PTSD, Control) as a between-factor and Trial Type (target, novel, standard) X Electrode Midline Site (prefrontal, frontal, central, parietal) X Electrode Side Site (left, midline, right) as within-factors, were conducted for N1, P2, N2, P3 and N1-P2 complex amplitudes. No significant effects involving the group factor were observed for N1, P2, N2 and P3.

A significant effect of group on N1–P2 amplitude was observed, $F(2, 46) = 3.82, p < .05, \eta^2_p = .14$. Post hoc testing revealed a significant difference between the PTSD ($M = 8.00, SE = 0.71$) and control ($M = 5.00, SE = 0.81, p < .01$) groups. When gender was entered as a covariate, the group effect remained significant, $F(2, 45) = 3.60, p < .05, \eta^2_p = .14$; gender had no significant effect.
In addition, a significant effect of electrode midline site on the N1-P2 complex amplitude was observed, $F(1.71, 78.98) = 36.69, p < .01, \eta^2_p = .44$. Bonferroni post hoc tests indicated significant N1-P2 complex amplitude differences between all midline site electrodes (prefrontal: $M = 4.88, SE = 0.39$; frontal: $M = 6.63, SE = 0.45$; central: $M = 7.75, SE = 0.56$; parietal: $M = 7.16, SE = 0.45$), excluding differences between frontal and parietal Sites. A significant effect of electrode side site was also observed, $F(1.49, 68.94) = 24.79, p < .01, \eta^2_p = .35$. Bonferroni post hoc testing revealed a significant difference in N1-P2 complex amplitude between Left ($M = 7.07, SE = 0.43, p < .01$) and Midline ($M = 6.90, SE = 0.46, p < .01$) to Right ($M = 5.89, SE = 0.38$) electrode sites. Both the electrode midline site and electrode side site effects on N1-P2 complex amplitudes remained significant when gender was entered as a covariate.

Additionally, a similar ANOVA was conducted, comparing only participants from the non-PTSD group that, in spite of previous traumatic exposure, reported no PTS symptoms on the PDS (total PDS score = 0; 7 participants; 5 females) to control participants (no history of trauma; 12 participants; 11 females). No significant effects involving the group factor were observed for P2, N2, P3 and the N1-P2 complex. However, a significant effect of group on N1 amplitude was observed, $F(1, 17) = 5.63, p < .05, \eta^2_p = .25$. Participants who reported previous traumatic event exposure (but no PTS symptoms) exhibited larger (more negative) N1 amplitudes ($M = -4.78, SE = 0.76$) compared to participants with no trauma history ($M = -2.49, SE = 0.58$). In addition, a significant interaction of GroupX Electrode Midline Site X Electrode Side Site was observed, $F(2.96, 50.39) = 2.95, p < .05, \eta^2_p = .15$. When gender was entered as a covariate, the group effect was only marginally significant ($p = .06$), and the interaction remained significant. No significant main effects of gender were observed.

In order to probe the interaction, repeated measures ANOVAs with group (non-PTSD trauma-exposed participants with no PTS, control) as a between-factor and electrode side site (left, midline, right) as a within-factor were conducted separately for each electrode midline site (prefrontal, frontal, central, parietal). A significant effect of group affiliation on N1 amplitude was observed at central site electrodes, $F(1, 17) = 7.50, p < .05, \eta^2_p = .30)$. Larger (more negative) N1 amplitudes were observed among trauma-exposed participants (with no PTS symptoms) ($M = -5.50, SE = 0.89$) as compared to
controls ($M = -2.64$, $SE = 0.64$). In addition, a significant Group X Electrode Side interaction for N1 amplitude at central electrodes was evident, $F(1.43, 24.34) = 6.43$, $p < .05$, $\eta^2_p = .27$. Independent t tests that were conducted for N1 amplitude at each of the central electrodes revealed a significant effect of group on middle ($t(17) = 3.40, p < .05$) and right ($t(17) = 3.40, p < .05$) electrodes side sites. Trauma-exposed participants (with no PTS symptoms) exhibited larger N1 amplitudes at middle ($M = -6.06$, $SD = 2.6$) and right ($M = -5.90$, $SD = 2.04$) side sites, as compared to controls ($M = -2.24$, $SD = 1.99$; $M = -2.65$, $SD = 2.05$, respectively). No other main effects or interactions involving the group factor were observed.

**Correlations.**

Table 3 presents the one-tail correlation coefficients between the PDS total severity score, THQ trauma history score, and the N1–P2 complex amplitudes for all trial types (target, novel, standard). Correlations were obtained between PTSD measures and the average ERP amplitudes of C3, Cz, and C4, since the highest N1–P2 peak amplitudes were observed at the Central midline site. For all the participants, a significant positive correlation was observed between the PDS total severity score, as well as THQ score, and the N1–P2 complex amplitudes in response to Novel stimuli. For the trauma-exposed groups (PTSD, non-PTSD), a marginally significant correlation was observed between the PDS total score and N1–P2 complex amplitudes in response to novel stimuli ($p = .065$). No significant correlations between trauma measures and P3 indices were observed.

**TABLE 3 ABOUT HERE**

3.2.1.2 ERP Component Latency.

Repeated measures ANOVAs for latency time for N1, P2, N2 and P3 yielded no significant effects. No significant correlations with any ERP component were observed.

4. DISCUSSION

The current study findings indicate a stepwise increase of N1–P2 complex amplitudes among trauma-exposed participants in response to a novelty paradigm consisting of neutral distractors. For all stimuli types (target, novel, standard), the largest N1-P2 complex amplitudes were observed among the PTSD group, midsized amplitudes were exhibited by the non-PTSD group, and the
smallest amplitudes were found among the control group (significant effects were found only among the PTSD and control groups). These findings support our first hypothesis, indicating increased cerebral activation in response to a neutral novelty paradigm among trauma-exposed individuals.

Our second hypothesis, regarding a positive association between ERP component indices and the level of PTS symptom severity and trauma history, was partly supported by the current findings. Among the entire study sample, a positive association was observed; the increase in N1–P2 complex amplitudes to novel stimuli was significantly correlated with the reported level of posttraumatic symptoms on a validated PTSD self-report scale (PDS) and previous trauma history (THQ). Among trauma-exposed participants, a positive correlation between N1–P2 complex amplitudes to novel stimuli and PTS severity was also observed, though with only marginal significance.

The preliminary potential implications of the findings related to our first two hypotheses are best perceived in light of the existing literature on attention, trauma exposure, and cortical modulation. Previous research associated early ERP components with attention. Numerous research findings have indicated the effects of attention on the exogenous N1 wave (see Horváth, 2015, for review; see also Hillyard, Hink, Schwent, & Picton, 1973). Other early ERPs, such as P2 and the N1–P2 complex, have also been associated with input processing related attention (Carretié, Mercado, Tapia, & Hinojosa, 2001; Carretié, Martín-Loeches, Hinojosa, & Mercado, 2001; Huang & Luo, 2006; Lavoie, Hink & Thornton, 2008; Morris et al., 2016; Nakahara & Ikeda, 1987; Weihting, Daniels, & Musiek, 2009). In the field of PTSD research, alterations in response to trauma-related stimuli have also been observed in early ERP components such as N1 and P2 (Attias et al., 1996; Ehlers et al., 2006; Felmingham et al., 2003; Gjini et al., 2013; Klimova et al., 2013; Lewine et al., 2002; Metzger et al., 2002; Metzger, Pitman, Miller, Paige, & Orr, 2008). However, no effects of traumatic event exposure on the information processing of neutral stimuli have been reported. To the best of our knowledge, the relatively small number of studies that employed novel, rare, and neutral (trauma-unrelated) distractors were mainly focused on examining late components. Moreover, these studies reported conflicting results: enhancement (Kimble et al., 2000), reduction (Kimble et al., 2010), or no significant differences (Johnson et al., 2013; Karl, Malta, & Maercker, 2006) in either P3b or P3a amplitudes.
Salient responsivity to trauma-related stimuli, in light of conflicting neutral stimuli findings, has lent support to the theory of specific attentional bias to trauma-related stimuli in PTSD (Ehlers & Clark, 2000; Rauch et al., 2006). However, the current study findings may provide preliminary evidence of the existence of a general hyperarousal among trauma-exposed participants at early stages of information processing. Furthermore, when comparing participants with previous trauma exposure without PTS symptoms (participants from the non-PTSD group with PDS score of 0) to participants without any trauma exposure (control group), larger N1 amplitudes were observed among the former group. This may possibly suggest that traumatic event exposure itself, even without the development of any PTS symptoms, may lead to enhanced neural activity associated with early attention mechanisms. This finding is novel and, to the best of our knowledge, has not been reported previously. It is possible that the use of a non-trauma-exposed control group in this study enabled detection of the effects of mere trauma exposure on information processing that may have been masked in previous studies comparing only two trauma-exposed groups (PTSD and non-PTSD). However, it is important to note that while N1 amplitudes differed between our controls and trauma-exposed participants with no PTS symptoms, no significant effects of group on N1 were found during comparison of the entire study sample. It is possible that the distinct subgroup of trauma-exposed participants with no PTS symptoms may be associated with unique information processing characteristics. Future studies should examine this question.

The current findings do concur with previous research findings suggesting that traumatic exposure, even without the development of PTSD, can significantly affect behavioral (Thomas et al., 2013), electrophysiological (Kimble et al., 2010) and structural (Karl, Schaeffer, Malta, Dörfel, Rohleder, & Werner, 2006) measures of cerebral function. In attempting to further conceptualize trauma-related alterations in cerebral information processing, the neurocircuitry model of PTSD (Rauch, Shin, Whalen, & Pitman, 1998) suggests that this disorder involves impaired ventro/medial prefrontal cortex top-down regulation of hyperresponsivity within the amygdala, leading to a deficit in suppression of attention to threatening/emotional stimuli. Support for this model has been provided by neuroimaging studies that indicate reduced activation of prefrontal areas involved in top-down regulation of the amygdala, both among individuals with PTSD (Blair et al., 2013; Shin et al., 2001) and among trauma-
exposed participants without PTSD (White, Costanzo, Blair, & Roy, 2014). With regard to the current study findings, the increase in the N1–P2 complex amplitudes may suggest that trauma can also lead to an impairment in suppression of attention to novel, rare and neutral (trauma-unrelated) stimuli during early stages of information processing. Further support for this proposition can be found in previous research. A recent study has asserted that larger N1–P2 complex amplitudes are associated with reduced function of the Behavioral Inhibition System (De Pascalis, Fracasso, & Corr, 2017), a neurobehavioral system that facilitates protective inhibition. Reduced function of this system, postulated to avert a sensory load of threatening stimuli, may result in overgeneralization to non-threatening stimuli. In fact, larger N1 amplitudes occurring in response to non-threatening stimuli have also been found in other populations prone to high levels of anxiety, such as those with panic attacks (Wise, McFarlane, Clark, & Battersby, 2009) and social anxiety (Felmingham, Stewart, Kemp, & Carr, 2016); such findings have also been considered indicative of hypervigilance of early automatic attention. Thus, the current study, taken together these previous research findings, may pinpoint a general hypervigilant information processing pattern unconfined to trauma-related stimuli that could be indicative of a decrement in cortical modulation.

Going further, in accordance with our third hypothesis, no effects of trauma exposure on latencies of any ERP component were observed. Both early and late ERP component latencies were neither affected by traumatic event exposure, nor correlated with either PTS symptom severity or quantitative magnitude of trauma history. This finding concurs with previous findings, mainly indicating no effect of trauma on P3 latency in response to neutral distractors (Johnson et al., 2013). One study that did report an association between P3 latency and hyperarousal scores in PTSD (Shucard et al., 2008) employed a Go/NoGo task that required response inhibition. Thus, it is possible that trauma leads to slowed central processing when inhibition is required. However, response inhibition was not tested in the current study. Further research is required to more deeply study the association between PTSD and P3 latency.

Our fourth hypothesis predicting trauma-related changes in both early and late ERP components was not confirmed; the effects of trauma were evident at early (N1–P2 complex, N1), but not in later (N2, P3), ERP components. Since N1–P2 complex and N1 ERPs have been associated with
preconscious processing of incoming stimuli (Boddy, 1981), the current findings may suggest that the response to neutral (trauma-unrelated) novel stimuli after trauma is characterized by hyperarousal at early stages of information processing, while later stage processing, which involves response categorization and working memory (P3, Luck, 2014), may remain intact. Previously, N1 and P2 alteration (in response to stress or threat) has been associated with alterations of the amygdala and PFC, leading to increased vigilance in threatening environments (Kuniecki, Coenen, & Kaiser, 2002; Pavlova & Vanetsian, 2006; Shackman, Maxwell, McMenamin, Grieschar, & Davidson, 2011; Yoshimura, Kawamura, Masaoka, & Homma, 2005). This postulation is supported by previous research showing that stress amplifies early sensory processing of non-threatening stimuli and increases the sensitivity (while decreasing the specificity) of amygdala reactivity (Shackman et al., 2011; van Marle, Hermans, Qin & Fernandez, 2009). Thus, our findings may indicate an over-responsivity of the amygdala and medial PFC system, akin to a quickly activated alarm system that facilitates early processing of threatening stimuli (Armony, Corbo, Clément, & Brunet, 2005; Bryant et al., 2008; Rabellino et al., 2015).

The current study provides novel findings regarding the effects of traumatic event exposure on the information processing of novel, rare, and neutral (trauma-unrelated) stimuli. Notwithstanding, the current study has several limitations. First, the generalizability of the current study may be limited, given that all participants were young, healthy students with minimal comorbidity; in addition, those participants with PTSD presented with only a “moderate” level of symptomatology. Nevertheless, since most prior ERP trauma studies were conducted with aging war veterans, our study sample’s age range and exposure to a variety of trauma types may also constitute a strength and, in fact, provide greater generalizability. A second study limitation is the lack of a formal mental health/psychiatric evaluation of study participants. Therefore, future studies should use a participant sample with a greater representation of ages and PTSD severity levels, as well as conduct a more comprehensive evaluation of participant mental health.

In addition, as in related studies (Felmingham, Bryant, Kendall, & Gordon, 2002; Lobo et al., 2014), the current study's sample is characterized by a higher representation of females (36 out of 49). There was also an imbalanced gender ratio within all of the groups (females were represented by 13 of
16 PTSD, 12 of 21 non-PTSD, and 11 of 12 control, group members), though our analyses indicated no significant differences in male/female ratios between the study groups. Furthermore, in all the analyses, no significant effects of gender as a covariate were observed. Future studies should use larger samples with balanced male to female ratios.

The results of the current study, though very preliminary, may have important implications for intervention and treatment after traumatic event exposure. Social-cognitive theories have characterized PTSD as the result of a defensive effort to reconcile previous cognitions with the traumatic experience, leading to extreme alterations ("overaccommodation") in such cognitions in order to feel secure ("If the traumatic event happened, I can't trust my judgment again. Therefore, I have to be alert all the time.") (Reisick, Monson, & Chard, 2007). Accordingly, current cognitive-based intervention therapies for PTSD focus on the conscious, conceptual aspects of cognitions, helping patients achieve a more balanced and realistic accommodation of such cognitions or beliefs (Reisick et al., 2007). However, if confirmed in future studies, our findings suggest that early changes in information processing, possibly stemming from changes at perceptual processing levels, may be resistant to psychological interventions that focus solely on semantic-based cognition (and thereby may affect information processing mainly at a conceptual levels). Development of innovative methods to treat altered information processing among those suffering from PTSD and subthreshold PTSD may be warranted.
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Author Notes

There are no conflicts of interest for any authors.

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**Figure Captions**

Figure 1 - Grand average global field power elicited by Target, Novel, and Standard stimuli across all participants.

Figure 2 - Grand averages of ERP's elicited by Target, Novel and Standard Stimuli for Fz, Cz, and Pz.