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Meta-analytic review of event-related potential studies in post-traumatic stress disorder

Anke Karl [a,*], Loretta S. Malta [b], Andreas Maercker [c]

[a] *Biopsychology, University of Technology Dresden, Zellescher Weg 17, D-01062 Dresden, FR, Germany*
[b] *Weill Medical College of Cornell University Program for Anxiety and Traumatic Stress Studies, NY, USA*
[c] *Clinical Psychology, Institute of Psychology, University of Zurich, Switzerland*

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Abstract

In recent years there has been an accumulation of studies that have utilized the measurement of event-related potentials (ERP) to examine the neuroelectric correlates of hypothesized alterations in information processing in persons with post-traumatic stress disorder (PTSD). The objective of this meta-analysis was to summarize the findings of ERP PTSD research, including studies that have examined P50 auditory sensory gating, augmenting-reducing P200, and P300 in target detection oddball tasks. The results suggest that persons with PTSD exhibit alterations in the amplitude and latency of ERP within these paradigms that support the hypothesis that changes in information processing can accompany PTSD. The results were also consistent with recent cognitive neuropsychological findings in PTSD research.

Keywords: PTSD; Psychophysiology; EEG; Event-related potentials; P300; Meta-analysis; Plasticity

1. Introduction

Exposure to trauma can produce long-lasting behavioral changes, including the development of post-traumatic stress disorder (PTSD). PTSD symptoms include altered sensory-perceptual functioning in the form of flashbacks, heightened physiological responses to trauma cues, and general hyperarousal symptoms such as exaggerated startle, poor concentration, insomnia, and hypervigilance (DSM-IV; American Psychiatric Association, 1994). Persons with PTSD may also exhibit altered information processing including deficits in attention and working memory as well as difficulty encoding information and inhibiting distracting stimuli (Vasterling et al., 1998, 2002). They may also exhibit enhanced processing of threat stimuli and an attention bias to trauma-related cues (see Buckley et al., 2000 for a review).

The measurement of event-related potentials (ERPs) is a valuable tool with which to investigate information processing in PTSD. ERPs are electro-encephalographic (EEG) measurements of the activity of neural populations in response to a stimulus, in which responses are time-locked to the stimuli and averaged together. EPRs can afford a level of temporal precision and resolution currently unavailable from other methods of measuring neural activity such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). As ERP research can more precisely speak to the dynamic nature of information processing, it may enhance our understanding of the neurophysiological correlates of altered information processing in PTSD. However, although an increasing number of studies have provided evidence of this phenomenon, to date there has been no systematic review of the literature. Thus, the goal of this meta-analysis was to provide a quantitative integration of the findings of ERP PTSD research. We begin with a description of paradigms typically used in PTSD ERP studies.

1.1. P50 sensory gating

The P50 auditory midlatency potential is a vertex-recorded potential that is elicited 40–80 ms after stimulus onset (Erwin and Buchwald, 1986). In the auditory sensory

* Corresponding author. Tel.: +49 351 46336002; fax: +49 351 46337274.
E-mail address: karl@biopsych.tu-dresden.de (A. Karl).

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gating paradigm, pairs of identical clicks are presented with a constant interstimulus (typically 250, 500, or 1000 ms) and a constant intertrial interval (typically 5–10 s). In healthy controls, the P50 auditory potential to the second click is suppressed, and this suppression has been interpreted as representing an inhibitory process or sensory gate (Waldo and Freedman, 1986). Reduced P50 suppression has been hypothesized to reflect deficits in filtering out irrelevant stimuli and may be mediated by altered cholinergic activity as well as transient, stress-related increases in noradrenalin and corticotrophin releasing factor in brainstem nuclei (Miyazato et al., 2000; Waldo et al., 1992). In PTSD research, there have been reports of a reduction of the P50 suppression response in persons with PTSD (e.g., Gillette et al., 1997; Neylan et al., 1999; Skinner et al., 1999) but negative findings as well (Metzger et al., 2002).

1.2. P200 augmenting-reducing (A/R) paradigm

The A/R paradigm measures the P200 potential, a positive EEG deflection elicited approximately 200 ms after stimulus onset to (acoustic) stimuli of increasing intensity. On the basis of the slope of the P200 amplitude, individuals are classified as ''augmenters'' (increasing amplitude to increasing sound intensity) or ''reducers'' (decreasing amplitude to increasing sound intensity). Differential P200 responses have been proposed to index the ''tuning'' properties of a gating mechanism that regulates cortical sensory input (Pritchard, 1986; Paige et al., 1990). Augmentation has been hypothesized to represent a cortex ''tuned'' to seek out increases in stimulus intensity, whereas reduction represents a sensory system tuned to shut out increased stimulation (Pritchard, 1986). There is also some evidence that the P200 augmenting-reducing response may involve serotonergic systems (Hegerl and Juckel, 1993). The P200 findings in the PTSD literature have been mixed, with reports of both a reducing response (e.g., Paige et al., 1990; Lewine et al., 1997) as well as an augmenting response (Metzger et al., 2002; McPherson et al., 1997) in persons with PTSD compared to controls.

1.3. P300 and the oddball paradigm

The P300 is a large positive EEG deflection elicited approximately 300 ms after stimulus onset that has been described as reflecting the level of tonic arousal and phasic alterations in arousal to specific stimulus events (Polich and Kok, 1995). The P300 is believed to index activity in temporo-parietal and prefrontal cortical regions, and to a lesser extent the hippocampus (Frodl-Bauch et al., 1999a; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Opitz et al., 1999a,b; Polich, 2003). P300 generation appears to involve GABAergic, cholingergic, and serotonergic systems (Frodl-Bauch et al., 1999a; d'Ardhuy et al., 1999).

The oddball task is a frequently employed P300 study paradigm. In the two-stimulus task, individuals are instructed to attend to ''oddball'' (i.e., infrequent) target stimuli while ignoring frequently presented standard stimuli. The three-stimulus oddball task presents distractor stimuli in addition to oddball targets and standard stimuli. The stimulus modality can be auditory, visual or somatosensory. However, the majority of PTSD studies (11/15) used auditory stimuli, and the rest used visual/verbal stimuli.

Oddball targets, but not standard stimuli or distractors, elicit a subcomponent of the P300 called the P3b. The P3b is distributed over central-parietal cortical regions with a maximal generation at parietocentral electrode sites (Johnson, 1993; Frodl-Bauch et al., 1999a; Sutton et al., 1965). Increased P3b amplitudes in the oddball task have been interpreted as representing the increased salience of relatively infrequent, but significant (i.e., target), stimuli. The P3b has also been associated with selective attention (Picton and Hillyard, 1974) and stimulus evaluation (Pritchard, 1981), and may represent the availability of attentional resources for stimulus processing (Donchin and Coles, 1988).

The three-stimulus oddball task has been used to investigate another P300 subcomponent, the P3a. The P3a is elicited at frontal-central cortical regions in response to distractors and precedes the P3b by approximately 50 ms (Courchesne et al., 1975; Squires et al., 1975). It is believed to originate from frontal cortex but can be elicited from central and parietal cortical regions as well (Katayama and Polich, 1998; Polich and Kok, 1995). The P3a has been hypothesized to reflect a form of preattentive processing in which changes in the sensory environment evoke an automatic shift in attention (Näätänen, 1990). In the oddball task, the P3a is presumably elicited when selective attention to oddball target is disrupted by distracting stimuli. Novel distractors (e.g., dog barks) elicit a P3a that habituates rapidly and is thought to reflect prefrontal-hippocampal functioning (Knight, 1996; Yamaguchi et al., 2004). Infrequently presented non-target distractors (tones, letters, etc.) also elicit a frontal-central P3a that is shorter in latency than the target P3b (Comerchero and Polich, 1999; Polich and Comerchero, 2003).

P300 amplitude has been hypothesized to index neural activity associated with the processing of new information when attention is engaged to update memory representations (Donchin, 1981; Polich, 1996). Larger amplitudes have been associated with superior memory performance (Fabiani et al., 1990) and they are proportional to the amount of attentional resources employed in the task (Kramer and Strayer, 1988). P300 latency has been proposed to represent stimulus classification speed (Polich, 1987) as well as the depth and duration of stimulus processing (Donchin, 1981). Latency is generally unrelated to the response selection process and the behavioral response time (Novak et al., 1990), but shorter latencies are associated with faster processing speed and better performance on cognitive tasks (Polich et al., 1983). P300 latency is often inversely related to P300 amplitude (Donchin, 1981). However, the strength of amplitude-latency correlations varies according to the

difficulty of discriminating target and standard stimuli, the salience of distractors, and the recording site (Katayama and Polich, 1996; Katayama and Polich, 1998; Polich and Comerchero, 2003; Polich et al., 1997).

Most of the PTSD P300 studies do not specify P3b and P3a subcomponents. The most common finding in the literature is reduced P300 (most likely P3b) amplitudes to target oddball stimuli in persons with PTSD compared to controls (e.g., McFarlane et al., 1993; Metzger et al., 1997a). The P3a has been less well researched, but there is some evidence of increased P300 (most likely P3a) amplitudes elicited by distractors in oddball tasks in persons with PTSD (e.g., Attias et al., 1996a; Kimble et al., 2000).

The collected P50, P200, and P300 research has provided evidence of altered neuroelectric information processing in PTSD. However, one limitation of the research is the small study sample sizes. Meta-analysis is a technique that can address this limitation, as it permits the analysis of results across studies. In the present study we used meta-analysis to test hypothesized differences in information processing in individuals with PTSD, including whether they reliably showed reduced auditory P50 suppression and decreased P200 to tones of increasing intensity (reduction response). We also examined whether persons with PTSD reliably exhibited reduced P3b amplitude and longer latencies to target oddball stimuli, and increased P3a amplitude to distractors. As most studies did not specify these subcomponents, we classified the P3b and P3a functionally, based on the nature of the stimuli (target versus distractors). We adopted this approach so as to provide more fine-grained analyses that would enable us to interpret the findings in accordance with current theoretical models.

2. Method

2.1. Studies/samples

A total of 40 candidate studies published in English were located through data bases (Medline, Psychlit, Current Contents; keywords PTSD and EEG, ERP, P3(00), mismatch negativity, oddball, P2(00), augmenting-reducing, P50 sensory gating) and through perusing psychophysiological journals from 1990 to 2004 (e.g., Psychophysiology, International Journal of Psychophysiology, Biological Psychology). To address the ''file drawer problem'' (Hunter and Schmidt, 1990), abstracts published in conference proceedings and unpublished conference presentations were also examined.

Candidate studies were classified according to their methodology. Those with similar methods (25/40) were included in the present meta-analysis, and the remaining 15 studies were qualitatively reviewed (Karl et al., submitted). The meta-analysis study inclusion criteria were: (1) inclusion of a PTSD group based on DSM-III-R or DSM IV diagnostic criteria and a comparison group (non-PTSD trauma-exposed or a non-trauma sample); (2) sufficient methodological specification (e.g., paradigm, recording method, sample size); and (3) sufficient reporting of statistics (i.e., M, S.D., d.f., p, t or F-value, etc.). As suggested by Glass et al. (1981), all available studies (not only those with the best methodology) were included. As noted, most of the studies did not identify P300 subcomponents, and for all analyses the classification of P3a and P3b was based on the nature of the stimuli that evoked the response (target versus distractor).

2.2. Statistical procedures

Meta-analyses were computed based on the single effect size (ES) r, the Pearson product–moment correlation, a standardized form of the size of the observed effect. ES r-values were calculated by the transformation of M and S.D., t, F, or χ^2 values into r to obtain unitary ESs (Kraemer and Thiemann, 1987), using the Meta Analysis Program version 5.3 software by Schwarzer (1989). Only one ES per construct, per study was included in the meta-analysis (Rosenthal, 1995).

The meta-analysis was based on the more conservative random-effects model (Hedges and Olkin, 1985), whose main assumption is that in addition to the within-study variance used in the fixed-effects model, a between-study variance (τ^2) is incorporated in the variance component used to calculate weights (Field, 2001). ES r-values were weighted according to study sample size (Hedges and Olkin, 1985; Hedges and Vevea, 1998) and converted into the common metric of Fisher's z transformation of r (Rosenthal, 1995). The mean of z and 95% confidence interval (CI) were calculated for each set of ERP components (k = number of studies; Rosenthal, 1995). Mean ESs and CI were then converted back to r for ease of interpretation. If the 95% CI did not include zero, the null hypothesis that the relationship between the ERP component and PTSD diagnosis was zero could be rejected at the $p = .05$ level. Cohen's (1988) guidelines for interpreting the ES of sample-weighted average correlations were used: small = .10, medium = .30, and large = .50.

Sample homogeneity was determined according to procedures proposed by Hedges and Olkin (1985) and Hedges and Vevea (1998) and Field (2001), in which heterogeneity is present if the between trials variance (τ^2) is greater than zero and/or the within-trials variance test (χ^2) is significant. To address the file drawer problem, Orwin's fail safe N (Orwin, 1983) was computed. For a specified critical r-value, the fail safe N is the number of studies with an ES of zero required to reduce the mean population ES to that critical value.

2.2.1. Moderator variables

Identification of moderator variables can account for sources of between-study heterogeneity in meta-analyses that may influence results. In the present study, the influence

of moderator variables was first tested in hypotheses-guided analyses of known potential moderator variables including stimulus modality, electrode position, type of control group, gender, age, comorbid diagnoses, and medication. If these analyses did not yield homogenous results, a disjoint cluster analysis (Hedges and Olkin, 1985; Mullen and Rosenthal, 1985) was performed to identify homogenous subsets of studies, based on rank-ordered effect sizes and a comparison of their differences to critical values at the .01 significance level. The disjoint cluster analysis reveals non-overlapping clusters of study effect sizes. The procedure includes a transformation of r into Fisher's z, which is then multiplied by the square root of the sample size. The resulting value (u) is then rank-ordered and the gap between each pair of consecutive u-values is compared to a predetermined critical value (Schwarzer, 1989).

3. Results

3.1. P50 auditory sensory gating

The demographic and methodological characteristics of the six studies that utilized P50 auditory sensory gating are detailed in Appendix A. Fig. 1 presents an example of the P50 ERP. All studies included in the meta-analysis used the ratio of the peak amplitude of the P50 amplitude to the second click to that of the first click (TC ratio) as a measure of the degree of sensory gating. As shown in the figure, persons with PTSD may show less habituation to the second click (indicated by reduced P50 ERP) compared to controls.

The ES for each study is displayed in Fig. 2. Three of the studies compared a PTSD group to non-PTSD trauma controls (ES range of .12–.73), five studies compared PTSD with a non-trauma control group (ES range of .41–.77), and two compared a PTSD group to a sample of alcoholics (both ES .58).

Table 1 presents the statistics for the meta-analysis. *For the meta-analysis comparing PTSD with a non-PTSD trauma population*,[1] the initial meta-analysis ($N = 78$) revealed significant reduced P50 suppression in the PTSD group. However, the analysis of study heterogeneity was also significant (see τ^2 and χ^2, Table 1). Thus, a second analysis was conducted in a homogenous sample ($N = 30$) that excluded study #5 (Metzger et al., 2002), the only study that did not include medicated adult male subjects. The results were that PTSD patients showed significantly less reduction of the P50 response to the second click compared to non-PTSD trauma groups. *The meta-analysis comparing PTSD with non-trauma controls* ($N = 111$) found significantly reduced P50 suppression in the PTSD group, but the analysis of study heterogeneity was also significant (see τ^2 and χ^2, Table 1). Cluster analysis classified a homogenous group of studies (#1, 3, 4 and 26, see Appendix A) each of which sampled PTSD patients with comorbid alcoholism. The meta-analysis with this sample ($N = 84$) found that the PTSD group again showed significantly less reduction of the P50 ERP to the second click compared to non-trauma controls. *The meta-analysis comparing a PTSD group versus alcoholics without PTSD*

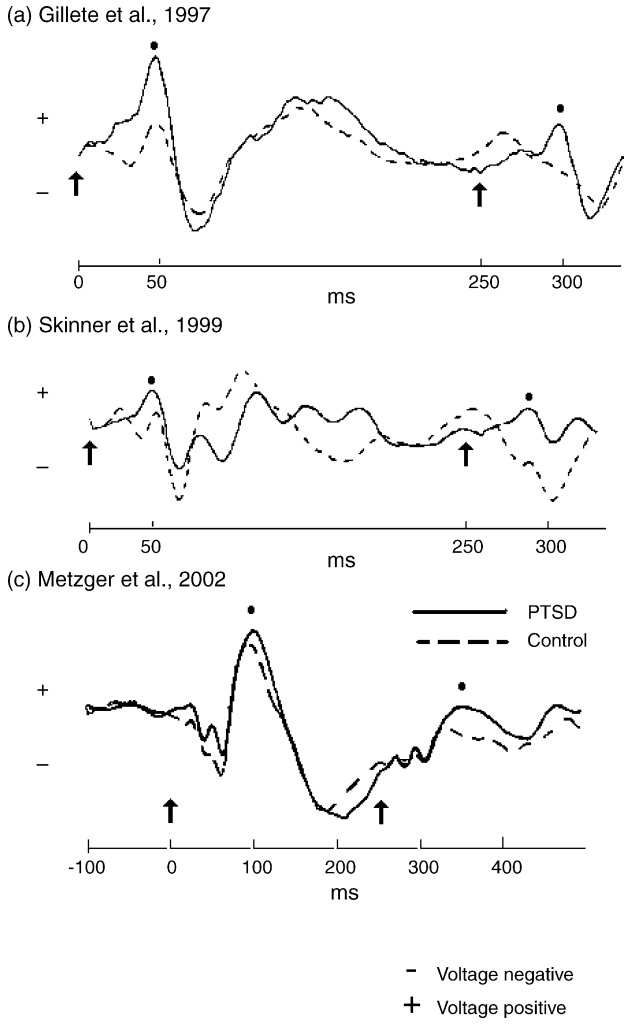

Fig. 1. Example ERPs in the P50 auditory sensory gating paradigm. Arrows indicate the occurrence of the first and second acoustic stimulus (click). About 50 ms later a positive deflection occurs (indicated by ●). Persons with PTSD may not show the response reduction (habituation) to the second click observed in healthy controls. Reprinted and modified from Life Sciences, Vol. 61, 5, Gilette et al., Combat veterans with posttraumatic stress disorder exhibit decreased habituation of the P1 midlatency auditory evoked potential, p. 1426, ©1997 with permission from Elsevier. Reprinted and modified from Depression and Anxiety, Vol. 9, Skinner et al., Reduced sensory gating of the P1 potential in rape victims and combat veterans with posttraumatic stress disorder, p. 126, ©1999 with permission from Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc. Reprinted and modified from Psychophysiology, Vol. 39, Metzger et al., Event-related potentials to auditory stimuli in female Vietnam nurse veterans with posttaumatic stress disorder, p. 54, ©2002 with permission from Cambridge University Press.

[1] Non-PTSD trauma-exposed sample indicates that the sample was exposed to the index trauma of the study (e.g., combat, sexual assault, etc.) but did not have PTSD.

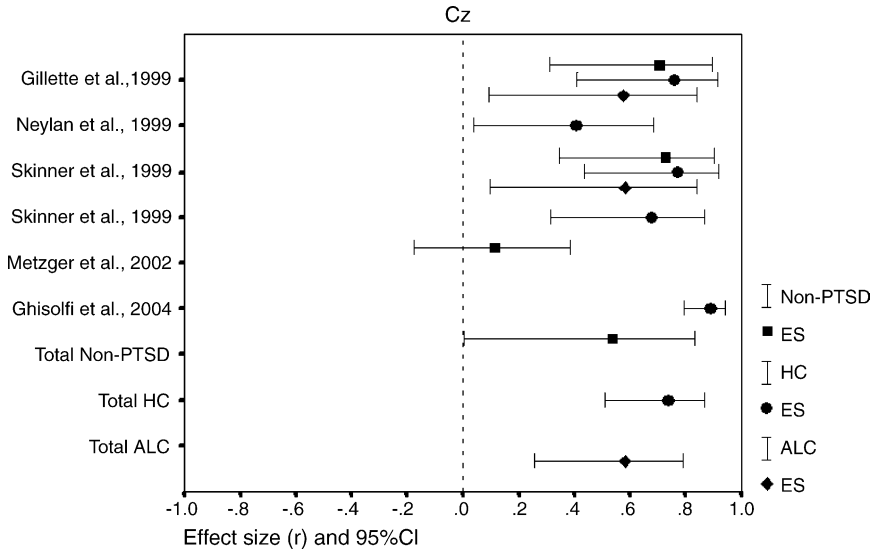

Fig. 2. P50 auditory sensory gating studies effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and non-PTSD groups. Non-PTSD: trauma-exposed, no PTSD; HC: healthy controls; ALC: alcoholic use disorder.

($N = 30$) also found significantly reduced P50 suppression in the PTSD group.

3.1.1. Brief summary of P50 auditory sensory gating results

The meta-analyses found that persons with PTSD reliably exhibited a reduction in the P50 habituation response compared to non-PTSD trauma groups, non-trauma controls, and alcoholic without PTSD. Of the six studies reviewed, only study #5 (Metzger et al., 2002), a comparison of female combat nurses with PTSD and a non-PTSD trauma-exposed control group, reported null results. It is not clear whether gender contributed to these null findings, as study #4 (Skinner et al., 1999) found significant results in a female sample compared to non-trauma controls. However, these two studies differed along a number of dimensions (type of comparison control group, medication use, and index trauma [combat versus sexual assault]) and therefore the reasons for the disparate findings are unclear.

3.2. P200 amplitude in augmenting-reducing paradigm (A/R)

Five studies investigated the P200 in the auditory A/R paradigm. Study demographics and methods are presented in Appendix A. Fig. 3 presents an example of ERP's superimposed for different tone intensities and P200 slopes obtained by different studies. The ES for each study is shown in Fig. 4. In four of the studies, PTSD was compared with a non-PTSD trauma group (ES range of −.51 to .35). Because only one study (Lewine et al., 2002) compared a PTSD group to non-trauma controls, this study was excluded from the meta-analysis but its ES is presented in Fig. 4.

Table 2 presents the statistics for the meta-analysis. For the meta-analysis comparing PTSD with a non-PTSD trauma population, the initial meta-analysis ($N = 271$) found no significant groups differences. However, the analysis of study heterogeneity was significant (see τ^2 and χ^2, Table 2). Cluster analysis revealed two homogenous subsamples:

Table 1
Meta-analyses of P50 findings: PTSD related to control groups

PTSD vs.	k	N	r_w	CI_w		τ^2	χ^2	Orwin's fail safe N
1. Non-PTSD trauma exposed	3	78	.538*	.004	.833	.218[a]	9.74[a]	5
1a. Non-PTSD trauma exposed (Study 5 excluded)	2	30	.719*	.700	.730	0	.017	5
2. Healthy Controls	5	111	.739*	.509	.870	.135[a]	13.92[a]	13
2a. Healthy Controls (Study 2 excluded)	4	84	.801*	.682	.889	.006	4.32	12
3. Non-PTSD Alcoholics	2	30	.580*	.257	.787	0	.002	4

Note: k: number of studies, r_w: weighted r, CI_w: 95% confidence interval for weighted r, τ^2: between trials variance; χ^2: within trials variance; Non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.

* $p < .05$.

[a] Heterogeneity.

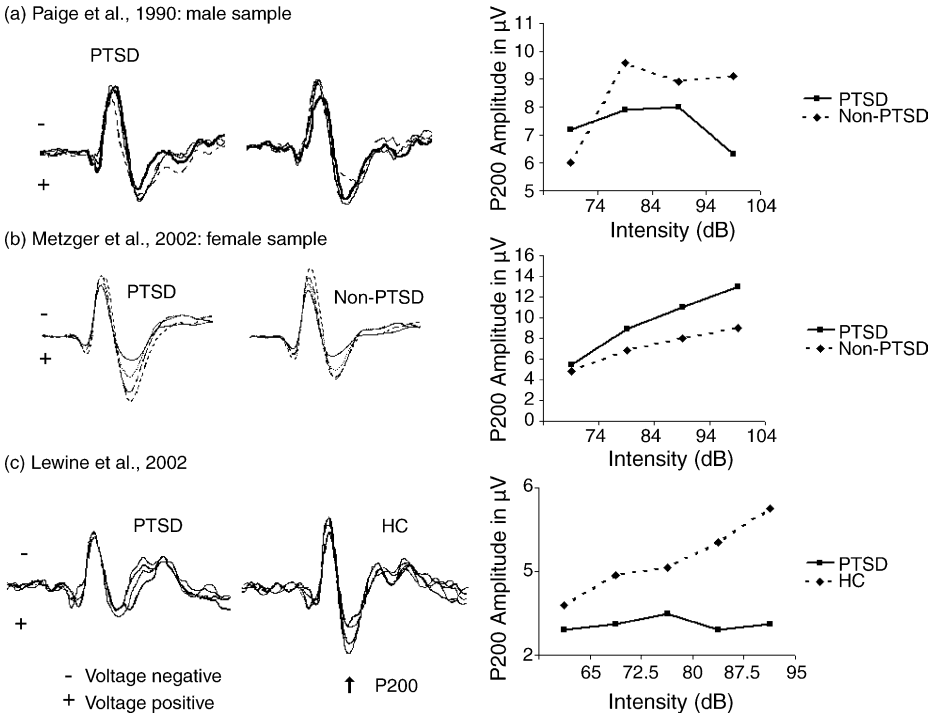

Fig. 3. P200 augmenting/reducing paradigm example ERPs (left) and slopes (right) to acoustic stimuli of increasing intensity. In the left panel, different lines in the A/R waveforms reflect different intensities. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls. Reprinted and modified from Biological Psychiatry, Vol. 27, Paige et al., Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans, p. 423, 425, ©1990 with permission from The Society of Biological Psychiatry. Reprinted and modified from Psychophysiology, Vol. 39, Metzger et al., Event-related potentials to auditory stimuli in female Vietnam nurse veterans with posttaumatic stress disorder p.58, ©2002 with permission from Cambridge University Press. Reprinted and modified from American Journal of Psychiatry, vol. 159, Lewine et al., Abnormal stimulus-response intensity functions in posttraumatic stress disorder: an electrophysiological investigation, p. 1691, 1692, ©2002 with permission from American Psychiatric Association.

Cluster 1 (Paige et al., 1990; Lewine et al., 1997); and Cluster 2 (McPherson et al., 1997; Metzger et al., 2002), and a separate meta-analysis was performed for each cluster. The meta-analysis for Cluster 1 ($N = 80$) revealed a significantly reduced P200 in the PTSD group compared to non-PTSD trauma controls in a homogenous male sample. However, the meta-analysis for Cluster 2 ($N = 191$) revealed a significantly enhanced P200 in the PTSD group compared to non-PTSD

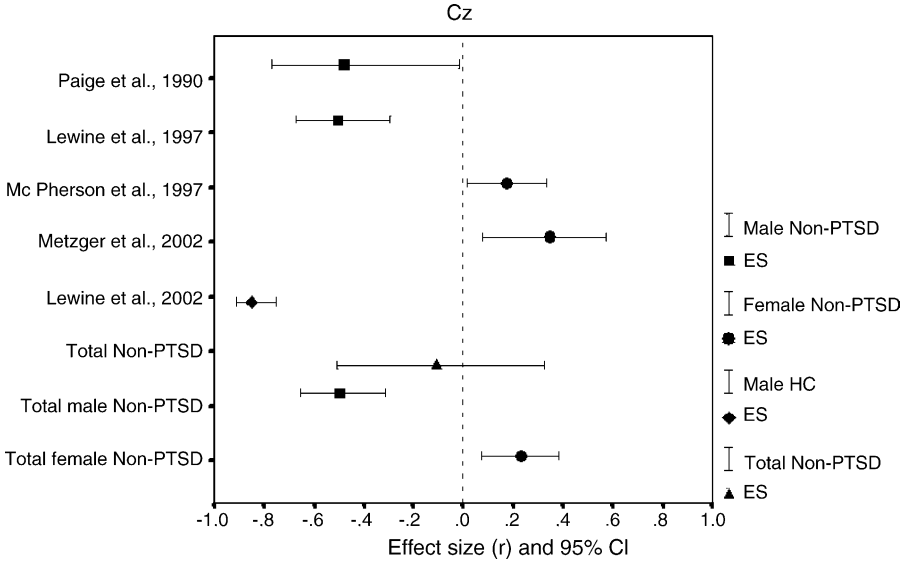

Fig. 4. P200 augmenting/reducing studies effect sizes (ES) and 95% confidence intervals (CI) for comparisons of P200 slopes in PTSD and non-PTSD groups. Negative ESs indicate smaller P200 to tones of increasing intensity in PTSD groups. Male: Samples only comprised males; female: sample composed of females (primarily) and children of both genders. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls.

Table 2
Meta-analyses of P200 findings: PTSD related to control groups

PTSD vs.	Gender	k	N	r_w	CI_w		τ	χ^2	Orwin's fail safe N
1. Non-PTSD trauma exposed	Female and male	4	271	−.111	−.509	.326	.185[a]	33.12[a]	−2
1a. Non-PTSD trauma exposed	Male	2	80	−.500[*]	−.651	−.311	0	.016	3
1b. Non-PTSD trauma exposed	Female and male	2	191	.231[*]	.069	.381	.003	1.21	0

Note: k: number of studies, r_w: weighted r, CI_w: 95% confidence interval for weighted r, τ^2: between trials variance; χ^2: within trials variance; non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.
[*] $p < .05$.
[a] Heterogeneity.

trauma controls in a sample of female and mixed gender non-adult subjects.

3.2.1. Brief summary of P200 amplitude A/R paradigm results

The results of the meta-analyses revealed significant gender effects on the P200 amplitude in the A/R paradigm. Compared to non-PTSD trauma controls, adult males reliably exhibited a lower P200 slope to sounds of increasing intensity. The one study that was excluded from the analysis (Lewine et al., 2002) also found that males with PTSD exhibited a lower P200 slope to sounds of increasing intensity compared to non-trauma controls, with a large ES of $r = -.85$. These findings suggest that in adult males with PTSD, sensory gating systems may be ''tuned'' protectively to mitigate overload (Pritchard, 1986).

In contrast, the results of the meta-analysis for Cluster 2, whose sample was composed of both genders and included children as well as adults, demonstrated an augmenting P200 response to sounds of increasing intensity, suggesting a sensory system ''tuned'' towards sensation seeking. Moreover, in the study by Metzger et al., 2002, (female combat nurses), P200-amplitudes were significantly positively correlated with PTSD symptom severity. These findings were consistent with those of Bruneau et al., 1986, who found a gender effect in frontal auditory-evoked potential augmenting-reducing in healthy controls, with females showing higher augmentation than males. However, the finding of augmented P200 in Cluster 2 should be interpreted with caution, as the two studies in this cluster were heterogeneous in several respects (age, gender, methodology), and the small sample size did not permit subgroup analyses. Moreover, the male combat veterans with PTSD that comprised the PTSD sample of Cluster 1 may differ from the sample in Cluster 2 in other respects, and the disparate findings may have been due to variables other than gender, or to variables that interacted with gender.

3.3. P3b in classical or modified oddball paradigms to target stimuli

3.3.1. P3b amplitude to neutral targets with neutral (non-emotional) or no distractors

Of the ten published reports of P3b amplitude to neutral target-stimuli presented with neutral distractors or no distractors, six compared PTSD patients with non-PTSD trauma controls, four used non-traumatized control groups, and one study compared PTSD patients with and without medication. Study demographic and methods are presented in Appendix A. Fig. 5 depicts ERPs elicited in response to neutral target stimuli in the context of no or neutral distracting stimuli, measured from different scalp electrode positions: frontal (Fz), central (Cz) and parietal (Pz). Meta-analyses were performed for ERP measurement according to electrode site. Fig. 6 displays the ES for each study.

Table 3 presents the statistics for the meta-analysis. *For site Fz, PTSD versus non-PTSD trauma group*, the initial meta-analysis ($N = 106$) was not significant; however, the analysis of study heterogeneity was significant (see τ^2 and χ^2, Table 3). Further analysis of a homogenous subset of two studies (Blomhoff et al., 1998; Metzger et al., 2002) found no significant group differences. *For Cz, PTSD versus non-PTSD trauma group*, the initial meta-analysis ($N = 132$) was not significant. The analysis of study heterogeneity was significant (see τ^2 and χ^2, Table 3), but no homogenous subsamples could be identified for further analyses.

For site Pz, PTSD versus non-PTSD trauma group, the initial meta-analysis ($N = 123$) was not significant; however, study heterogeneity was significant (see τ^2 and χ^2, Table 3). Further analysis yielded a homogenous subset by excluding the study by Metzger et al., 2002. The meta-analysis of this sample ($N = 56$) revealed a significantly reduced P300 at Pz to neutral target stimuli in the PTSD group. The analysis was repeated, excluding the study by Blomhoff et al., 1998, which used a different methodology, but the results remained significant, weighted $r = -.47$; 95% CI = −.58 to −.36, fail safe N (critical r of .10) = 3. *Meta-analyses of studies comparing PTSD versus non-trauma controls* (homogenous samples) found significantly reduced P300 to neutral target stimuli in PTSD for all three electrode positions.

3.3.2. P3b amplitude to neutral (non-emotional) target stimuli with non-neutral (trauma-related, novel and emotional, non-trauma-related) distractors

Table 3 presents the statistics for the meta-analysis. *For site Fz, PTSD versus non-PTSD trauma group*, the initial meta-analysis ($N = 100$) revealed significantly increased P300 to target stimuli in the context of trauma-related distractors. However, the analysis of study heterogeneity was significant (see τ^2 and χ^2, Table 3). A homogenous subset of three studies (Attias et al., 1996a, 1996b; Bleich et al., 1996) that utilized visual stimuli (pictures) was

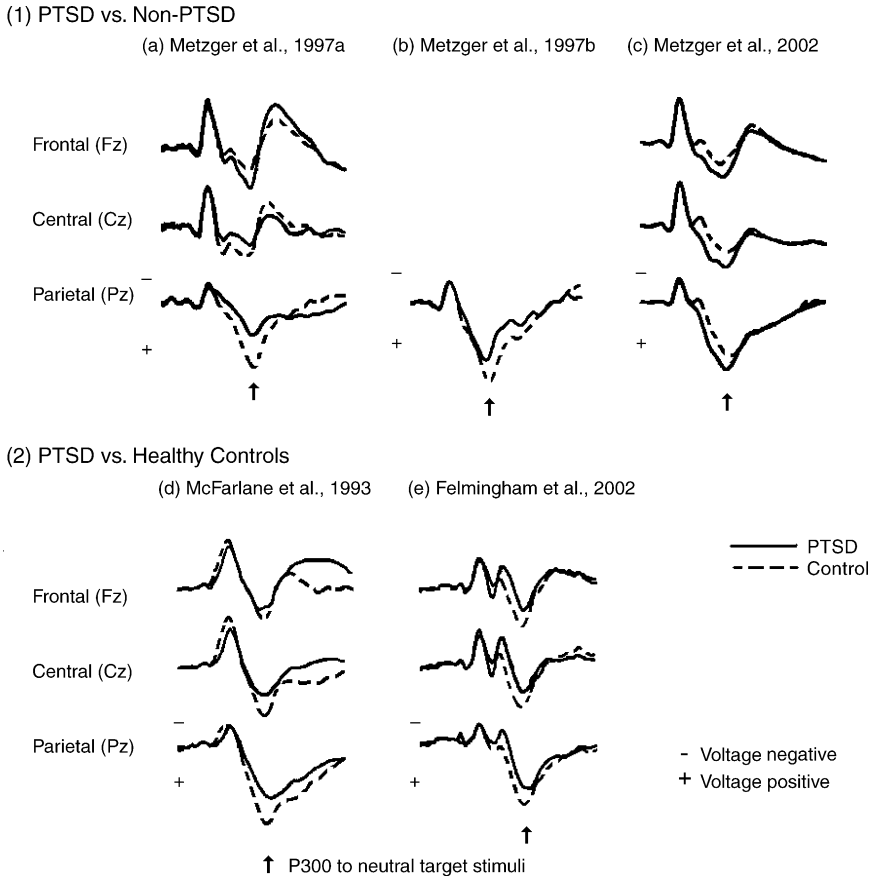

Fig. 5. Example ERPs to auditory oddball targets in detection tasks with neutral or no distractors. A P3b positive deflection occurs at around 300 ms after presentation of the target stimulus. Reprinted and modified from Biological Psychiatry, Vol. 34, McFarlane et al., Abnormal stimulus processing in posttraumatic stress disorder, p. 315, ©1993 with permission from The Society of Biological Psychiatry. Reprinted and modified from Biological Psychiatry, Vol. 42, Metzger et al., Auditory event-related potentials to tone stimuli in combat-related posttraumatic stress disorder, p. 1010, 425, ©1997 with permission from The Society of Biological Psychiatry. Reprinted and modified from Psychiatry Research, Vol. 109, Felmingham et al., Event-related potential dysfunction in posttraumatic stress disorder: the role of numbing, p. 176, ©2002 with permission from Elsevier. Reprinted and modified from Annals of the New York Academy of Sciences, Vol. 821, Metzger et al., Evidence for diminished P3 amplitudes in PTSD, p. 502, ©1997 with permission from the New York Academy of Sciences. Reprinted and modified from Psychophysiology, Vol. 39, Metzger et al., Event-related potentials to auditory stimuli in female Vietnam nurse veterans with posttaumatic stress disorder, p. 55, ©2002 with permission from Cambridge University Press.

identified. The result of the meta-analysis of this subgroup ($N = 80$) revealed that the PTSD group showed increased P300 to neutral stimuli in the context of trauma-related distractors compared to non-PTSD trauma controls. *At Cz, the meta-analysis comparing PTSD versus non-PTSD trauma group* ($N = 134$) also found increased P300 to target stimuli in the context of trauma-related stimuli in PTSD in a homogenous sample. At both electrode positions (Fz and Cz), there were no significant findings of between-group differences in P300 amplitude to neutral stimuli in the context of non-trauma-related emotional and novel stimuli. At site Pz, there were no significant group differences in P300 to neutral stimuli in the context of any type of distractor stimulus.

3.3.3. P3b latency to target stimuli in the context of distractors

Study ESs and the statistics of the meta-analyses are also shown in Fig. 7 and Table 3, respectively. *Meta-analysis comparing PTSD versus non-PTSD trauma group*, (homogenous sample) found no significant effects for the latency to neutral target stimuli in the context of neutral or trauma-related distractors for any electrode site. The effects of emotional distractors were only measured for electrode site Cz, and the meta-analysis was also not significant. *Meta-analysis comparing PTSD versus non-traumatized controls* ($N = 71$, homogenous sample) revealed a significant longer latency to neutral target stimuli in the context of neutral distractors for both the Cz and Pz electrode sites, with non-significant results for the Fz electrode site.

3.3.4. Brief summary of P3b studies

The results of the meta-analyses demonstrated that persons with PTSD exhibited reduced P3b amplitude to neutral target stimuli in the context of neutral distractors or no distractors, compared to non-traumatized controls, at all electrode sites, and significantly longer P3b latencies measured at central and parietal electrode sites (but not

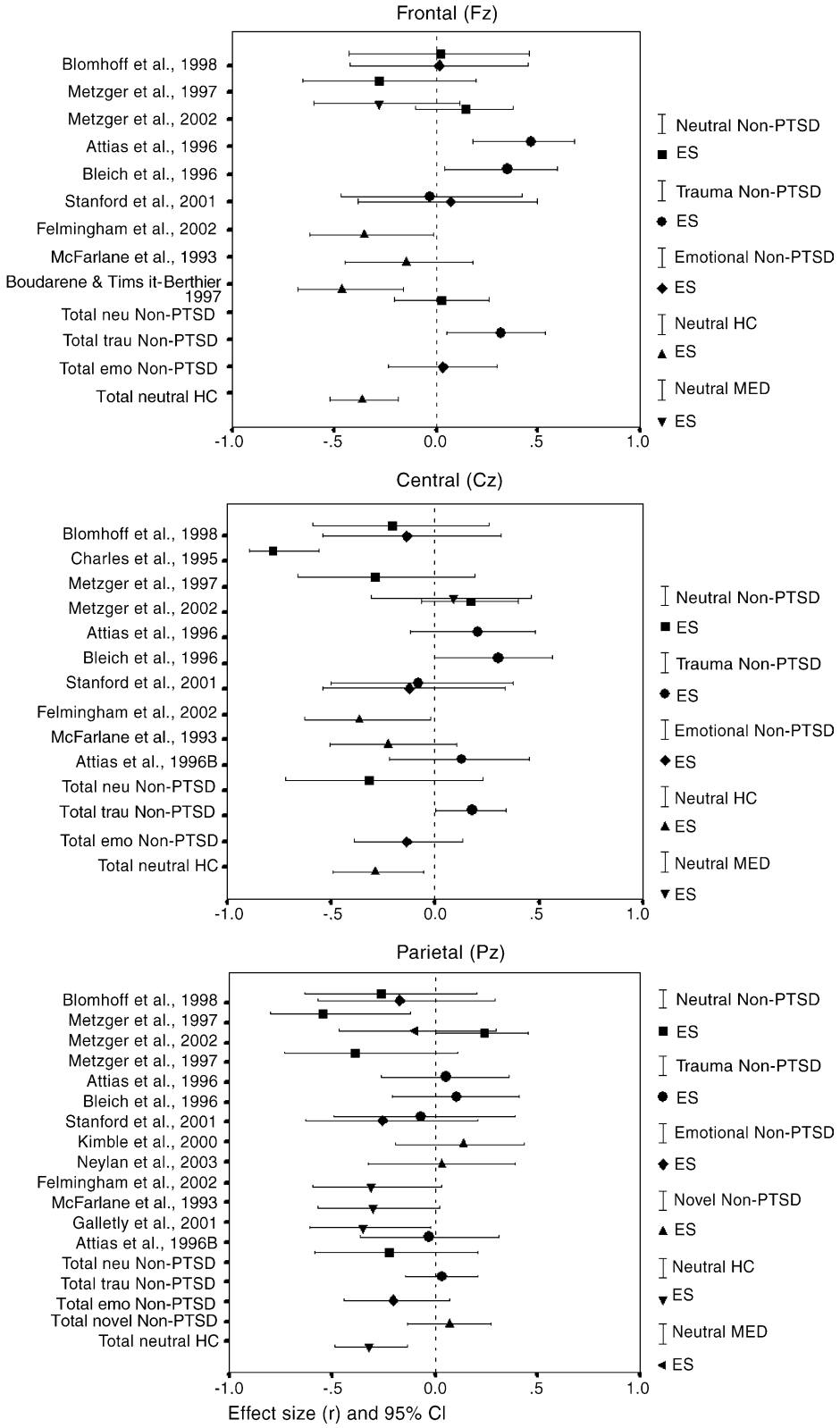

Fig. 6. P3b amplitude to target stimuli (in the context of different types of distractors) in oddball tasks effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and non-PTSD groups, plotted per scalp region (frontal, central, parietal). Negative ESs indicate smaller P300 amplitudes in PTSD groups. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls; MED: medicated PTSD sample. Neutral: neutral/no distractors; trauma: trauma-related distractors; emotional: emotional, non-trauma-related distractors; novel: novel distractors.

Table 3
Meta-analyses of P3b to targets findings: PTSD related to control groups

P300	Electrode position	Stimulus type	PTSD vs.	*k*	*N*	r_w	CI_w		τ	χ^2	Orwin's fail safe *N*
Amplitude	Fz	Neutral	1. Non-PTSD trauma exposed	3	106	.031	−.203	.262	.009[a]	2.46	−3
			1a. Non-PTSD trauma exposed	2	87	.120	−.097	.326	0	.219	−1
	Cz	Neutral	1.Non-PTSD trauma exposed	4	132	−.320	−.716	.232	.292[a]	25.45[a]	2
	Pz	Neutral	1. Non-PTSD trauma exposed	4	123	−.221	−.581	.212	.151[a]	13.21[a]	0
			1a. Non-PTSD trauma exposed	3	56	−.401*	−.611	−.139	0	.965	3
	Fz	Neutral	2. Healthy Controls	4	144	−.362*	−.519	−.182	.009	3.94	3
	Cz	Neutral	2. Healthy Controls	2	71	−.287*	−.492	−.052	0	3.80	1
	Pz	Neutral	2. Healthy Controls	2	71	−.307*	−.508	−.074	0	.002	1
	Fz	Trauma	3. Non-PTSD trauma exposed	3	100	.315*	.054	.536	.023[a]	3.35	2
			3a. Non-PTSD trauma exposed	2	80	.410*	.205	.581	0	.350	2
	Cz	Trauma	3. Non-PTSD trauma exposed	4	134	.179*	.004	.344	0	1.94	0
	Pz	Trauma	3. Non-PTSD trauma exposed	4	134	.034	−.143	.208	0	.509	−3
	Fz	Emotional	4. Non-PTSD trauma exposed	3	60	.037	−.233	.302	0	.35	−2
	Cz	Emotional	4. Non-PTSD trauma exposed	3	60	−.135	−.389	.137	0	.81	−1
	Pz	Emotional	4. Non-PTSD trauma exposed	3	60	−.199	−.443	.072	0	.092	0
	Pz	Novel	5. Non-PTSD trauma exposed	3	69	.048	−.196	.287	0	.669	−2
Latency	Fz	Neutral	1.Non-PTSD trauma exposed	2	86	−.017	−.232	.199	0	.254	−2
	Fz	Trauma	2. Non-PTSD trauma exposed	2	60	.113	−.279	.472	.043[a]	2.01	−1
	Cz	Neutral	1.Non-PTSD trauma exposed	4	132	.092	−.086	.265	0	.174	−2
	Cz	Trauma	2. Non-PTSD trauma exposed	2	60	−.087	−.340	.178	0	.886	−1
	Cz	Emotional	3. Non-PTSD trauma exposed	3	60	−.143	−.396	.130	0	.786	−1
	Pz	Neutral	1.Non-PTSD trauma exposed	2	86	−.136	−.342	.082	0	.936	−1
	Pz	Trauma	2. Non-PTSD trauma exposed	2	60	−.028	−.602	.564	.190[a]	5.43	−2
	Fz	Neutral	4. Healthy Controls	2	71	.201	−.039	.420	0	.036	0
	Cz	Neutral	4. Healthy Controls	2	71	.252*	.014	.463	0	.060	1
	Pz	Neutral	4. Healthy Controls	2	71	.347*	.119	.541	0	.112	1

Note: *k*: number of studies, r_w: weighted *r*, CI_w: 95% confidence interval for weighted *r*, τ^2: between trials variance; χ^2: within trials variance; non-PTSD trauma exposed refers to those exposed to the study index trauma, but without PTSD.

* $p < .05$.

[a] Heterogeneity.

frontal) in response to neutral stimuli presented in the context of neutral distractors. The inverse amplitude-latency relationship is consistent with previous findings by Polich and Comerchero (2003) and Polich et al. (1997). The weaker amplitude-latency relationship at frontal sites may have been due to task characteristics, as the strongest correlations have been found when target-standard stimuli are harder to discriminate and distractors are highly discrepant (Polich et al., 1997).

The reduced amplitudes and longer latencies appear to be associated with trauma exposure rather than PTSD, as there were no significant group differences between trauma populations with and without PTSD. The results suggest that individuals exposed to a traumatic event may exhibit altered information processing of neutral information even if they do not develop PTSD. A reduced P3b amplitude in response to neutral stimuli in the context of neutral or no distractors elicited at parietal (Pz) scalp electrodes did differentiate between PTSD and non-PTSD trauma controls, which suggests that reduced processing of neutral information in parietal cortex in particular may be associated with PTSD. The meta-analyses also found that persons with PTSD reliably showed enhanced processing (increased P3b amplitude) of neutral targets in the context of trauma-related distractors, but not distractors that were merely novel, or emotional, but not trauma-related. As amplitude magnitudes may also vary according to task difficulty and the distinctness of distractors (Polich et al., 1997), this finding may represent increased difficulty discriminating targets and standard stimuli and/or the greater salience of trauma-related distractors for the PTSD group. Taken together, the findings suggest that information processing in PTSD patients and trauma populations may be enhanced or attenuated, depending upon the context of the stimuli.

3.4. P3a in classical or modified oddball paradigms to distractor stimuli

3.4.1. P3a amplitude to neutral distractor stimuli

Of the five published studies reporting P300 amplitude to non-emotional neutral distractors, three compared PTSD patients with non-PTSD trauma controls, one compared PTSD patients with non-trauma controls, and one compared PTSD groups with and without medication. Study demographic and methods are presented in Appendix A. Fig. 8

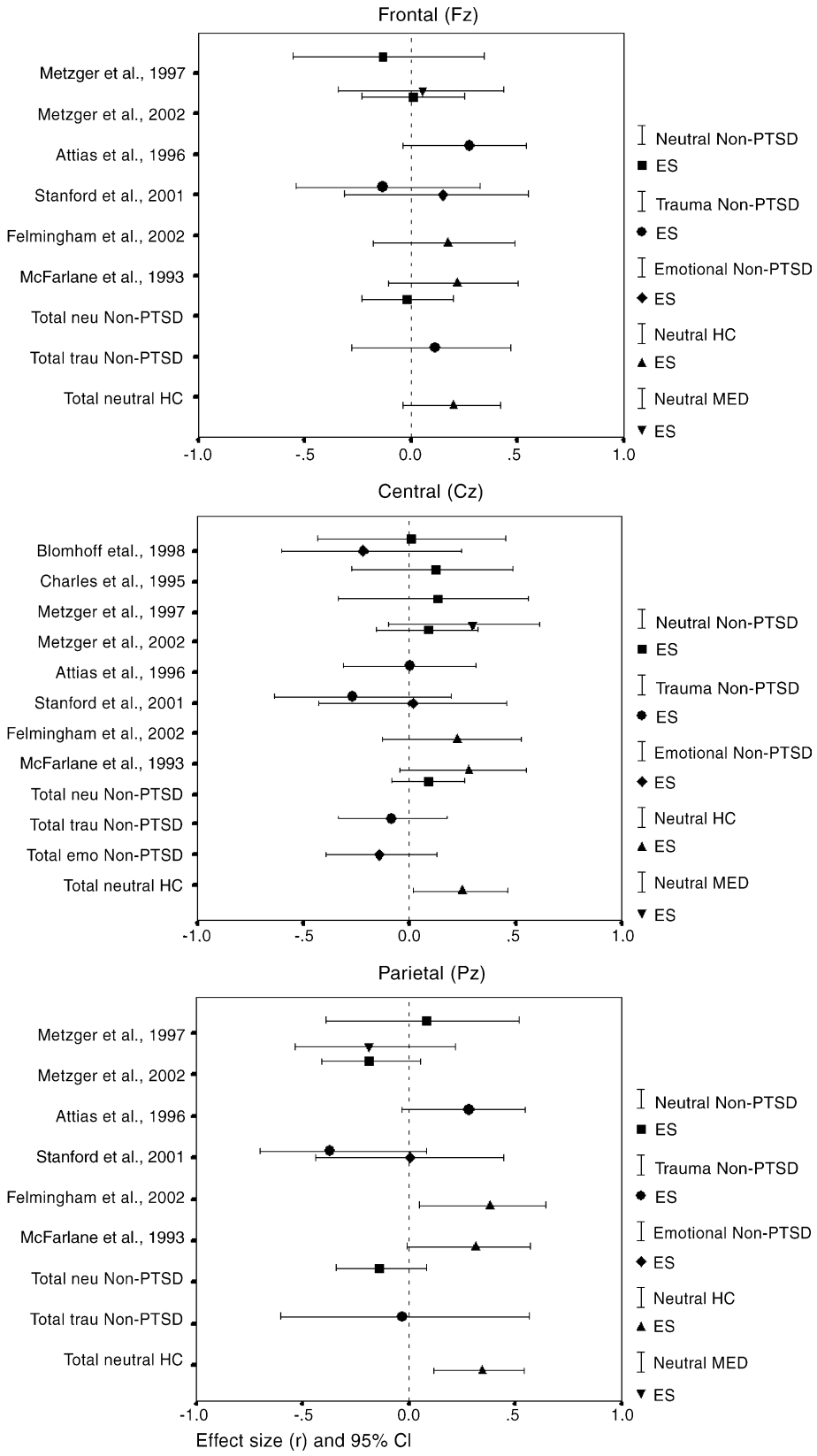

Fig. 7. P3b latency to target stimuli (in the context of different types of distractors) in oddball tasks effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and non-PTSD groups, plotted per scalp region (frontal, central, parietal). Negative ESs indicate shorter P300 latency in PTSD groups. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls; MED: medicated PTSD sample. Neutral: neutral/no distractors; trauma: trauma-related distractors; emotional: emotional, non-trauma-related distractors; novel: novel distractors.

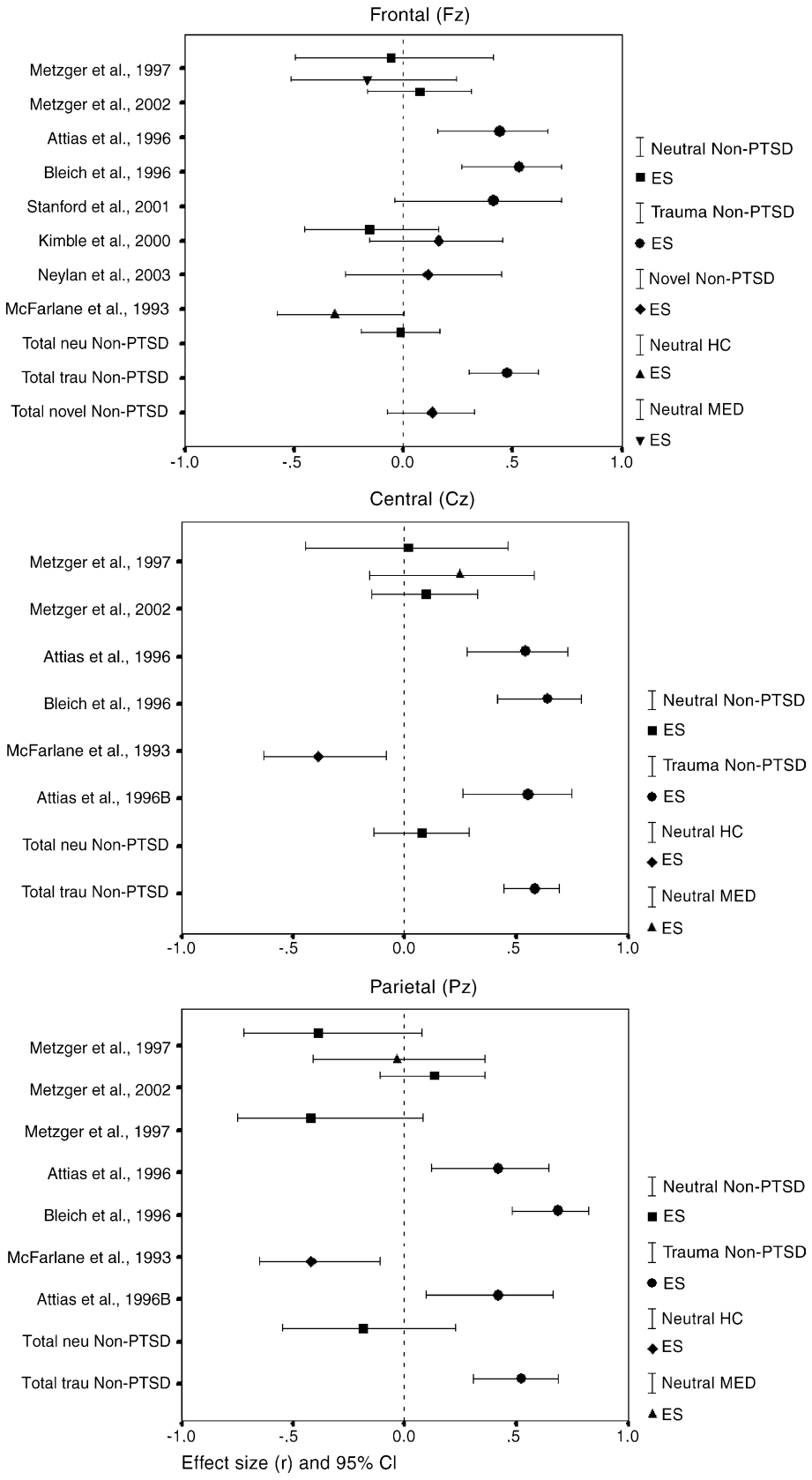

Fig. 8. P3a amplitudes to different types of distractors in oddball tasks effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and non-PTSD groups, plotted per scalp region (frontal, central, parietal). Negative ESs indicate smaller P300 amplitudes in PTSD groups. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls; MED: medicated PTSD sample. Neutral: neutral/no distractors; trauma: trauma-related distractors; emotional: emotional, non-trauma-related distractors; novel: novel distractors.

Table 4
Meta-analyses of P3a to distractor findings: PTSD related to control groups

P300	Electrode Position	Stimulus Type	PTSD vs.	*k*	*N*	r_w	CI_w		τ	χ^2	Orwin's fail safe N
Amplitude	Fz	Neutral	1. Non-PTSD trauma exposed	3	125	−.014	−.194	.166	0	1.34	−3
	Cz	Neutral	1. Non-PTSD trauma exposed	2	86	.079	−.139	.289	0	.087	−1
	Pz	Neutral	1. Non-PTSD trauma exposed	3	103	−.189	−.548	.228	.095[a]	6.32[a]	0
			1a. Non-PTSD trauma exposed	2	36	−.402[*]	−.655	−.068	0	.008	2
	Fz	Trauma	1. Non-PTSD trauma exposed	3	100	.476[*]	.303	.619	0	.394	4
	Cz	Trauma	1. Non-PTSD trauma exposed	3	114	.581[*]	.440	.694	0	.509	6
	Pz	Trauma	1. Non-PTSD trauma exposed	3	114	.524[*]	.308	.680	.026[a]	3.78	6
			1a. Non-PTSD trauma exposed	2	74	.418[*]	.204	.593	0	.004	2
	Fz	Novel	Non-PTSD	2	69	.129	−.117	.360	0	.115	−1
Latency	Fz	Neutral	Non-PTSD	2	86	.004	−.212	.220	0	.310	−2
	Cz	Neutral	Non-PTSD	2	86	.050	−.168	.262	0	.004	−2
	Pz	Neutral	Non-PTSD	2	86	−.043	−.256	.175	0	.001	−2

Note: *k*: number of studies, r_w: weighted *r*, CI_w: 95% confidence interval for weighted *r*, τ^2: between trials variance; χ^2: within trials variance.
[*] $p < .05$.
[a] Heterogeneity.

displays each study's ES and Table 4 presents the statistics of the meta-analysis.

The *meta-analysis comparing PTSD versus non-PTSD trauma group* found no significant effects at Fz or Cz in a homogenous sample. At electrode site Pz, the initial analysis also found no significant effects, but study heterogeneity was significant (see τ^2 and χ^2, Table 4). A meta-analysis with a homogenous subsample ($N = 36$) consisting of two studies (Metzger et al., 1997a; Kimble et al., 2000) revealed significantly lower P300 amplitudes to neutral distractors in PTSD patients compared to the non-PTSD trauma group.

3.4.2. P3a amplitude to trauma-related distractors

Fig. 9 depicts example ERPs to trauma-related distractor stimuli. Four studies examined P300 elicited by trauma-related distractors in a visual oddball paradigm. In three of them, color pictures (neutral, emotional and trauma-related) were presented (study #17, #18, # 21, see Appendix A), and in one study words were presented (study #20). In all studies, PTSD was compared with a non-PTSD trauma control group. Study demographic and methods are presented in Appendix A, and the ES for each study is shown in Fig. 8. Meta-analysis was performed for different scalp regions: frontal (Fz), central (Cz) and parietal (Pz). Table 4 presents the statistics of the meta-analysis.

The meta-analysis revealed significantly higher P300 amplitudes to trauma-related distractor stimuli in *PTSD versus non-PTSD trauma group at Fz, Cz and Pz*. For site Pz, study heterogeneity was also significant (see τ^2 and χ^2, Table 4). A meta-analysis for a homogenous subsample ($N = 74$) consisting of two studies (Attias et al., 1996a, 1996b) revealed significantly higher P300 amplitudes to trauma-related distractor stimuli in the PTSD group compared to the non-PTSD trauma group.

3.4.3. P3a amplitude to novel distractors

Two studies compared P3a amplitudes in response to novel (but not trauma-related) distractors elicited at electrode site Fz, in PTSD versus non-PTSD trauma controls. Study demographic and methods are presented in Appendix A, study ESs are shown in Fig. 8, and the statistics of the meta-analysis are presented in Table 4. The meta-analysis ($N = 99$, homogenous sample) revealed no significant between-group differences.

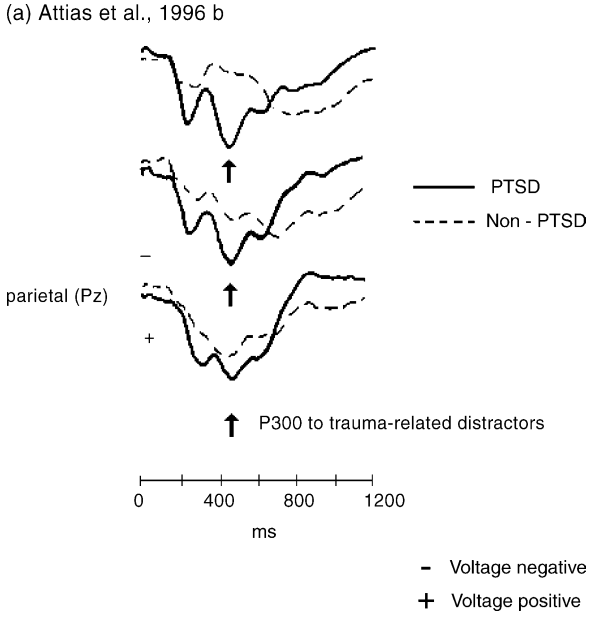

Fig. 9. Example ERPs to visual oddball targets in detection task with trauma-related distractors. Reprinted and modified from Biological Psychiatry, 5, Attias et al., Event-related potentials in post-traumatic stress disorder of combat origin, p. 377, ©1996 with permission from The Society of Biological Psychology.

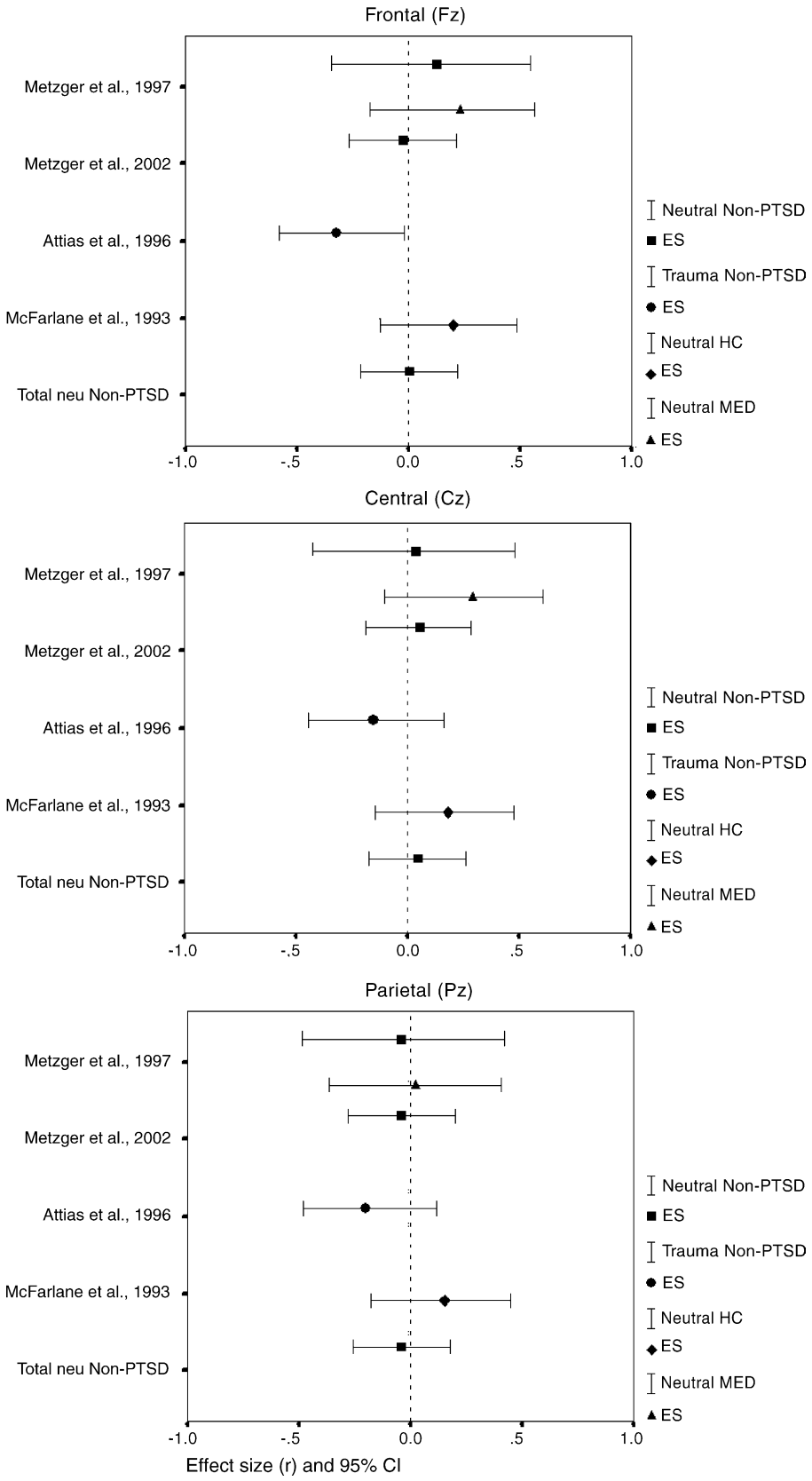

Fig. 10. P3a latency to different types of distractors in oddball tasks effect sizes (ES) and 95% confidence intervals (CI) for comparisons of PTSD and non-PTSD groups, plotted per scalp region (frontal, central, parietal). Negative ESs indicate shorter P300 latency in PTSD groups. Non-PTSD: exposed to index trauma, but no PTSD; HC: healthy controls; MED: medicated PTSD sample. Neutral: neutral/no distractors; trauma: trauma-related distractors; emotional: emotional, non-trauma-related distractors; novel: novel distractors.

3.4.4. P3a latency to neutral distractor stimuli

Two studies compared P300 latency to neutral distractor stimuli in persons with *PTSD versus non-PTSD trauma controls*. Study demographic and methods are presented in Appendix A, study ESs are shown in Fig. 10, and the statistics of the meta-analysis are presented in Table 4. The meta-analysis ($N = 86$, homogenous sample) found no significant effects. For each of the other types of distractor stimuli, only single studies were located, and thus no meta-analyses were performed. However, the ES for each study is also presented in Fig. 10.

3.4.5. Brief summary of P3a Studies

The meta-analyses of studies that examined P3a responses elicited by trauma-related distractors found that persons with PTSD reliably exhibited higher amplitudes compared to non-PSTD trauma controls. This finding was consistent with the attention bias towards trauma-related stimuli often reported in PTSD (cf. Buckley et al., 2000). In contrast, the meta-analyses found no significant group differences in ERPs elicited by novel distractors. This finding was contrary to the hypothesized increased P3a response in PTSD patients that has been interpreted as being related to hyperarousal. However, it should be noted that one study included in this meta-analysis included medicated patients, which may have reduced their hyperarousal. It is also possible that general hyperarousal is associated in varying degrees with trauma exposure, and group differences might have emerged if the studies had utilized non-trauma control groups.

The findings for ERP to neutral distractors were mixed, with no significant group differences in P3a latency, and, contrary to hypothesis, reduced P3a amplitude elicited at parietal (Pz) sites rather than the expected enhanced response at frontal sites, also believed to be associated with hyperarousal. This meta-analysis included a study with medicated patients (Metzger et al., 1997a), which may have been a factor, and also did not include studies with non-traumatized controls. However, Katayama and Polich (1998) found that for easy discrimination tasks, healthy controls exhibited the largest P3a amplitudes at parietal sites, whereas difficult discrimination tasks with highly discrepant distractors evoked the largest P3a amplitudes at frontal sites. Therefore, it is possible that the restriction of effects to the parietal site was due to the ease of the discrimination task, whereas the relatively reduced P3a amplitude in the PTSD group represented the attenuated processing of neutral, and hence less threat-relevant and salient, distractors. This latter interpretation is supported by the results of the P3b meta-analyses, which found reduced P3b amplitudes to neutral target stimuli in the context of neutral distractors or no distractors in persons with PTSD compared to non-traumatized controls at all electrode sites, and compared to non-PTSD trauma controls at the Pz site.

4. Discussion

In accordance with our hypotheses, meta-analyses revealed reduced P50 suppression in persons with PTSD compared to healthy controls, non-PTSD traumatized controls, and alcoholics. However, contrary to hypothesis, we found no generalized P200 reducing responses in the augmenting-reducing (A/R) paradigm, but instead identified gender as a potential moderator variable. We did find some evidence that traumatized individuals exhibit reduced P3b amplitudes and prolonged latencies in response to neutral target stimuli in the context of neutral or no distractors. These differences appeared to be primarily related to trauma exposure rather than the presence of PTSD. However, at parietal cortex (site Pz), persons with PTSD did show reduced P3b amplitudes in response to neutral targets and reduced P3a in response to neutral distractors, compared to non-PTSD trauma controls. The meta-analyses revealed no evidence of increased P3a amplitudes in response to novel or neutral distractors, and instead revealed reduced P3a amplitudes to neutral distractors at parietal cortex (site Pz). We did find evidence increased of P3a amplitudes in response to trauma-related distractors, as well as increased P3b amplitudes in response to neutral target stimuli when distractors were trauma-related.

4.1. P50 auditory sensory gating paradigm: Reduced sensory filtering in PTSD?

In five of six studies analyzed, persons with PTSD showed reduced P50 suppression compared to trauma-exposed non-PTSD groups and non-traumatized controls. One study (Metzger et al., 2002) failed to find differences in P50 suppression between female combat nurses with and without PTSD. As noted, Skinner et al. (1999) found reduced P50 suppression in female sexual assault survivors with PTSD compared to non-trauma exposed controls, but this study did not include a trauma-exposed comparison group. Metzger et al. (2002) noted that the mean P50 ratio of their comparison group was higher than reported norms for females, and that the elevated ratios did not appear to be related to trauma exposure, as studies comparing trauma and non-trauma exposed males have not observed this. Citing Waldo et al. (1992) finding that P50 ratios are sensitive to the novelty of the testing situation, Metzger et al. (2002) further noted that the P50 task was the first to be completed in their study. However, Hetrick et al. (1996) also found increased P50 ratios in females, and the lack of elevated P50 ratios due to trauma exposure in males does not rule out the possibility that gender and trauma exposure interact to influence baseline P50 ratios or P50 suppression. Future P50 studies should continue to explore gender effects.

Reduced P50 suppression has been hypothesized to index deficits in filtering out irrelevant sensory stimuli, presumably due to the dysfunction of central inhibitory processes involved in attention modulation (White and Yee, 1997). Regulating sensory input involves many systems; however, research supports the involvement of the brain's reticular

activating system (RAS) in P50 suppression (Erwin and Buchwald, 1986). Studying a rat analogue of the P50, the P13, Miyazato et al. (2000) found that immobilization stress reduced P13 suppression, and that the effect was mediated by corticotrophin releasing factor (CRF) and noradrenalin (alpha-2 adrenergic projections) in RAS nuclei (the locus coeruleus and the pedunculopontine nucleus). In humans, noradrenalin-mediated increases in locus coeruleus activity also reduce P50 suppression (Adler et al., 1994; Fein et al., 1996). PTSD patients also show dysregulated noradrenergic functioning (Southwick et al., 1997) including reductions in platelet alpha-2 adrenergic receptors (Perry et al., 1987), and abnormalities in hypothalamic-pituitary-axis functioning that involve CRF (cf. Yehuda et al., 1991).

The findings of the meta-analysis and those cited above support a relationship between reduced P50 suppression and PTSD. However, the relationship between reduced P50 suppression and specific PTSD symptomology is unclear. McFarlane et al. (1993) suggested that sensory gating deficits might be related to concentration problems as indexed by reduced P3b. However, Metzger et al. (2002) found no correlation between the P50, P200, and P3b responses. Miyazato et al. (1996, 2000) suggested that RAS dysregulation (indexed by reduced P50 suppression) might be involved in the etiology of hyperarousal symptoms. However, Gillette et al. (1997) found that reduced P50 suppression was significantly correlated only with the intensity of re-experiencing symptoms. The authors suggested that the non-significant correlations with other symptoms might have been due to the small sample. They further noted that re-experiencing symptoms include physiological reactivity to trauma cues, but also suggested that reduced P50 suppression might index the abnormal sensory-perceptual processing associated with flashbacks.

Metzger et al. (2002) found that reduced P50 suppression was not correlated with PSTD symptoms, but was significantly correlated with general psychopathology. This latter finding is unsurprising, as reduced P50 suppression has been found in schizophrenia (Waldo et al., 1991) depression (Baker et al., 1990) and dementia (Buchwald et al., 1989). Like PTSD, schizophrenia and dementia can include abnormalities in sensory-perceptual processing as well as general anxiety and agitation (cf. DSM-IV, APA, 1994). Thus, more research is needed to elucidate the relationship between reduced P50 suppression and specific symptomology, as well as to understand the extent to which the phenomenon represents distinct etiological factors that produce common changes in brain functioning across disorders, or a non-specific predispositional factor, such as a heightened vulnerability to the effects of stress.

4.2. P200 A/R paradigm: gender- or symptom-dependent responses to intensifying stimuli?

Compared to trauma-exposed controls, male combat veterans with PTSD reliably showed a P200 reducing response. However, in samples of female combat nurses (Metzger et al., 2002) and abused children of both genders (McPherson et al., 1997), PTSD was associated with an augmenting response. In the sample of female nurses the P200 augmenting response was also positively correlated with PTSD severity. These finding suggest that gender and age of trauma exposure may influence P200 augmenting-reducing responses.

Gender effects have also been found in samples of healthy controls, with females exhibiting a greater augmenting response compared to males (Bruneau et al., 1986). Migraine patients also show a greater augmenting response compared to controls (Wang et al., 1999) and migraines are more prevalent in females (Perry Carson et al., 2004). Moreover, Paige et al. (1994) found that in depressed patients, P200 augmenting responses were associated with better response to selective serotonin reuptake inhibitors (SSRIs), and depressed females have shown a greater response to SSRI treatment compared to males (Kornstein et al., 2000).

These findings and those of the present meta-analyses suggest that gender may moderate the P200 augmenting-reducing response. However, as noted, the samples in the meta-analyses may have differed from each other on other variables, including trauma severity, duration of PTSD, age of exposure, comorbidity, and traits such as sensation seeking, which has been positively correlated with the P200 augmenting response in some studies (Brocke et al., 2000) but not in others (Wang et al., 1999). Moreover, findings by McPherson et al. (1997) suggest that differential PTSD symptomology might affect the P200 response. Although their overall comparison revealed a greater augmenting response in abused children with PTSD versus abused children without PTSD, when children were classified according to symptom cluster (high versus low numbers of re-experiencing, avoidance, and hyperarousal symptoms), the group with the highest number of hyperarousal symptoms showed a *reducing* response compared to the group with the lowest number of hyperarousal symptoms, with no group differences for the other symptom clusters. If, as Pritchard (1986) suggested, the P200 reducing response represents an attempt to decrease sensory input, a reducing response in PTSD patients could represent a compensatory mechanism for chronic hyperarousal. However, Metzger et al. (2002) reported a positive correlation between augmenting responses and each symptom cluster. Thus, the generalizability of McPherson et al. (1997) findings awaits further research.

PTSD is believed to involve the dysregulation of several neurotransmitter systems, including the noradrenergic and serotonergic systems, and PTSD patients can exhibit heterogeneity in terms sensitivity to noradrenergic and serotonergic agonists (cf. Hageman et al., 2001). As discussed, Hegerl and Juckel (1993) proposed that the P200 augmenting-reducing response reflects the functioning of serotonergic systems and Miyazato et al. (1996, 2000), among others, proposed that noradrenergic dysregulation is involved hyperarousal symptoms. Thus, it is possible that in

PTSD, the P200 response may be either reduced or augmented, depending upon the pattern of symptom presentation and the relative involvement of different neurotransmitter systems. Future research should continue to examine the relationship between the P200 augmenting-reducing response, symptom presentation, and differential response to medication and other psychoactive drugs to determine if PTSD subgroups can be identified, as this could have utility in treatment planning and inclusion in medication clinical trials.

4.3. P300 in the "oddball" paradigm: Context-dependent information processing in PTSD?

Persons with PTSD exhibited reduced P3b amplitudes and prolonged latencies in response to neutral targets in the context of neutral/no distractors compared to non-trauma exposed controls at all electrode sites. At electrode site Pz, PTSD patients showed reduced P300 amplitudes to both neutral targets (P3b) and neutral distractors (P3a) compared to trauma-exposed controls. Interestingly, when distractors were trauma related, persons with PTSD showed increased P3b amplitudes in response to neutral targets and increased of P3a amplitudes in response to trauma-related distractors compared to trauma-exposed controls. These findings suggest context-dependent variations in information processing in PTSD.

Reduced P3b responses have been interpreted as an index of general cognitive impairment (Polich, 1998) as well as more specific deficits in attention (Portin et al., 2000), working memory (Mecklinger et al., 1992), and in the allocation of information processing resources to tasks (Donchin and Coles, 1988; Metzger et al., 2002). Reduced P3b amplitudes have been associated with a number of pathological conditions including schizophrenia (Frodl et al., 2002; Jeon and Polich, 2003), depression (Gangadhar et al., 1993), dementia (Pfefferbaum et al., 1990), and alcoholism (Enoch et al., 2001). However, our results suggest that in contrast to other disorders, in PTSD P3b amplitudes to target stimuli may be reduced or enhanced, depending upon the nature of contextual non-target stimuli. In PTSD, reduced P3b to neutral targets in the presence of non-trauma related stimuli could reflect the reduced allocation of information processing resources to stimuli evaluated as non-threatening. This interpretation is supported by evidence of poorer memory for neutral words (but not trauma-related words) in persons with PTSD compared to trauma-exposed controls (McNally et al., 1998; Zeitlin and McNally, 1991). PTSD has also been associated with impaired attention, working memory, and encoding of neutral stimuli on standard neuropsychological tests (Vasterling et al., 1998, 2002).

Increased P3b amplitudes to neutral targets in the context of trauma-related distractors could reflect increased task difficulty for persons with PTSD due to the presence of more conspicuous distractors (Polich et al., 1997), which is consistent with the finding of enhanced processing of trauma-related stimuli on behavioral measures of cognitive and perceptual functioning in persons with PTSD (cf. Buckley et al., 2000). It is also possible that the previously neutral targets acquired increased threat relevance in the presence of trauma cues. This interpretation is consistent with the proposition that P3b amplitudes reflect stimulus evaluation (Pritchard, 1981) and the engaging of attention to update memory representations and the context in which the stimuli occur (Donchin, 1981; Polich, 1996, 1998). As the increased P3b amplitudes could also reflect increased anxious arousal in the presence of trauma cues, the results are also consistent with the suggestion that the P300 indexes fluctuations in arousal and attention (Frodl-Bauch et al., 1999b) as well as phasic alteraltions in arousal associated with task demands and stimuli salience (Polich and Kok, 1995; Polich et al., 1997). This interpretation is supported by the finding of increased P3a amplitudes to trauma-related distractors in the meta-analysis, which also suggests increased arousal. Level of arousal has long been known to affect information processing as well as ERPs (cf. Polich and Kok, 1995). There are also reports of enhanced P300 amplitudes in patients with other anxiety disorders (Chattopadhyay et al., 1980; Enoch et al., 2001) and in healthy controls exposed to anxiety-provoking situations (Grillon and Ameli, 1994).

The findings of increased P3a amplitudes to trauma-related distractors, and reduced P3a to neutral distractors (at site Pz) also support the notion of context-dependent information in PTSD. Abnormal P3a responses may be related to re-experiencing symptomology, as P300 latencies to distracting stimuli correlate with the severity of re-experiencing symptoms (Attias et al., 1996). Clark et al. (1996), who found increased frontal P3a responses in patients with Panic Disorder, suggested that increased P3a may reflect a failure to inhibit irrelevant stimuli. Our findings suggest that in PTSD, such inhibition failure may occur primarily with trauma-related distractors. This interpretation is supported by findings of an attention bias towards trauma-related stimuli in PTSD (Harvey et al., 1998; Vrana et al., 1995) as well as enhanced automatic processing of fear-relevant stimuli (Bryant and Harvey, 1997), even when stimuli are masked to prevent conscious detection (Rauch et al., 2000).

To summarize, the overall P300 results suggest a context-dependent information processing dissociation in PTSD, such that the processing of neutral stimuli is reduced, but the processing of trauma-related stimuli, or neutral stimuli presented in the context of trauma-related cues, is enhanced. This dissociation mirrors the findings of studies that have examined functional neuroanatomical correlates of the encoding of emotional stimuli. Williams et al. (2001) measured event-related skin conductance fMRI responses during the presentation of fearful faces and concurrent activity in the brain. They found that activity in the amygdala and medial frontal cortex occurred *only with* evoked skin

conductance responses whereas activity in the hippocampus occurred *only in the absence* of evoked skin conductance responses. Moreover, activity of the amygdala during encoding correlates with long-term recall of emotional (but not neutral) stimuli (Cahill et al., 1996) whereas activity of the hippocampus (but not the amygdala) during encoding correlates with long-term recall of neutral stimuli (Alkire et al., 1998). PTSD patients have shown both heightened activation of the amygdala in response to trauma-related stimuli (Rauch et al., 1996; Shin et al., 1997; Shin et al., 1999; Shin et al., 2004) as well as hippocampal dysfunction (Gilbertson et al., 2002; Schuff et al., 2001; see also Elzinga and Bremner, 2002 for a review).

As noted, P300 ERPs are believed to represent functioning in cortical (temporo-parietal and prefrontal) regions, and to some extent the hippocampus (Frodl-Bauch et al., 1999a; Kirino et al., 2000; Linden et al., 1999; McCarthy et al., 1997; Opitz et al., 1999a,b; Polich, 2003). Persons with PTSD have shown functional abnormalities in these regions (Bremner et al., 1999; Elzinga and Bremner, 2002; Shin et al., 2004; Shaw et al., 2002) and in the case of the hippocampus, both structural and functional abnormalities (Elzinga and Bremner, 2002; Gilbertson et al., 2002; Schuff et al., 2001). As discussed, the P3b has its maximal generation at parietocentral electrode sites (Johnson, 1993; Frodl-Bauch et al., 1999a). This may in part explain why in the present study, the P3b at parietal cortex (electrode site Pz), showed the best ability to discriminate PTSD patients and non-PTSD trauma-exposed controls, although as noted this finding may have been due to task and stimuli characteristics (Polich et al., 1997). Abnormalities in frontal-parietal functional neural circuits involved in working memory have been reported in PTSD (Bremner et al., 1999; Shaw et al., 2002), and anxious arousal has been associated with predominant right-hemispheric parietal activity, including enhanced P300 and reduced EEG alpha waves activity (cf. Heller and Nitschke, 1998).

As discussed, the P3a is believed to be generated from the frontal cortex but can be elicited from central and parietal cortical regions (Comerchero and Polich, 1999; Katayama and Polich, 1998; Polich and Comerchero, 2003; Polich and Kok, 1995) and is thought to index activity in prefrontal–limbic system neural circuitry (Knight, 1996; Kirino et al., 2000; Polich, 2003; Yamaguchi et al., 2004). In the present study we found differential P3a responses to non-target stimuli at frontal, central, and parietal recording sites in the PTSD and non-PTSD samples. Rule et al. (2002) found enhanced P300 amplitudes to repeated presentations of aversive and novel stimuli in patients with orbitofrontal lesions compared to controls, and persons with PTSD have shown increased activation of orbitofrontal cortex in response to trauma-related stimuli compared to trauma-exposed controls (Shin et al., 1999). These findings suggest that orbitofrontal regions are involved in modulating neural responses to aversive stimuli. McCarthy and associates have found that activity in the medial frontal gyrus is associated with P300 to target stimuli (Kirino et al., 2000; McCarthy et al., 1997), and persons with PTSD have also shown reduced activity in medial cortical regions in response to trauma-related stimuli (Shin et al., 2001, 2004). Moreover, Shin et al. (2004) also found that PTSD symptoms severity was positively correlated with activation of the amygdala, but negatively correlated with activation of the medial frontal gyrus, and suggested that these regions comprise a reciprocal-opposing functional circuit in PTSD. Taken together, these findings suggest that abnormal P300 responses in PTSD may in part reflect functional alterations in medial frontal cortical–amygdala neural pathways.

Frodl-Bauch et al. (1999a) proposed that P300 generation is directly related to glutamatergic mediated excitatory neural activity, and that cholinergic and gabaergic activity modulates P300 amplitude and latency indirectly through the inhibition of excitatory neural activity. They further posit that the adrenergic system, and to a lesser extent, serotonergic and dopaminergic systems, may influence P300 through their modulation of acetylcholine and GABA. As PTSD has been associated with dysfunction in noradrenergic, glutamatergic, and serotonergic systems (cf. Hageman et al., 2001), the exact relationship between alter neurochemical functioning and P300 responses in PTSD is unclear. However, the involvement of noradrenalin is consistent with context-dependent information processing in PTSD, as exposure to trauma-related stimuli is associated with sympathetic nervous system arousal (cf. Blanchard and Buckley, 1999). Future research should try to ascertain the relationship between altered P300, neurotransmitter functioning, and PTSD symptomology.

4.4. Limitations

The meta-analyses are limited by the small number of studies and small sample sizes in each study. In addition, some of the studies utilized the same sample to test different types of ERPs, thus further limiting the generalizability of the findings. Moreover, although we attempted to address the ‘‘file drawer problem,’’ we obviously would not have access to unpublished papers and all conference presentations. In addition, although we attempted to identify homogenous samples and grouped studies for analysis according to common paradigms, sample and methodological heterogeneity could have influenced the findings. Lastly, as discussed we classified P300 subcomponents functionally based on the nature of the stimuli. Thus, component-specific results should be interpreted with some caution. Identifying P300 subcomponents is germane to interpreting the type of information processing that they may index and their potential relationship to PTSD symptomatology. The future application of techniques such as independent component analysis developed by Makeig et al. (1999a,b, 2002), principal component analysis (Dien et al., 2003), wavelet transformation (Demiralp et al., 2001) or Woody filter processing (Gratton et al., 1989) might help

to identify P300 subcomponents and clarify PTSD-specific P300 phenomena.

4.5. Conclusions

Despite its limitations, this study represents the first attempt to empirically integrate the results of ERP PTSD research. To reiterate the findings, we found evidence of reduced P50 suppression in PTSD, and gender- or possibly PTSD symptom-related patterns of augmenting-reducing responses to intensifying auditory stimuli. We also found increased P300 amplitudes to trauma-related distractors and target stimuli in the context of trauma-related distractors. Lastly, persons with PTSD showed reduced P300 amplitudes and latencies to neutral target stimuli in the context of neutral/no distractors, and reduced P300 amplitudes to neutral distractors. Within the ERP and cognitive neuroscience literatures, reliable evidence has accrued in support of the hypothesis of altered central nervous system functioning in PTSD, and the results of the present meta-analyses have further strengthened the evidence. The continued refinement of ERP paradigms and their integration with other neuroimaging, biochemical, and behavioral assessment techniques hold promise for elucidating the effects of trauma on the brain and on cognitive-perceptual functioning.

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Appendix A

A.1. P50 sensory gating: studies' sample characteristics

No.	Study	Trauma type	Gender	PTSD (*N*)	Controls (*N*)	Comorbid axis I disorder	Medication[a]	Alcohol dependence	Time post-trauma
1.	Gillette et al. (1997)	Combat	M	10	5 (trauma exposed) 5 (non-trauma-exposed)	Yes	AN	Yes	Not reported
2.	Neylan et al. (1999)	Combat	M	15	12 (non-trauma-exposed)	No	SSRI	No	>20 years
3.	Skinner et al. (1999)	Combat	M	10	5 5 (non-trauma-exposed)	No	AN	Yes	Not reported
4.	Skinner et al. (1999)	Sexual Assault	F	9	9 (non-trauma-exposed)	No	AN	Yes	Not reported
5.	Metzger et al. (2002)	Combat Nurses	F	24	24	Yes	No	Yes ($N = 2$)	>20 years
26.	Ghisolfi et al. (2004)	Violence	M/F	12	24 (non-trauma-exposed)	Yes	Yes	No	<1–15 years

[a] SSRIs: serotonin re-uptake inhibitors; AN: over the counter analgesics.

A.2. P50 sensory gating: studies' methdoological characteristics

Study	No. of trials	Stimuli duration (MS)	Interstimulus interval (ms)	Intertrial interval (s)	Intensity[a] (dB)	Recording position
Gillette et al. (1997)	64	100	250, 500, 1000	5	HT + 50	Cz
Neylan et al. (1999)	100	Not reported	500	7–8	HT + 55	SVD[b]: FC1, FCz, FC2, C2
Skinner et al. (1999)	64	100	250, 500, 1000	5	HT + 50	Cz
Skinner et al. (1999)	64	100	250, 500, 1000	5	HT + 50	Cz
Metzger et al. (2002)	75	100	250	5	95	Cz
Ghisolfi et al. (2004)	30	Not reported	500	10	HT + 60	Cz

[a] HT: hearing threshold.
[b] SVD: singular value decomposition.

A.3. P200 in augmentation-reduction paradigm: studies' sample characteristics

No.	Study	Trauma Type	Gender	PTSD (N)	Controls (N)	Comorbid axis I disorder	Medication[a]	Alcohol dependence	Time post-trauma
6.	Paige et al. (1990)	Combat	Male	12	6	No	No	No	>5 years
7.	Lewine et al. (1997)	Combat	Male	42	20	Not reported	Not reported	Yes	Not reported
8.	McPherson et al. (1997)	Childhood abuse	Male/female	60	81	Not reported	Not reported	Not reported	Not reported
9.	Metzger et al. (2002)	Combat nurses	Female	23	27	Yes	No	Yes (2)	>20 years
24.	Lewine et al. (2002)	Combat	Male	31	20[a]	Yes	Yes	Yes/No	Not reported

[a] Non-trauma-exposed sample.

A.4. P200 in augmentation-reduction paradigm: studies' methdoological characteristics

Study	No. of trials	Stimulus type (Hz)	Duration of stimuli (ms)	Interstimulus interval (s)	Intensity (number: dB SPL[a])	Recording position
Paige et al. (1990)	256	780	500	2–4	4: 74, 84, 94, 104	Cz
Lewine et al. (1997)	110	2000	50	Not reported	5: 65, 72.5, 80, 87.5, 95	Cz
McPherson et al. (1997)	Not reported (>80)	Not reported	500	2–5	4: 65, 80, 95, 102	Cz
Metzger et al. (2002)	256	780	500	2–4	4: 74, 84, 94, 104	Cz
Lewine et al. (2002)	110	2000	Not reported	1–2	5: 65, 72.5, 80, 87.5, 95	Cz

[a] db SPL: decibel sound pressure level.

A.5. P3b to target stimuli in oddball task: studies' sample characteristics

No.	Study	Method	Trauma type	Gender	PTSD (N)	Controls (N)	Comorbid axis I disorder	Medication[a]	Alcohol Dependence/ substance abuse	Time post-trauma
Paradigm: "Oddball" task; neutral target, neutral distractor										
10	McFarlane et al. (1993)	3-Tone oddball	Not reported	F/M	18	20[b]	No	No	No	Not reported
11	Charles et al. (1995)	2-Tone oddball, no distractor	Civilian	F/M	16	10	No	No	Not reported	4–5 weeks
12	Metzger et al. (1997a)	3-tone oddball	Combat	M	9	10 16[c]	Yes	No Yes	No	>20 years
13	Metzger et al. (1997b)	3-Tone oddball	Childhood sexual assault	F	9	8	No	No	Not reported	>20 years
22	Bourdarene and Timsit-Berthier (1997)	2-Tone oddball, no distractor	Not reported	F/M	19	18[b], 17[b]	Not reported	Not reported	Not reported	>10 months
14	Blomhoff et al. (1998)	2-Tone-oddball; non-words distractors	Civilian	F/M	11	9	Yes	Not reported	Not reported	2 years
15	Galletly et al. (2001)	Auditory target detection	Civilian	F/M	18	18[b]	Not reported	No	No	Not reported
25	Neylan et al. (2003)	3-Tone oddball	Combat	M	30	15	Yes	SSRI	Yes	Not reported
16	Metzger et al. (2002)	3-Tone oddball	Combat	F	29	38	Yes	No	Yes (2)	>20 years
23	Felmingham et al. (2002)	2-Tone oddball, no distractor	Civilian	F/M	16	17[b]	No	*No*	No	10 months
Paradigm: "Oddball" task; neutral target, emotional/novel/ trauma-related distractors										
17	Attias et al. (1996a)	Visual oddball; trauma-related distractors	Combat	M	*20*	20	No	No	No	1 to >10 years
18	Bleich et al. (1996)	Visual oddball; trauma-related distractors	Combat	M	*20*	20	No	No	No	>10 years
19	Kimble et al. (2000)	3-Tone oddball; novels	Combat	M	*24*	15	Yes	Yes	No	Not reported
25	Neylan et al. (2003)	3-Tone oddball; novels	Combat	M	*30*	15	Yes	SSRI	Yes	Not reported
20	Stanford et al. (2001)	3 Word oddball, trauma-related and non-related words as distractors	Combat	M	*10*	10	Yes	No	No	> 20 years
21	Attias et al. (1996b)	Visual oddball; tauma-related distractors	Combat	M	*20*	20	No	No	No	1 to >10 years
14	Blomhoff et al. (1998)	2-Tone-oddball; non-trauma-related emotional words as distractors	Civilian	F/M	*11*	9	Yes	Not Reported	Not Reported	2 years

[a] SSRIs: serotonin re-uptake inhibitors.
[b] Non-trauma-exposed sample.
[c] Medicated sample.

A.6. P300 oddball task: studies' methdoological characteristics

Modality/paradigm	No. of stimuli	Target stimuli (% of total stimuli)	Standard stimuli (% of total stimuli)	Distractor (% of total stimuli)	Duration (ms)	Interstimulus interval (S)	Intensity	Response
Acoustic 2-tone								
Charles et al. (1995)	300	2000 Hz (10%)	750 Hz (90%)	–	700	2.5	75 dB	Count
Bourdarene and Timsit-Berthier (1997)	NR[a]	1470 Hz (20 %)	800 Hz (80%)	–	NR[a]	1	NR[a]	Press
Felmingham et al. (2002)	287	1500 Hz (15%)	1000 Hz (85%)	–	50	1.32	60 dB	Press
Acoustic 3-tone, neutral distractor								
McFarlane et al. (1993)	360–600	2000 Hz (14%)	1000 Hz (72%)	500 Hz (14%)	70	1.95–2.05	70 dB	Press
Metzger et al. (1997a)	285	2000 Hz (14%)	1000 Hz (72%)	500 Hz (14%)	70	1.95–2.05	70 dB	Press
Metzger et al. (1997b)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Press
Metzger et al. (2002)	285	2000 Hz (14%)	1000 Hz (72%)	500 Hz (14%)	NR[a]	1.95–2.05	NR[a]	Press
Kimble et al. (2000)	600	2000 Hz (7.5%)	1000 Hz (85%)	500 Hz (7.5%)	50	1.1	80 dB	Press
Blomhoff et al. (1998)	200	1200 Hz (20%)	800 Hz (60%)	Nonsense words (20%)	500–1000	2.5	95 dB	NR[a]
Acoustic 3-tone, novel distractor								
Kimble et al. (2000)	600	2000 Hz (7.5%)	1000 Hz (85%)	Novel (7.5%)	50/200	1.1	80 dB	Press
Neylan et al. (2003)	NR[a]	2000 Hz (15%)	1000 Hz (70%)	Novel (15%)	52	1.9–2.0	55 dB	Press
Acoustic 3-tone, emotional distractor								
Blomhoff et al. (1998)	200	1200 Hz (20%)	800 Hz (60%)	Positive words (20%)	500–1000	2.5	95 dB	NR[a]
Blomhoff et al. (1998)	200	1200 Hz (20%)	800 Hz (60%)	Negative words (20%)	500–1000	2.5	95 dB	NR[a]
Visual, 3 stimuli								
Stanford et al. (2001)	240	Neutral words (20%)	Neutral words (60%)	Trauma words (20%)	1000	1.5	NR[a]	Press
Attias et al. (1996a) BMJ	480	Animal pictures (20%)	Furniture, flowers pictures(60%)	Combat pictures (20%)	267	2	50 Lux	Press
Attias et al. (1996b) BPs	480	Animal pictures (20%)	Neutral pictures (60%)	Combat pictures (20%)	267	2	50 Lux	Press
Bleich et al. (1996)	4ssss80	Animal pictures(19%)	Furniture, flowers (62%)	Combat pictures (19%)	267	2	NR[a]	Press
Neylan et al. (2003)	NR[a]	Horizontal line (15%)	Vertical line (70%)	Novel (15%)	796	1.9–2.0	NR[a]	Press
Stanford et al. (2001)	240	Neutral words (20%)	Neutral words (60%)	Emotional words (20%)	1000	1.5	NR[a]	NR[a]
Acoustic 5-tone								
Galletly et al. (2001)	800–1000	1000 Hz (NR[a])	1250, 1500,1750 Hz (NR[a])	2000 Hz (20%)	70	1.2–1.4	70 dB	Press

[a] NR: not reported.

A.7. P3a to distractor stimuli in oddball task: studies' sample characteristics

No.	Study	Method	Trauma type	Gender	PTSD (*N*)	Controls (*N*)	Comorbid axis I disorder	Medication[a]	Alcohol dependence/ substance abuse	Time post-trauma
Neutral distractors										
10	McFarlane et al. (1993)	3-Tone oddball	NR[a]	F/M	18	20[b]	No	No	No	NR[a]
12	Metzger et al. (1997a)	3-Tone oddball	Combat	M	9	10 16[c]	Yes	No Yes	No	>20 years
13	Metzger et al. (1997b)	3-Tone oddball	Childhood Sexual Assault	F	9	8	No	No	NR	>20 years
19	Kimble et al. (2000)	3-Tone oddball	Combat	M	24	15	Yes	Yes	No	NR[a]
15	Galletly et al. (2001)	Auditory target detection	Civilian	F/M	18	18[b]	No	No	No	NR
16	Metzger et al. (2002)	3-Tone oddball	Combat	F	29	38	Yes	No	Yes (2)	>20 years
Trauma-related distractors										
17	Attias et al. (1996a)	Visual oddball	Combat	M	20	20	No	No	No	1 to >10 years
21	Attias et al. (1996b)	Visual oddball	Combat	M	20	20	No	No	No	1 to >10 years
18	Bleich et al. (1996)	Visual oddball	Combat	M	20	20	No	No	No	> 10 years
20	Stanford et al. (2001)	3 Word oddball	Combat	M	10	10	Yes	No	No	>20 years
Emotional non-trauma-related or novel										
18	Bleich et al. (1996)	Visual oddball	COM	M	20	20	No	No	No	>10 years
19	Kimble et al. (2000)	3-Tone oddball, novel	COM	M	24	15	Yes	Yes	No	NR[a]

[a] NR: not reported.
[b] Non-trauma-exposed sample.
[c] Medicated sample.

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