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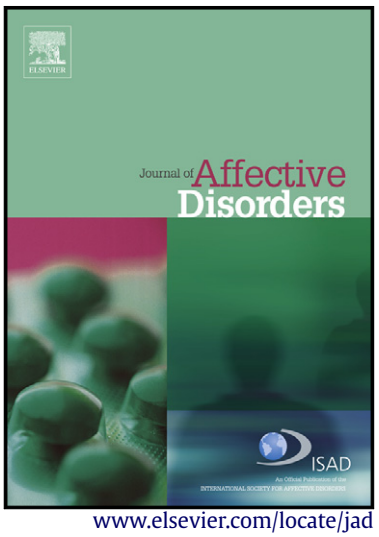

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EEG correlates of the severity of posttraumatic stress symptoms: a systematic review of the dimensional PTSD literature

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Abstract

Background: Considering the Research Domain Criteria (RDoC) framework, it is crucial to investigate posttraumatic stress disorder (PTSD) as a spectrum that ranges from normal to pathological. This dimensional approach is especially important to aid early PTSD detection and to guide better treatment options. In recent years, electroencephalography (EEG) has been used to investigate PTSD; however, reviews regarding EEG data related to PTSD are lacking, especially considering the dimensional approach. This systematic review examined the literature regarding EEG alterations in trauma-exposed people with

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posttraumatic stress symptoms (PTSS) to identify putative EEG biomarkers of PTSS severity.
Method: A systematic review of EEG studies of trauma-exposed participants with PTSS that reported dimensional analyses (e.g., correlations or regressions) between PTSS and EEG measures was performed.
Results: The literature search yielded 1178 references, of which 34 studies were eligible for inclusion. Despite variability among the reviewed studies, the PTSS severity was often associated with P2, P3-family event-related potentials (ERPs) and alpha rhythms.
Limitations: The search was limited to articles published in English; no information about non-published studies or studies reported in other languages was obtained. Another limitation was the heterogeneity of studies, which made meta-analysis challenging.
Conclusions: EEG provides promising candidates to act as biomarkers, although further studies are required to confirm the findings. Thus, EEG, in addition to being cheaper and easier to implement than other central techniques, has the potential to reveal biomarkers of PTSS severity.

Keywords: posttraumatic stress symptoms, PTSD, trauma, EEG, ERP, spectral analysis.

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Introduction

During the course of our lives, we all risk experiencing a traumatic situation. We lose people we love, and we are exposed to diseases, natural disasters, wars and many other situations of interpersonal violence. Statistics indicate that 60% of men and 50% of women have been exposed to at least one traumatic event in their lifetime, but the rate of posttraumatic stress disorder (PTSD) among the general population is less than 10% (Kessler et al., 2005; Pietrzak et al., 2011). The search for factors that increase the risk of development of PTSD (e.g., vulnerability) and the factors that protect people from developing this disorder (e.g., resilience) has become crucial (Yehuda et al., 2006). The diagnosis of PTSD (and many other psychiatric disorders) is still based on categorization and relies only on self-reports of symptoms and

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observations of behavior. Individuals with PTSD experience a number of distressing symptoms that fall into three main categories: re-experiencing/intrusion, avoidance/numbing, and hyperarousal (American Psychiatric Association, 2000). Recently, in the DSM-V (Diagnostic and Statistical Manual of Mental Disorders), PTSD was moved from the class of anxiety disorders into a new class of "trauma and stressor-related disorders". The symptoms of PTSD are mostly the same as in DSM-IV; a key alteration is the definition of four clusters of symptoms instead of three—intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity (American Psychiatric Association, 2013).

However, these behavioral changes exhibited by individuals with PTSD may be the tip of an iceberg—a late manifestation of a change that has been occurring in the brains of people who were still considered psychiatrically "healthy", thereby suggesting that these disorders may be better conceptualized as “brain disorders”. Taking this perspective, the NIMH developed the Research Domain Criteria (RDoC) project to create an agenda for pathophysiology research to provide a framework for classifying brain disorders based on empirical data (Insel et al., 2010). Unlike conventional diagnostic systems (e.g., the DSM), the RDoC is explicitly dimensional in its approach: the biological and clinical variables examined in a research project can be measured on a spectrum that ranges from normal to abnormal (Simmons and Quinn, 2013).

Considering the RDoC framework, there is a great need to better understand the pathophysiology of PTSD and to determine possible PTSD biomarkers. This knowledge could eventually aid in the detection of vulnerability and resilience factors. Furthermore, this approach is especially important to enable detection of PTSD as early as possible, thereby allowing for earlier interventions for vulnerable individuals and perhaps improving the general prognosis. Specifically, identifying neural biomarkers that are related to the severity of posttraumatic stress symptoms (PTSS) has the potential to guide better treatment choices for these individuals.

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The most common findings regarding the brain alterations in PTSD support the model of hyperresponsivity of the amygdala, whose activity cannot be regulated by the concomitantly hyporeactive medial prefrontal cortex, and deficient hippocampal function, which prevents re-assessment of the trauma (Lobo et al., 2011; Michopoulos et al., in press; Rauch et al., 2006; Sartory et al., 2013; Shin et al., 2006). Trauma-exposed people that exhibit PTSD symptoms but have not been diagnosed with PTSD are often included in PTSD studies as control subjects. The impact of trauma exposure on these people has not been well investigated (Bunce et al., 1995; McFarlane, 1997). For instance, few studies have explored the effects of trauma exposure in individuals without PTSD, and the existing studies typically use only peripheral indicators of stress (e.g., urinary cortisol, dopamine, or epinephrine) (Yehuda et al., 2005; Young and Breslau, 2004; Young et al., 2004). Considering the RDoC recommendation, it is crucial to investigate people with PTSS both with and without a PTSD diagnosis, using a dimensional approach to identify biomarkers for this mental illness.

Accordingly, some electroencephalography (EEG) studies have focused primarily on determining biomarkers of PTSD. For instance, Attias et al. (1996) used the Fisher linear discrimination method and found that P300 measures correctly classified 90% of PTSD patients and 85% of controls. Compared with other central techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), EEG has the advantage of having a very high temporal resolution (on the order of milliseconds) and is simpler and less expensive to implement in clinics and laboratories. Furthermore, contrast administration is not necessary, and claustrophobia is not an issue (Luck and Girelli, 1998). For these and other reasons, the EEG has attracted great interest in studies seeking biomarkers in psychiatry (McLoughlin et al., 2014).

Although there are some literature reviews regarding PTSD susceptibility biomarkers (e.g., Schmidt et al., 2013), systematic or meta-analytic reviews about EEG data and PTSD biomarkers are lacking, especially ones that consider a dimensional approach, as suggested by the RDoC proposal (Simmons and Quinn, 2013). It would be interesting to consider EEG biomarkers as important

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information to determine potential PTSD disease markers. Furthermore, the brain is the central organ of stress, which makes central measures such as EEG very informative.

It is interesting to note that past reviews of the PTSD/EEG literature explored the differences between PTSD and controls primarily using group analysis (Javanbakht et al., 2011; Johnson et al., 2013; Karl and Maercker, 2006) but did not focus on PTSD as a continuum that ranges from normal to pathological, as recommended by the National Institute of Mental Health RDoC.

Adopting the dimensional approach advocated by the RDoC, the objective of this systematic review is to examine the literature regarding EEG alterations in trauma-exposed people, with or without a PTSD diagnosis, to identify putative EEG biomarkers of PTSS severity. Hence, we reviewed EEG studies that applied a dimensional approach to people with PTSS and searched for neural measures that are associated with the symptom severity.

Methodology

In October and November 2014, we performed electronic searches using the following databases: ISI/Web of Knowledge, PUBMED/MEDLINE, and PsycINFO. The keywords included terms that describe the sample and the technique of interest:

- PTSD OR "posttraumatic stress symptom*" *OR* PTSS OR "symptoms of PTSD" OR "PTSD symptoms" OR "posttraumatic stress symptomatology" OR "stress disorder".

- Electroencephalography OR EEG OR "event related potential*" OR ERP.

The terms indicated in each item were combined using ''AND'', a function that is available in all databases. In the ISI/Web of Knowledge database, we restricted the search criteria to include only "articles" that contained the

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combination of sample of interest keywords and techniques keywords. In addition to these searches of electronic databases, manual searches were also performed using the reference sections of published texts to find articles that were eligible for inclusion. After removing duplicates, the articles were first assessed by seeking exclusion criteria (see below) in the title and abstract. Two reviewers (authors I.L. and L.C.P.) independently performed this double-checking exclusion process. Disagreements were resolved through discussion between the two review authors; if no agreement could be reached, a third author decided whether the article should be excluded. If no exclusion criteria were found, the full text was checked for the inclusion criteria (Liberati et al., 2009). If the full text of an article was not available for download, it was requested from the authors via e-mail or accessed through the authors' Research Gate profiles. The articles included in the final selection had to fulfill the following criteria:

Criteria for inclusion: Trauma-exposed participants with posttraumatic stress symptoms (PTSS) in an EEG experiment where were described dimensional analysis (e.g., correlations or regressions) between the severity of PTSS and the EEG measures in studies published from 2000.

Criteria for exclusion: theoretical articles, reviews, theses, dissertations, book chapters, articles not published in a peer-reviewed journal, case studies, articles that included patients with traumatic brain injuries or people with a history of seizures, acute PTSD samples, and publications in languages other than English.

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Results

After performing electronic searches of the aforementioned databases and removing duplicates, 669 articles were obtained for review. Fig. 1 shows the steps of the electronic search that led to 34 articles being included in the systematic review. The exclusions based on the title and abstract (n= 583) were usually theoretical articles; articles that included patients with traumatic brain injuries or a history of seizures or acute PTSD patients; studies that did not

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perform EEG; and publications in languages other than English. Of the remaining full-text articles, articles were excluded because of a lack of a correlation analysis between the PTSS and EEG parameters (n = 41), a lack of EEG (n = 6), use of acute PTSD samples (n = 4) or inclusion of traumatic brain injury patients (n = 1). The 34 studies selected are described below and grouped in two categories: event-related potential (ERP) studies and EEG spectral analysis studies.

ERP studies

ERP studies comprise the majority of the dimensional studies included in the review: Twenty-two of the 34 articles were ERP studies. The most common stimuli used in the ERP studies were auditory and visual. Table 1 describes the selected ERP studies.

P2

Findings based on auditory ERPs revealed significant associations between P2 responses and PTSS. In Metzger et al., 2002, Vietnam War nurse veterans underwent an auditory ERP and four-tone stimulus-intensity modulation task in which subjects have to listen to a series of tones (74, 84, 94, and 104 dB). The tones varied in loudness from soft to very loud. The participants did not have to respond to the tones but rather only pay attention to the tones while EEG was recorded. The P2 slope was calculated for analysis as the slope of the regression line for the P2 component peak amplitude across tones of increasing intensity. The results indicated that the P2 slope was positively correlated with the psychometric scales of PTSD severity, thereby indicating that a higher P2 slope was associated with more severe PTSD symptomatology.

Later work from the same group (Metzger et al., 2008) investigated the P2 responses of male combat veterans of the Vietnam War during a four-tone stimulus-intensity modulation procedure. Pearson correlations performed on the PTSD and non-PTSD combat-exposed veterans revealed that the P2 slopes

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were positively related to the PTSS severity. There was also a positive correlation between the P2 slope and re-experiencing symptom clusters.

Additional evidence for the association between the P2 slope and PTSS comes from veterans with combat-related PTSD who were instructed to listen to tones that varied in intensity (65, 72.5, 80, 87.5, or 95 dB) (Lewine et al., 2002). Veterans with PTSD exhibited a positive correlation between the P2 slope and PTSS. These results suggest an auditory hyperreactivity (indexed by P2) that correlates with PTSS severity and may reflect a deficiency in the cortical inhibitory system (which protects against overstimulation).

Apart from auditory studies, a visual ERP study from Wessa et al. (2005) investigated the responses of motor vehicle accident victims to emotional images. The images could be positive, neutral, or two types of negative: motor vehicle accident (trauma-related) or negative but not accident-related. P200 was defined as the positive maximum within a time window of 120–250 ms. The study found a negative correlation between the P200 in response to accident-related images and avoidance/numbing cluster symptoms, thereby indicating that the degree of avoidance and numbing strategies is related to the P200 exhibited in response to trauma-related content.

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P3 Family

Additional auditory ERP findings included data from oddball tasks; these studies report contrasting results regarding the association between P300 and PTSS. In the auditory oddball paradigm, the presentations of sequences of repetitive auditory stimuli are infrequently interrupted by a deviant auditory stimulus. The subjects are asked to press a button as quickly as possible upon hearing the target stimulus that is hidden among a series of more common sounds. Some auditory oddball studies reported correlations between P300 and one of the three symptom clusters of PTSD (re-experiencing, avoidance/numbing, and hyperarousal). For example, a Japanese study (Kimura et al., 2013) investigated students with PTSS living in surrounding areas of the

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epicenter of the Great East Japan Earthquake and reported a positive correlation between P300 and hyperarousal cluster symptoms (Kimura et al., 2013). Felminghan et al. (2002) studied non-sexual assault and motor vehicle accident victims with PTSD who performed a conventional auditory oddball task; these authors found a negative correlation between P300 and numbing symptoms and no significant correlations between P300 and other symptom clusters. Likewise, another study that investigated never-treated, comorbid-free PTSD patients following the Tokyo subway sarin attack reported a negative correlation between P300 and avoidance/numbing (Araki et al., 2005). However, some oddball studies did not find significant correlations between P300 and PTSS (Kimble et al., 2010; Lamprecht et al., 2004; Neylan et al., 2003; Veltmeyer et al., 2005), which demonstrates the conflicting findings regarding the relationship between PTSS and P300 obtained using this paradigm.

Curiously, Bae et al. (2011) performed a current-source analysis of the P300 component of auditory oddball. Studying motor vehicle accident victims with PTSD, they found a significant inverse correlation between PTSS and the P300 current source density only in the posterior cingulate gyrus. Other significant correlations were connected with PTSD cluster symptoms. The correlation patterns varied depending on the symptom characteristics. Re-experiencing was positively correlated with the P300 current source density in several parietal regions, such as the inferior and superior parietal lobule, postcentral gyrus, angular gyrus, precuneus; in some temporal regions, such as the supramarginal gyrus, superior temporal gyrus, middle temporal gyrus; and in the precentral gyrus of the frontal lobe. Avoidance and numbing items exhibited a significant positive correlation with the P300 current source densities in parietal regions, including the inferior and superior parietal lobule; the supramarginal gyrus; and in temporal regions, such as the superior and inferior temporal gyrus. In contrast, the P300 current source densities in frontal regions, such as the superior and middle frontal gyrus, exhibited a significant inverse correlation with scores of avoidance and numbing. They also observed a significant positive correlation between the total scores of hyperarousal and the

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P300 current source densities in several frontal regions, including the precentral gyrus and the inferior, middle and superior frontal gyrus; in temporal regions, such as the superior, middle, and inferior temporal gyrus; in the postcentral gyrus; in the parietal lobe; and in the insula. These findings demonstrate that the P300 current source density might reflect the pathophysiology of PTSD and that various neural networks might contribute to the symptom characteristics of PTSD.

A visual working memory task was used to investigate associations between PTSS and P3 responses (Veltmeyer et al., 2009). PTSD subjects (divided into a medicated and non-medicated group) performed a visual working memory task that consisted of a series of letters for which participants were asked to respond when any letter that was identical to the one presented previously (1-back) appeared. Interestingly, the medicated group (but not the non-medicated group) exhibited a positive correlation between the P3 amplitude to the target and the PTSS severity. However, a study that used a similar working memory paradigm (1-back), but with auditory stimuli, did not find correlations between ERPs and PTSS severity in a medication-free sample (Galletly et al., 2001), thereby suggesting that psychotropic medication may impair the working memory performance of individuals with PTSD.

Shucard et al. (2008) studied male Vietnam War combat veterans with PTSD and healthy civilian controls using both auditory and visual stimuli in a Go/NoGo task. Regarding the auditory paradigm, the task consisted of the presentation of 11 auditory letters (A, B, C, D, E, F, G, H, J, L, and X) in a quasi-random order. Participants were instructed to attend as quickly and accurately as possible to the letter ‘‘X’’ only when it followed an ‘‘A’’ (A–X). Participants were told to withhold responding to any letter other than ‘‘X’’ that followed an ‘‘A’’ (e.g., A–G). The letter ‘‘X’’ also appeared intermittently without being preceded by the letter ‘‘A’’ (X-only). Thus, there were target X Go stimuli (A–X), NoGo stimuli (e.g., A–G), X-only stimuli and Non-target stimuli (the other task-irrelevant letters). There was also a visual task that was similar to the auditory task; it featured white capital letters on a black background that were presented at eye

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level in the center of a computer screen. The same task instructions as for the auditory were given for the visual task. Collapsed across auditory and visual tasks and electrode sites, the correlation with P3 latency indicated that the P3 latency for Go stimuli was positively associated with hyperarousal scores. The NoGo stimuli P3 latency was also positively related to hyperarousal scores, but this correlation was also significant in the full sample (including healthy controls subjects). Together, these results indicate that a longer P3 latency in response to both Go and NoGo stimuli was associated with heightened arousal, but there was a non-PTSD-specific effect related to the NoGo condition. Furthermore, re-experiencing scores was positively correlated with the Non-target P3 latency, with longer latency being related to greater re-experiencing. These findings suggest that a longer time to process Go stimuli is associated with greater levels of hyperarousal symptoms. Additionally, the Non-target P3 latency was related to re-experiencing symptoms, thereby suggesting that delayed processing of cognitive stimuli may be a consequence of a preoccupation with traumatic recollections.

Using a task that was similar to that of the above study (a visual Go/NoGo task with an A-X paradigm), Covey et al. (2013) investigated the relationship between P3 and PTSS in police officers with a range of PTSS symptomatology that did not meet the criteria for a current diagnosis of PTSD. The results indicated positive associations between the P3 amplitude at Fz and lifetime (past symptoms) and total (lifetime + current) scores of PTSS; there was also a positive association between the P3 amplitude at Cz and the lifetime scores of PTSS for the NoGo trials. Thus, the pattern of relationships for the NoGo trials indicates that more severe PTSS were associated with greater fronto-central P3 amplitudes among police officers. Additional correlations with the years of experience as an officer and the number of past incidents that could potentially result in a traumatic experience were not related to the P3 amplitude. These results suggest that there are alterations in the brain mechanisms of inhibitory control in trauma-exposed police officers that are most likely due to the severity of PTSS in populations with sub-threshold PTSD (with symptoms but without a

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diagnosis).

Lobo et al. (2014) studied a sample of traumatized college students with PTSS engaged in an emotional task to investigate another P3-family ERP: the late positive potential (LPP), which is an emotional reactivity index. Participants had to judge whether images were unpleasant or neutral while EEG was recorded. Unpleasant images consisted of mutilated bodies, and neutral images portrayed people in daily life situations. A spatiotemporal principal components analysis (PCA) was performed on the EEG data to avoid biases of time windows and channels choices. The PCA identified components that reflect LPP in response to unpleasant stimuli relative to neutral stimuli. These components were input into a multiple regression model to determine which of them best explained the severity of PTSS. The results indicated two PCA factor scores (occipital and central, with both in the range of 300-500 ms) that were more important in predicting PTSS. The higher the amplitude of these two factors, the greater the severity of the PTSS. In other words, these analyses indicate that LPP in response to unpleasant relative to neutral stimuli were positively associated with PTSS, thereby reflecting an overreaction to unpleasant content in people with PTSS.

It is interesting to note that even works that failed to find correlation between overall PTSS and LPP reported negative correlations using cluster symptoms separately. Whereas a study that applied a face-matching paradigm to male combat veterans found a negative association between the LPP response to fearful faces and re-experiencing cluster symptoms (MacNamara et al., 2013), Wessa et al. (2005) found a negative correlation between the LPP response to trauma-related images and avoidance/numbing cluster symptoms.

In summary, despite some contrasting results, studies suggest a relationship between the severity of PTSS and the P3-family ERPs.

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Other ERPs

Including auditory and visual modalities for the same individuals, Gjini et al. (2013) studied two sensory gating paradigms (one auditory and one visual) in Iraqi refugees with and without PTSD. The auditory task consisted of listening to two identical auditory stimuli, S1 and S2 (with a duration of 4 ms, rise/fall time of 1 ms, intensity of 85 dB, and frequency of 1000 Hz), with a small inter-stimulus interval that varied randomly. The visual sensory gating task consisted of passive viewing of a pair of large white circles (stimulus duration: 20 ms) flashed centrally on a black background on a computer monitor with a small inter-stimulus interval that varied randomly. The results of the auditory task indicated that amplitudes of P50 auditory-evoked responses to S1 positively correlated with PTSS. The authors attributed the effect largely to a significant positive correlation between the dissociation sub-scores and the P50 S1 amplitudes. The visual sensory gating task indicated that the amplitudes of N150 through S1 were negatively correlated with PTSS, largely because of a negative correlation between avoidance sub-scores and the N150 through S1 amplitudes. These findings suggest significant deficits in stimulus encoding during a relatively early phase of information processing. However, another sensory gating study that used auditory stimuli did not find significant results regarding P50 and PTSS (Holstein et al., 2010).

The relation between mismatch negativity (MMN) and PTSS was investigated by Ge et al. (2011). The sample consisted of high school teenagers that survived the Wenchuan earthquake. The task was an auditory oddball task in which frequent “standard” tones were occasionally interrupted by infrequent “deviant” tones. Although the amplitude of the MMN was significantly greater in the group of students with high PTSS severity compared with the low-PTSS severity group (the control group), there were no significant correlations between PTSS severity and MMN in the high-PTSS severity or control groups.

Apart from visual and auditory stimuli, an interesting work investigated the relations between emotional information processing and chemosensory event-related potentials (CSERPs) that reveal olfactory function in female victims of

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childhood maltreatment (Croy et al., 2010). The study used phenyl ethyl alcohol (PEA, which has a rose-like odor), CO_2 (carbon dioxide) and H_2S (hydrogen sulfide) for olfactory stimulation. Although they found no significant difference between the groups (childhood-maltreated women and two control groups), the PTSS severity was correlated significantly with the CSERPs in response to unpleasant odors. Specifically, there was a significant negative correlation between all PTSS clusters with the N1 peak latencies of CSERPs in response to the unpleasant stimulus CO_2. Furthermore, the avoidance symptoms exhibited a significant negative correlation with both the N1 peak latency and amplitude in response to the unpleasant odor of H_2S. Avoidance scores were positively correlated with the P2 amplitude in response to H_2S. The results suggest faster early processing of unpleasant stimuli (CO_2 and H_2S) with increasing severity of PTSD-related symptoms.

EEG Spectral Analysis Studies

Only a few works that performed frequency domain analysis reported significant correlations between severity of PTSS and EEG parameters. Table 2 describes the selected spectral studies.

The majority of studies were concerned about alpha activity, especially alpha asymmetry studies. For example, two works found results about EEG alpha asymmetry analysis in resting state conditions (Kemp et al., 2010; Metzger et al., 2004). The first study (Kemp et al., 2010) compared EEG data from patients with major depressive disorder (MDD) and patients with PTSD with data from healthy controls to examine the specificity of frontal asymmetry in these disorders. Frontal asymmetry indices were calculated by subtracting the natural log of the alpha power of the left hemisphere electrode from the homologous right hemisphere electrode (i.e., right – left). Negative scores for the asymmetry measures reflect greater left-sided alpha, which is right relative to left-sided cortical activation, because a decrease in the alpha power is assumed to reflect increased cortical activity. Although a group analysis did not find differences in

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the frontal asymmetry between PTSD and healthy controls, a correlation analysis of the PTSD group exhibited an inverse correlation between the PTSS severity and the frontal alpha asymmetry: PTSD patients with more-severe PTSS exhibited greater right-lateralized frontal cortical activity (more-negative scores), thereby demonstrating that right-frontal activity in the resting state may be related to PTSS severity.

The second study (Metzger et al., 2004) reported a negative association between hyperarousal symptoms and parietal alpha asymmetry scores in female Vietnam War nurse veterans. This result indicates that PTSD arousal symptoms were associated with greater relative right-sided, compared with left-sided, parietal activation. However, the combination of hyperarousal, depression symptoms, and their interactions explain more than twice the variance in the parietal asymmetry compared with hyperarousal alone. The correlations were not statistically significant for either overall PTSS or frontal asymmetries. In other studies (Rabe et al., 2006b; Shankman et al., 2008), neither alpha, beta nor theta asymmetries in the frontal, central or posterior regions was correlated with PTSS.

Another work investigated the alpha asymmetry in an emotion paradigm in patients with PTSD who were victims of motor vehicle accidents (MVA), subsyndromal PTSD (MVA), traumatized controls (without PTSD with MVA), and healthy controls (without MVA). EEG was recorded during baseline and exposure to neutral, positive, negative, and accident-related pictures (Rabe et al., 2006a). Alpha asymmetry scores (right minus left hemisphere) for the frontal and parietal regions were recorded. Although the authors did not find any correlation between the EEG baseline and PTSS, when they computed the alpha asymmetry scores for the anterior and posterior regions on the basis of the EEG alpha power change scores (neutral minus emotion condition), significant correlations were found. In this case, positive correlations reflected relatively increased right hemisphere activation. For only the trauma-related condition (accident-related pictures), the results indicated positive correlations between the frontal asymmetry and overall PTSS and the three symptoms clusters (re-experiencing, avoidance, and hyperarousal). Furthermore, the authors also observed positive

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correlations of the parietal asymmetry for the trauma-related condition with overall PTSS, re-experiencing, and hyperarousal. Even after controlling for depression symptoms, the principal correlations remained significant, thereby demonstrating that relative right-hemispheric frontal and parietal activation was associated with greater total PTSS severity.

Wahbeh and Oken (2013) studied the peak alpha frequency in combat veterans under resting state conditions. They found significant positive correlations between the global peak alpha frequency and overall PTSS severity and sub-scores of re-experiencing, avoidance, and hyperarousal, which have been suggested to reflect increased distress.

Veltmeyer et al. (2006) computed the average power spectra during an eyes-open task that involved PTSD patients watching a red dot on a computer monitor for 3 minutes. They reported an inverse correlation between the frontal alpha-2 power (a sub-band alpha) and hyperarousal symptoms cluster. The correlation indicates that decreased alpha-2 power may be related to hyperarousal symptoms.

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A recent study that investigated the functional connectivity (FC) of PTSD patients in the resting state (Lee et al., 2014) observed that measures of FC were significantly correlated with PTSS. The FC measures were the nodal degree (Dnodal), which reflects the strength of the connection represented at a node, and the nodal efficiency (Enodal), which reflects the communication efficiency. The results indicated that in the gamma frequency band, the Dnodal of FC2 was positively correlated with the hyperarousal symptoms cluster. The Enodal measure correlated inversely with the PTSS severity. In the beta frequency band, the Enodal of C1 was negatively correlated with the overall PTSS severity, re-experiencing, and hyperarousal. The Enodal of FC4 was correlated with re-experiencing. In the gamma frequency band, the Enodal of C1 was significantly correlated with the overall PTSS severity. The results suggest that subjects with PTSD exhibit decreased FC in terms of connection strength and efficiency over the frontocentral electrodes; these decreases correlated significantly with PTSS severity.

Dimensional data regarding the relationship between sleep EEG activity and PTSS are scarce and puzzling. Non-REM alpha activity was inversely associated with the overall PTSS severity and avoidance symptoms cluster in traumatized combat veterans without PTSD (Cohen et al., 2013); however the correlations were no longer significant after Bonferroni correction for multiple comparisons, and these correlations were not significant for the PTSD group. Woodward et al. (2000) found that the non-REM-sleep sigma-band spectral power exhibited a strong positive correlation with the hyperarousal symptoms cluster. The non-REM delta energy did not exhibit a significant correlation with the overall PTSS severity or symptoms clusters (Richards et al., 2013).

Finally, in attempt to determine whether PTSD patients exhibit changes in the nonlinear structure of the EEG data, Chae et al. (2004) estimated the D2 (a nonlinear dynamical measure) values for the EEG data from PTSD patients. There were no significant correlations between PTSS and the average D2 values in all EEG channels.

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Thus, data from spectral studies are still scarce, but there are interesting findings from the alpha studies that indicate increased distress and alterations in cortical activity.

Discussion

Main Results

To our knowledge, despite the current relevance of the topic, this is the first systematic review that evaluates the relationships between the severity of PTSS and EEG parameters using a dimensional approach, according to the RDoC proposal. Despite the variability among the reviewed studies with respect to study designs, analytic methods, constructs to access PTSS, and PTSS populations, some consistent results emerged. The results yield promising perspectives regarding P2, P3-family ERPs and alpha measures.

ERP studies

Based on the evaluations of the ERP studies, some interesting results can be obtained from P2 slope measures. In healthy populations, there is an increase in the amplitude of P2 as the intensity of an auditory stimulus is increased. However, with very loud sounds, healthy subjects ultimately enter into a state of protective inhibition characterized by decreased responsivity, which protects the cortex from overstimulation (Metzger et al., 2005). Group analysis had not yielded converging results regarding the role of P2 in PTSD (Lewine et al., 2002; McPherson et al., 1997; Metzger et al., 2008, 2002; Paige et al., 1990). Nevertheless, in three auditory studies, the P2 slope was positively correlated with PTSS severity; that is, higher scores on severity of PTSS are related to greater amplitude intensity slope (Lewine et al., 2002; Metzger et al., 2008, 2002), thereby suggest that higher auditory responsivity may reflect deficiencies in the cortical inhibitory system, which protects against overstimulation. Although the tone stimulus-intensity modulation task and P2 slope appear to offer a

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promising clinical tool, the existing studies observed this association only in samples of veterans. Therefore, further studies are needed to assess this relationship in other populations.

Other auditory tasks, such as the auditory oddball task, though numerous, have yielded a number of dimensionally negative data regarding ERPs and PTSS severity (Ge et al., 2011; Holstein et al., 2010; Kimble et al., 2010; Lamprecht et al., 2004; Neylan et al., 2003; Veltmeyer et al., 2005). Among the auditory oddball studies, the exception was a current source analysis of the P300 component that observed a significant inverse correlation between PTSS and the P300 current source density in the posterior cingulate gyrus (Bae et al., 2011). The posterior cingulate gyrus is involved in cognitive functions such as memory retrieval, coping with physical threats, and processing of distressing material, all of which are linked to PTSD (Bremner, 2002; Buckner et al., 2008; Maddock et al., 2001). In addition, the current source densities of ERPs have been demonstrated to be useful potential biomarkers of schizophrenia (Wang et al., 2010; Winterer et al., 2001). In sensory gating, another auditory task, the exception was a study that found a direct relationship between P50 and PTSS (Gjini et al., 2013). Moreover, a study that used magnetoencephalography (MEG) found a distinct result for of Gjing et al. (2013): an inverse relationship between M50 (MEG equivalent to P50) and the PTSS severity, where M50 were negatively correlated to PTSS (Hunter et al., 2011). Studies that have used auditory tasks, such as auditory oddball tasks, have yielded contradictory results, and further investigations are necessary to confirm the usefulness of the auditory P300 or P50 as biomarkers for evaluating PTSS severity.

Visual stimuli elucidate relationships between P3-family ERPs and the severity of PTSS. The P3 family is composed of the P3a and P3b subcomponents, which have been hypothesized to index attention and initial memory storage events (Polich, 2007). The subsequent slow wave activity appears to be related to task demands that involve working memory operations (Azizian and Polich, 2007). In emotion paradigms, slow wave activity indicates elevated positivity in response to highly arousing stimuli (Cuthbert et al., 2000;

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Mocaiber et al., 2010, 2009). In fact, using distinct tasks, three studies found positive correlations between these variables: increased severity of PTSS was related to greater P3-family ERP amplitudes (Covey et al., 2013; Lobo et al., 2014; Veltmeyer et al., 2009). This evidence is consistent with a study that found that compared with healthy control subjects, traumatized groups (with and without PTSD) exhibited increased P300 and late positive complex amplitudes in response to trauma-specific questions (Wessa et al., 2006). Likewise, a group analysis performed by Lobo et al. (2014) indicated that students with more severe PTSS (high-PTSS group) had significantly greater LPP compared to students with less severe symptoms (low-PTSS group). The results were strengthened by joining the two groups in a multiple regression model, which found that two PCA factor scores that corresponded to the LPP were able to predict the severity of PTSS. In fact, a recent meta-analysis from Johnson et al. (2013) investigated the potential clinical utility of P3-family ERPs to distinguish individuals with PTSD from controls. They found elevated P3 amplitudes in patients with PTSD in the context of trauma-related distracters and reduced amplitudes when neutral distracters were used in the oddball paradigm, thus confirming previous results (Karl and Maercker, 2006). These evidences indicate that P3-family ERPs are promising candidate biomarkers for evaluating PTSS severity. Because each of these studies used a different type of task (e.g., go/no go, working memory, or emotional pictures), further studies are needed to determine which tasks are best suited to observe the relationships between PTSS and P3-family ERPs.

It is also worth remembering that other studies that used visual stimuli found no relationships between P3-family ERPs and overall PTSS (MacNamara et al., 2013; Shucard et al., 2008; Wessa et al., 2005), but these studies observed associations between separate symptom clusters and LPP (MacNamara et al., 2013; Wessa et al., 2005) and P300 (Shucard et al., 2008). We believe that the correlations with the separate symptom clusters are important in some cases (McEwen, 2015) but may not represent specificity to PTSD. For example, Shucard et al. (2008) found that the P3 latency in response

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to NoGo stimuli was related to hyperarousal scores for the full sample (PTSD and healthy subjects). Consequently, the longer P3 latency in response to NoGo stimuli may not be specific to PTSD. In summary, the P3-family results suggest promising possible biomarkers for evaluating PTSS severity.

EEG Spectral Analysis Studies

Regarding spectral studies, some interesting findings have been yielded by studies of alpha rhythms and PTSS. Wahbeh and Oken (2013) found a direct relationship between the peak alpha frequency and PTSS severity. Slower peak alpha frequencies are associated with relaxation (Nunez et al., 2001), thus the higher peak alpha frequency can reflects increased distress. Using a resting-state paradigm to observe the alpha asymmetry, Kemp et al. (2010) found greater right-frontal activity in association with more-severe PTSS. However, Rabe et al. (2006a) did not find significant associations in their resting-state paradigm, consistent with other works (Rabe et al., 2006b; Shankman et al., 2008), but they did find greater right-frontal activity to be associated with greater PTSS severity when the subjects viewed trauma-related pictures. Given the inverse relationship between alpha power and cortical activity (Oakes et al., 2004), a decrease in alpha power is assumed to reflect an increase in cortical activity. Therefore, there is evidence that cortical activity (observed by alpha asymmetry pattern), especially in frontal regions, may vary with the severity of PTSS, especially with greater right-frontal activity. The negative results regarding alpha can be explained as follows: first, EEG studies of PTSD populations, especially combat veterans, are biased toward patients who are usually older, taking medications, or may be anxious during the recording. Second, distinct tasks are used to observe alpha asymmetry. Furthermore, the clinical definition of alpha varies among studies. These factors tend to work against the production of robust, widespread alpha. Thus, comparisons between studies are challenging. Nevertheless, the existing findings are promising.

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Current dimensional data regarding sleep EEG activity and PTSS are scarce because only few studies have used this approach. Of the three sleep studies reviewed, only one found a significant correlation between EEG parameters and overall PTSS severity, and the correlation was no longer significant after Bonferroni correction (Cohen et al., 2013).

A connectivity study indicated that greater PTSS severity was associated with lower the connectivity parameters for the beta and gamma bands (Lee et al., 2014). Because the beta and gamma bands are believed to be involved with higher cognitive functions (Engel and Fries, 2010; Fries, 2009), the functional connectivity in these high-frequency bands could indicate higher cognitive information flow. Consequently, the negative correlations between PTSS severity and the beta and gamma FC parameters could suggest a reduced efficiency for cognitive functions, such as control of the subcortical limbic regions, because of the low functional connectivity.

General Discussion

Recent advances in signal processing and visualization of EEG data, such as better spatial resolution, proven useful for comprehension of brain alterations that are associated with several psychiatric disorders. The low cost of EEG data collection makes it a suitable method for investigations of large populations, which are necessary to identify reliable biomarkers. Furthermore, EEG is the most non-invasive and portable of all of the neuroimaging methods (McLoughlin et al., 2014). Thus, EEG is an easy technology that can be implemented in laboratories and clinics with promising candidate biomarkers.

It is important to note that in some cases, single biomarkers can be very informative (McEwen, 2015), but we should consider that the heterogeneity that is inherent in PTSD symptomatology makes it highly unlikely that a single unique biomarker for PTSD will be identified (Schmidt et al., 2013; Zoladz and Diamond, 2013). A recent review emphasized the role of monoaminergic systems, inflammation, genomics, physiology, and the neuroanatomical differences as a

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diagnostic biomarkers of PTSD (Michopoulos et al., in press). To gain a deeper understanding of the pathophysiology of PTSD and, thus, to improve diagnostic effectiveness, future studies should investigate potential biomarkers using the combination of neuroimaging techniques e.g, EEG, MRI and fMRI that provide different aspects of brain function: fMRI measures hemodynamic response related to brain activity dynamically while structural MRI offers information about tissue type, both with good spatial resolution. EEG measures electrical activity of the brain with a higher temporal resolution (but lower spatial resolution). Approaches for combining information from these different techniques, associating time and space, will improve the ability to track changes in the brain that characterize the development and the progression of PTSD. For instance, Araki et al. (2005) found that lower P300 amplitude showed a trend toward a significant correlation with smaller gray matter voxel densities in the anterior cingulate cortex of the PTSD group but not the control group. Additionally, the RDoC proposal encourages the development of studies that combine genetics and neuroscience approaches to understand the cause-and-effect relationships in brain changes observed in patients (Insel et al., 2010) because it is clear that mental illnesses involves highly complex interactions between genetic factors and experience (Cuthbert and Insel, 2013)." Furthermore, it is critical to understand that biomarkers might be relevant at one time (i.e., before or after trauma exposure) and not at another (Schmidt et al., 2013).

Group analysis is very useful for categorization; however, correlation-based analysis may be more appropriate for detecting mild changes in response to interventions. The present systematic review focused on the search for biomarkers of PTSS severity. A symptom severity biomarker offers many advantages: providing information about a patient's treatment progression, informing about possible vulnerability to co-morbid disorders, and helping psychiatrists choose better treatments. In addition, monitoring PTSS in traumatized people can be relevant for preventing PTSD as a result of a new traumatic event, for example. Regarding this last point, it is remarkable a limitation of some reviewed studies with the "traumatized without PTSD"

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population. More than half of the studies reviewed demonstrated correlations between EEG and PTSS only in the PTSD group, largely because of the lack of a "trauma-exposed without PTSD" group or because the researchers split the traumatized volunteers (with and without PTSD) into two distinct groups and correlations. According to the RDoC proposal, traumatized populations without PTSD diagnoses must be considered because it is necessary to understand the disorder dimensionally, ranging from normal to pathological (Simmons and Quinn, 2013).

Another limitation of the reviewed studies is the fact that a large portion of the traumatized population was taking medication and had co-morbid disorders. Thus, is it possible that some EEG parameters behave differently in populations that do not use psychotropic medication or have no associated co-morbidities. Although these "clean" profiles are quite unusual in PTSD studies (Pietrzak et al., 2011), it is important to know the behavior of the relevant biomarkers in these cases, especially when considering using these biomarkers in people with acute PTSD to investigate vulnerability to develop chronic PTSD.

The role of the trauma type must also be better characterized. It is possible that mixed-trauma samples prevent significant results from being achieved in the EEG studies. In fact, most of the studies that used a mixed-trauma sample found no significant correlation between EEG parameters and the severity of symptoms—very few exceptions were found (Lobo et al., 2014; Veltmeyer et al., 2009, 2006).

Limitations

One limitation of the present systematic review concerns the use of three electronic databases, even though they are the principal databases used in the field. Moreover, the search was limited to articles published in English. Consequently, this review provides no information regarding unpublished studies or studies published in other languages. The search was restricted to articles published since 2000, the publication year of the text revision of the DSM-IV. Another limitation was the heterogeneity of the studies, which made it impossible

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to perform a meta-analysis.

Conclusions

In summary, the present systematic review highlights the promising potential of P2, P3 family ERPs and alpha measures to act as potential biomarkers of PTSS severity; however, there is much work needed to confirm that these EEG parameters are effective biomarkers of PTSS severity. Only a few studies have performed a correlation analysis, and considering the important differences in terms of study design, analytic methods, constructs to access PTSS, and PTSS populations, further studies are required to establish EEG as a biomarker of PTSS severity in psychiatry

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Conflict of Interest

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Table 1: Main correlations findings between PTSS and ERP measures.

Legend: (+) = Positive Correlation; (-) = Negative Correlation; MVA = motor vehicle accident; CAPS = The Clinician Administered PTSD Scale (Blake et al., 1995); DTS = Davidson Trauma Scale (Davidson et al., 2002); IES= Impact of Event Scale (Weiss and Marmar, 1997); PCL-C = PTSD Checklist (Weathers et al., 1993); PCL-M = PTSD Checklist (Weathers et al., 1991); PDS= Posttraumatic Diagnostic Scale (Foa et al., 1997); PSS = PTSD Symptom Scale (Foa et al., 1993); SIP = Structured Interview for PTSD (Davidson et al., 1997). *Sample size in correlation analysis.

Table 2: Main correlations findings between PTSS and EEG spectral measures.

Legend: (+) = Positive Correlation; (-) = Negative Correlation; MVA = motor vehicle accident; CAPS = The Clinician Administered PTSD Scale (Blake et al., 1995); PCL = PTSD Checklist (Weathers et al., 1993); PCL-M = PTSD Checklist (Weathers et al., 1991); DTS = Davidson Trauma Scale (Davidson et al., 2002); SIP = Structured Interview for PTSD (Davidson et al., 1997). *Sample size in correlation analysis.

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Figure 1: Summary of literature search, adapted from PRISMA (Moher, 2009).

Highlights

- Systematic review about dimensional EEG data and PTSD.
- P2 and P3 family were ERPs often associated with posttraumatic stress symptoms (PTSS).
- Alpha rhythms were often associated with PTSS.
- EEG can reveal potential biomarkers of PTSS severity

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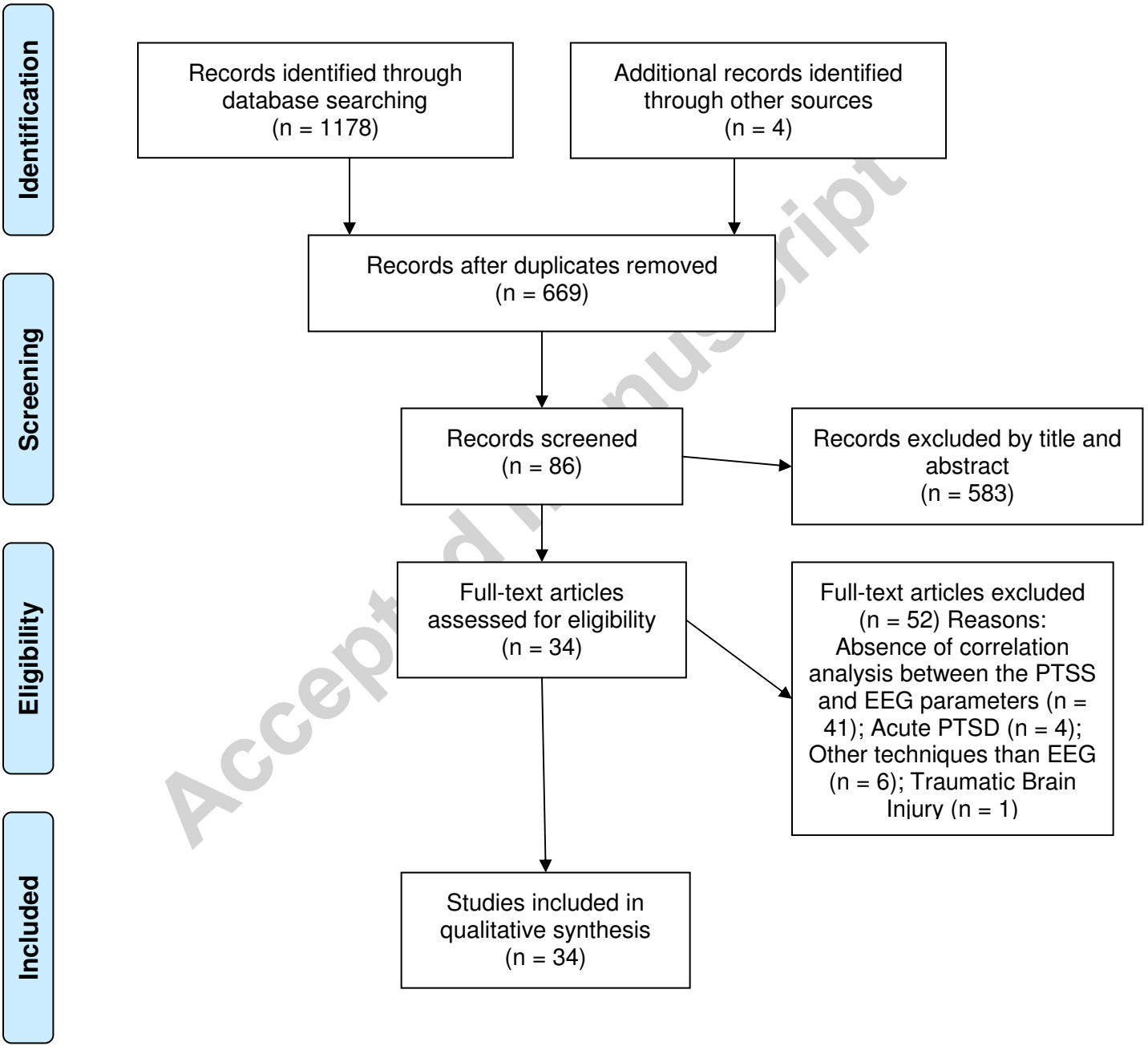
Figure 1: Summary of literature search, adapted from PRISMA (Moher, 2009).



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Study	Female /Male*	Trauma	PTSS Scale	Task	Overall PTSS Correlation Result	Separate Cluster Correlation Result
(Metzger et al., 2002)	29/0	Combat-related	CAPS; PCL-M	Auditory Oddball	(+) P2 slope and CAPS; (+) P2 slope and PCL-M	
(Araki et al., 2005)	3/5	Subway attack	CAPS; IES	Auditory Oddball		(-) P300 and Avoidance/Numbing
(Felmingham et al., 2002)	11/6	Assault and MVA	CAPS	Auditory Oddball		(-) P300 and Numbing
(Kimura et al., 2013)	8/21	Earthquake	IES	Auditory Oddball		(+) P3a and Hyperarousal
(Bae et al., 2011)	14/16	MVA	DTS; SIP	Auditory Oddball	(-) Source P300 at posterior cingulated gyrus and DTS	
(Kimble et al., 2010)	0/27	Mixed	PSS	Auditory Oddball	no significant results	
(Veltmeyer et al., 2005)	17/18	Mixed	CAPS	Auditory Oddball	no significant results	
(Lamprecht et al., 2004)	6/4	Mixed	IES	Auditory Oddball	no significant results	
(Ge et al., 2011)	5/8	Earthquake	PCL-C	Auditory Oddball	no significant results	
(Neylan et al., 2003)	0/25	Combat-related	CAPS; IES	Auditory and Visual Oddball	no significant results	
(Metzger et al., 2008)	0/45	Combat-related	CAPS	Listen to tones	(+) P2 slope and CAPS	
(Lewine et al., 2002)	0/9	Combat-related	CAPS	Listen to tones	(+) P2 slope and CAPS	
(Holstein et al., 2010)	20/7	Mixed	CAPS-DX; IES	Sensory gating	no significant results	

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(Gjini et al., 2013)	20/20	Torture	CAPS-2	Sensory gating (visual and auditory)	Visual: (-) N150 and CAPS-2; Auditory: (+) P50 and CAPS-2	
(Shucard et al., 2008)	0/23	Combat-related	CAPS-DX	Auditory and Visual Go/ NoGo		(+) P3 Latency and Reexperiencing (+) P3 Latency and Hyperarousal
(Covey et al., 2013)	4/10	Police job-related	CAPS; PCL-C	Visual Go/ NoGo	(+) P3 and CAPS	
(Wessa et al., 2005)	7/7	MVA	CAPS; PDS	Viewing emotional pictures		(-) P200 and Avoidance (-) LPP and Avoidance
(MacNamara et al., 2013)	0/19	Combat-related	CAPS; PCL-M	Emotional face matching		(-) LPP and Reexperiencing
(Lobo et al., 2014)	38/5	Mixed	PCL-C	Judge valence pictures	(+) LPP and PCL-C	
(Veltmeyer et al., 2009)	8/6	Mixed	CAPS; PCL-C	Visual working memory	(+) P3 and PCL-C	
(Gallety et al., 2001)	8/10	Mixed	IES	Auditory working memory	no significant results	
(Croy et al., 2010)	31/0	Childhood maltreatment	IES	Odor identification		(-) N1 peak latency to CO_2 and the 3 separate cluster (-) N1 peak (latency and amplitude) to H_2S and Avoidance (+) P2 amplitude to H_2S and Avoidance

Table 1: Main correlations findings between PTSS and ERP measures.

Legend: (+) = Positive Correlation; (-) = Negative Correlation; MVA = motor vehicle accident; CAPS = The Clinician Administered PTSD Scale (Blake et al., 1995); DTS = Davidson Trauma Scale (Davidson et al., 2002); IES= Impact of Event Scale (Weiss and Marmar, 1997); PCL-C = PTSD Checklist (Weathers et al., 1993); PCL-M = PTSD Checklist (Weathers et al., 1991); PDS= Posttraumatic Diagnostic Scale (Foa et al., 1997); PSS = PTSD Symptom Scale (Foa et al., 1993); SIP = Structured Interview for PTSD (Davidson et al., 1997). *Sample size in correlation analysis.

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Table 2: Main correlations findings between PTSS and EEG spectral measures.

Study	Female/Male*	Trauma	PTSS Scale	Task	Overall PTSS Correlation Result	Separate Cluster Correlation Result
(Wahbeh & Oken, 2013)	0/86	Combat-related	CAPS; PCL-M	Listen to tones	(+) Global Peak Alpha and CAPS; (+) Global Peak Alpha and PCL-M	
(Cohen et al., 2013)	0/11	Combat-related	CAPS; PCL-M	Sleep Study	(-) NREM Alpha and PCL-M	
(Woodward et al., 2000)	0/56	Combat-related	CAPS;	Sleep Study		(+) NREM Sigma and Hyperarousal
(Richards et al., 2013)	21/19	Not reported	CAPS	Sleep Study	no significant results	
(Lee et al., 2014)	17/16	MVA	DTS; SIP	Resting State	(-) enodal Beta and SIP; (-) enodal Beta and DTS; (-) enodal Gamma and DTS	
(Metzger et al., 2004)	42/0	Combat-related	CAPS	Resting State		(-) Parietal Alpha asymmetry and Hyperarousal
(Kemp et al., 2010)	9/5	Not reported	CAPS	Resting State	(-) Frontal Alpha asymmetry and CAPS	
(Shankman et al., 2008)	16/16	Mixed	CAPS	Resting State	no significant results	
(Rabe et al., 2006b)	55/27	MVA	CAPS	Resting State	no significant results	
(Chae et al., 2004)	14/13	Mixed	CAPS2	Resting State	no significant results	
(Veltmeyer et al., 2006)	17/17	Mixed	CAPS	eyes open task		(-) Frontal Alpha-2 and Hyperarousal
(Rabe et al., 2006a)	44/20	MVA	CAPS	Passive Viewing	(+) Anterior Alpha asymmetry and CAPS, (+) Posterior Alpha asymmetry and CAPS	

Legend: (+) = Positive Correlation; (-) = Negative Correlation; MVA = motor vehicle accident; CAPS = The Clinician Administered PTSD Scale (Blake et al., 1995)*; PCL = PTSD Checklist* (Weathers et al., 1993)*; PCL-M = PTSD Checklist* (Weathers et al., 1991)*; DTS = Davidson Trauma Scale* (Davidson et al., 2002)*; SIP = Structured Interview for PTSD* (Davidson et al., 1997)*. *Sample size in correlation analysis.*

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