Impaired Fear Inhibition and Early Life Trauma in Veterans with PTSD: a Systematic Review and Meta-Analysis

Anna Keramari

6488919

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Abstract

Objective: One of the learning theories for the development of posttraumatic stress disorder (PTSD) suggests that individuals have difficulty in inhibiting fear under safety conditions. In addition, other factors such as prior exposure to traumatic events have been found to play a major role in the risk for developing the disorder. PTSD is a common disorder among veterans and offering the right treatment is essential. Therefore, the aim of this meta-analysis was to investigate if there is robust evidence for fear inhibition in veterans and to explore if fear inhibition is related to early life trauma, leading to a possible prevention of the disorder in this population and to the design of more effective interventions. **Data Sources:** The database **PubMed** was searched for studies referring to learning theories of PTSD in veterans and 2165 articles were screened. **Study Selection:** Four studies met the eligibility criteria and were included in the analysis with a total number of 1378 participants. **Results:** Data synthesis revealed no significant results regarding impaired fear inhibition (-.85) and its association with early life trauma (.65). **Conclusion:** No evidence was found to support the hypotheses that veterans with PTSD exhibit impaired fear inhibition and that this is affected by early life trauma.

Keywords: veterans, PTSD, fear-inhibition, trauma, meta-analysis

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a mental health illness that occurs after direct or indirect exposure to a traumatic event and the main symptoms involve re-experiencing of the event, avoidance of any reminders of the trauma and persistent distress (American Psychiatric Association, 2013), however, not all individuals exposed to life-threatening events develop the disorder. So far, various models and learning theories tried to explain the reason behind the development and maintenance of PTSD and extensive research on traumatized general population has been performed (Acheson et al., 2015; Lissek & van Meurs, 2015; Norrholm et al., 2011). For example, the fear conditioning theory suggests that the traumatic event (US) causes an unconditioned fearful response (UR) which is connected with cues (CSs) present in the event. Consequently, the CSs can still trigger fearful responses even when there is no traumatic event, which may explain the development of PTSD (Blechert et al., 2007). The mental health, specifically of veterans, is being of great concern because of their increased exposure to traumatic events while being on duty (Barrera et al., 2013). However, less than 20% of them develop PTSD after returning from deployment but many are resistant to treatment (Haverman-Gould & Newman, 2018; Myers et al., 2012). Thus, it is important to investigate learning theories in PTSD patients, especially in veterans in order first, to detect vulnerability during the selection process and, second, develop new interventions for the treatment of PTSD.

One learning theory model is fear inhibition. According to this theory, individuals with PTSD continue to respond with fear to the conditioned stimuli, even when they are aware of a safety condition and, therefore, the extinction of fear is impaired (Jovanovic et al., 2010; Lissek & van Meurs, 2015).The ability to inhibit fear is measured in experimental settings with two main models, that of extinction and conditioned inhibition (Jovanovic et al., 2010). Extinction refers to a gradual decrease in responding with fear to a conditioned danger cue after being repeatedly presented without an aversive stimulus (Lissek & van Meurs, 2015). However, PTSD patients show persistent fear in the condition where danger is not present. Conditioned inhibition refers to a decline of fear in the presence of safety cues (Lissek & van Meurs, 2015). In contrast, individuals with PTSD cannot discriminate between safe and dangerous situations and continue to have fearful responses even when safety signals are present (Lissek & van Meurs, 2015). What is common in those two models

is the extinction of fear, however, the main difference is that in inhibition paradigms individuals learn to suppress their fear when a safety cue is present whereas in extinction paradigms individuals learn that the conditioned stimulus does not produce a fearful response anymore (Lissek & van Meurs, 2015). Nevertheless, extinction paradigms are used because of their inhibitory effects, meaning that extinction is successful when individuals inhibit their fear (Lissek & van Meurs, 2015). Thus, both inhibition and extinction paradigms can indicate fear inhibition and, therefore, it is important to investigate them.

Besides the fear inhibition theory, other variables were also examined as risk factors for the later development and maintenance of PTSD with prior trauma history being among them. This means that individuals exposed to at least one potentially traumatic event (PTE) have higher chances to be exposed again and to develop PTSD (Breslau et al., 1999; Brewin et al., 2000; Cougle et al, 2009; King et al., 1996; Ozer et al., 2003). For instance, a PTSD prevalence of 7.3% was found in young people who had been already exposed before the index trauma (Cougle et al., 2009). Furthermore, the severity of the PTE seems to be strongly related with the risk of developing PTSD (Cougle et al., 2009). For example, childhood trauma, with physical and sexual abuse being frequently reported, was found to be mostly associated with PTSD compared to other kind of traumatic exposures, such as car accidents (Brewin et al., 2000; Cougle et al., 2009; King et al., 1996; Ozer et al., 2003). Therefore, it is important to take into account not only the learning process of fear inhibition but pre-exposure factors, such as prior –to the index trauma- exposure, when explicating PTSD.

Although, previous studies have documented deficits in individuals with PTSD, it is essential to explore learning mechanisms the veteran population as well, because of their frequent exposure to multiple traumas. In addition to that, research has shown that, although there are a variety of interventions available for veterans with PTSD, some of them do not benefit from treatment and continue to experience symptoms of the disorder (Owens et al., 2011). Therefore, the aim of this meta-analysis is to summarize the existing evidence on the association between fear inhibition and prior to combat exposure in veterans with PTSD. Based on scientific literature, it is hypothesized that: 1) veterans diagnosed with current PTSD show decreased fear inhibition and 2) veterans with PTSD who exhibit decreased fear

inhibition have also experienced at least one traumatic event before deployment. This systematic review and meta-analysis will show whether the theory of impaired fear inhibition can contribute in predicting the risk of developing combat-related PTSD and whether new treatments based on fear inhibition techniques should be designed in order to increase treatment response rates.

2. Methods

The present study was conducted according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Moher et al., 2015).

2.1 Search Strategy

An electronic systematic literature search was conducted on the 29th of November, 2018 using the database PubMed. The search included terms referring to posttraumatic stress disorder, veterans or military, fear-learning theories and early life trauma and can be found in more details in Appendix 1. The search was not restricted to publication date and included studies which were screened independently and then, at a second stage, peer-reviewed by two researchers (A. K and A. F) to confirm eligibility and to avoid bias and uncertainty by reading abstracts and full-texts.

2.2 Selection Criteria

For the purpose of the current review, the search included quantitative English-language studies that evaluated fear-learning theories in veterans with PTSD. All participants had to be a) veterans or military soldiers, b) diagnosed with PTSD based on the criteria of DSM or ICD and c) showed fear based on models of learning theories. However, the final analysis included only studies whose participants were veterans diagnosed with PTSD and had deficits in inhibiting fear. Studies were excluded if they a) were written in any language other than English, b) involved animals or c) did not contain sufficient information regarding learning models for veterans diagnosed with PTSD.

2.3 Data Extraction

Qualitative data such as demographic information of participants (sample size, gender, age, military group and country of deployment) were extracted for the current

analysis. Moreover, as mean scores of the Clinician-Administered PTSD Scale (CAPS) and mean scores of questionnaires measured early life trauma were also included. Because of the hypothesis that veterans with PTSD exhibit difficulties in inhibiting fear, information regarding fear response measures were extracted, as, including means, standard deviations and *p*-values. Statistical information, such as means, variance and standard deviations that could not be obtained otherwise, were estimated from figures using PlotDigitizer Java program,version 3.9 (Rohatgi, 2015).

2.4 Statistical Analysis

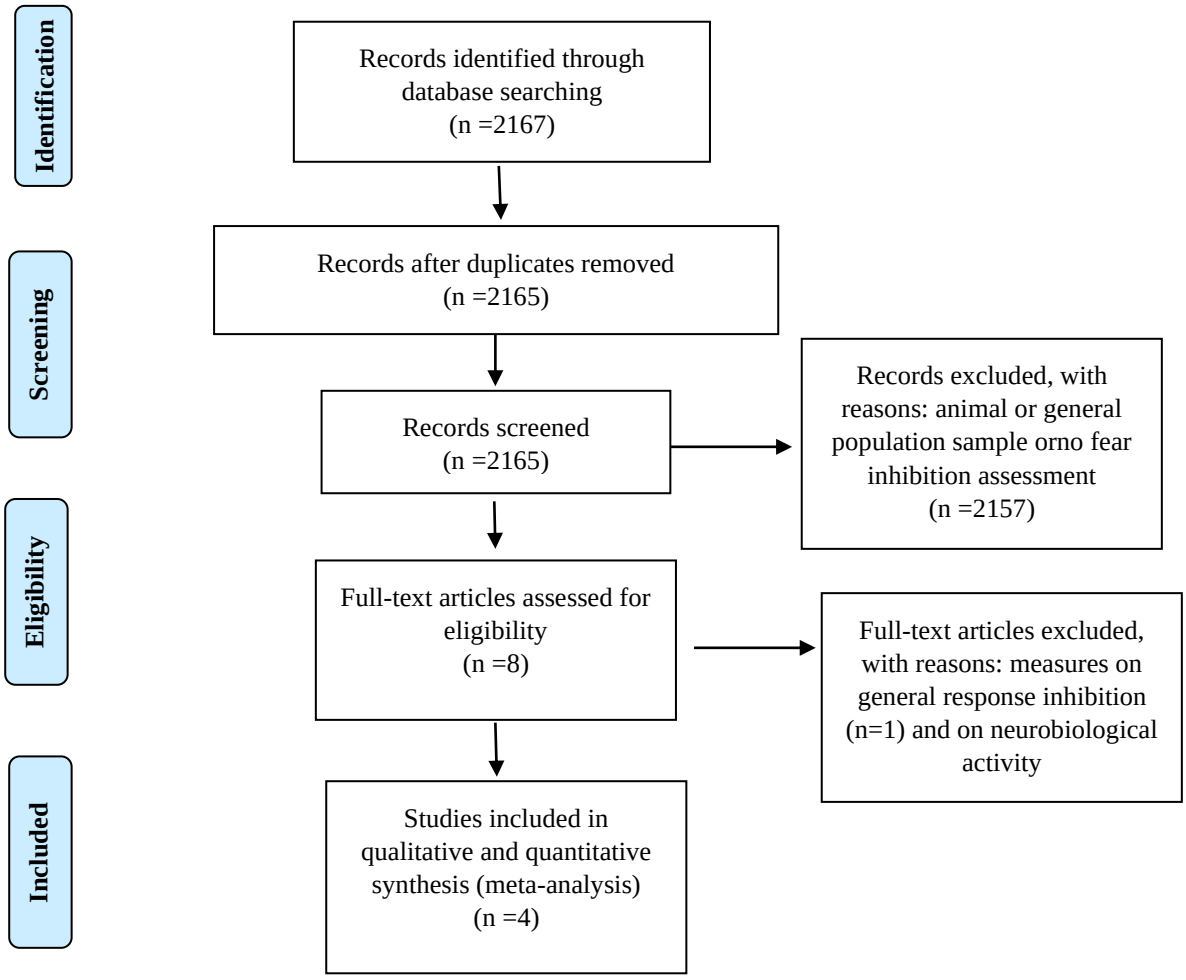
All meta-analytic calculations were carried out using Comprehensive Meta-Analysis (CMA) statistical software for Windows, version 3. Hedge's *g*statistic was used to estimate the effect size between veterans with PTSD and the controls and confidence intervals were set at 95% (Hedges & Olkin, 1985). A random effects model was used instead of fixed effects model for the reason that a variation was assumed in terms of study characteristics, for example different sample size and age or different method for the assessment of fear inhibition (Kelley & Kelley, 2012). Direction of effect size values was adjusted in such way that negative direction indicates decreased inhibition of fear in veterans with PTSD whereas positive direction indicates increased fear inhibition. For studies that had more than one outcome, effect sizes were combined so that for each study one effect size was included in the final analysis. Heterogeneity across the included studies was tested using Cochran's *Q* statistic, with a *p*-value ≤ 0.10 indicating significant heterogeneity (Higgins & Green, 2011) and inconsistency was evaluated with an *I*-squared statistic at a level of >50% (Higgins et al., 2003).The probability of publication bias was evaluated with Egger's test (Egger et al., 1997) and its effect was assessed using Duval & Tweedie's (2000) Trim and Fill method. However, the Cochrane guidelines suggest that in case of high heterogeneity a funnel plot for publication bias is better not be performed (Higgins & Green, 2011). Early life trauma and PTSD scores, age and gender were used as moderators on fear inhibition. Finally, a meta-regression was performed to investigate the impact of moderator variables on the outcome and more specifically, to assess the effect of early life trauma (independent variable) on the effect size (dependent variable), with a *p*-value level of significance ≤ 0.05.

3. Results

3.1 Study Selection

The number of articles identified on PubMed and the number of the included and excluded papers on the current meta-analysis are portrayed in the flowchart in Figure 1. 2167 studies were identified through the search in PubMed. After the removal of 2 duplicates, 2165 studies were screened for eligibility based on titles and abstracts. 2157 studies were excluded because the sample size comprised either animals or a general population, there as a co-morbid disorder or there was no assessment on fear inhibition. Eight studies were initially included but 4 of them were excluded for the reason that they measured response inhibition in general and not specifically inhibition of fear. Eventually, 4 articles met the eligibility criteria and were selected for the present analysis and data from 1378 male participants were analysed.

Figure 1:Flow chart indicating the search results of PubMed database, of study selection and of included and excluded studies from the final analysis.



3.2 Study Characteristics

Four studies were included in the current meta-analysis and their characteristics are presented in the table below. All studies included a male veteran population, deployed mostly to Vietnam and Afghanistan. The age of participants ranged from 22 to 53 years. The PTSD diagnosis was confirmed in 3 studies with the Clinical Administered PTSD Scale (CAPS) and in 1 study with the PTSD Symptom Scale-Self Report (PSS-SR). Only 1 study used two groups (healthy vs. veterans with PTSD) (Jovanovic et al., 209) while the other 3 studies looked for differences within the veteran population based on symptom severity or for differences before and after deployment. Fear inhibition in all studies was assessed by measuring fear-potentiated startle using a conditional discrimination paradigm. Early life trauma was assessed in 2 studies (Sijbrandij et al., 2013; Deslauriers et al., 2017) using self-report questionnaires, the Potentially Traumatic Events Scale questionnaire (PTES) and the Childhood Trauma Questionnaire (CTQ), respectively.

Author(s), publication year	**Type of study**	**Study Design**	**Total sample size (*N*)**	**Age (*M*)**	**Gender**	**Veterans with PTSD (*N*)**	**Target Population**	**Instrument for PTSD diagnosis**	**Fear inhibition assessment**	**Stimuli responses**	**Instrument for Early Life Trauma assessment**	**Time period**	**Outcome**
Jovanovic *e*t al., 2009	observational	Veterans vs. healthy civilian group (control)	55	53	Males	27	Vietnam veterans	CAPS	Conditioned inhibition paradigm	Fear-potentiated startle in danger (AX+) and safety (BX-) trials	Not measured	After deployment	Veterans with higher PTSD symptoms, exhibited more difficulties in inhibiting fear.
Straus et	observat	In-lab	13	31.8	Males	13	Army,	CAPS	Fear	Fear-	Not	Post	Veterans

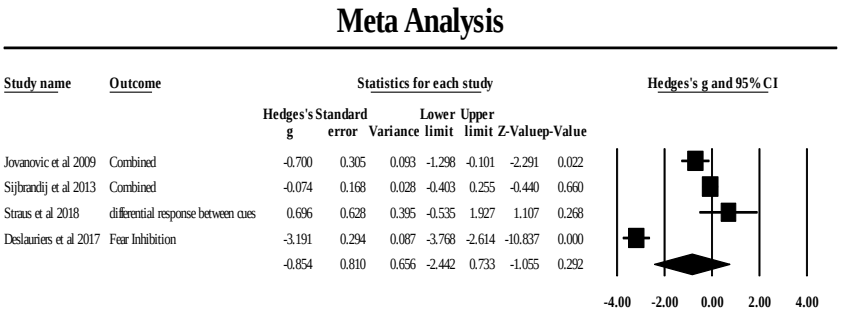
al., 2018	ional	assessment of experimental group					Navy and Marine Corps		extinction paradigm	potentiated startle to a conditioned stimulus trial (CS+) and to a safety signal (CS-)	measured	deployment	with PTSD did not have difficulties in inhibiting fear
Sijbrandij et al., 2013	observational	post deployment assessment	144	23.5	Males	144	Dutch soldiers deployed to Afghanistan	PSS-SR	Conditioned inhibition paradigm	Startle responses in danger signal phase (AX+) and in safety signal phase (BX-)	Potentially Traumatic Events Scale (PTES)	2 and 9 months after deployment	Veterans who showed impaired fear inhibition, also reported more critical

													incidents
Deslauriers et al., 2017	observational	pre/post deployment assessment	1166	22	Males	1166	European-American Marines and Navy Corpsmen deployed to Afghanistan	CAPS	Fear extinction paradigm	Startle responding under conditioned and non-reinforced stimuli	Childhood Trauma Questionnaire (CTQ)	Prior and 4-6 months after deployment	Veterans with PTSD who also experience childhood trauma, showed impaired fear inhibition.

3.3 Meta-Analysis

Table 2 shows the overall results after analysing the data provided by the 4 included studies at 95% confidence interval. The effect size was *g*=-.85, ranging from -2.44 to 0.73. A statistically non-significant effect size was found across the studies, as the p-value was >.05.

Table 2: *Overall results*



Results from the heterogeneity test that was performed revealed a *Q* value of 90.3 and an I^2 of 96.67% (*p*<.005), indicating a significant heterogeneity within the studies included in the analysis and thus, justifying the use of random effects modelling. Because of the presence of significant heterogeneity and following the Cochrane guidelines, the funnel plot to detect publication bias was not performed.

3.4 Meta-Regression

It was previously mentioned that 2 out of the 4 studies that were included in the current analysis measured early life trauma. Results from the meta-regression analysis showed a statistically non-significant impact of early life trauma on the effect size of those studies, accepting the null hypothesis of no effect (*d*=-.17; 95% CI, -.94-.59; *p*>.05) (Appendix 2).

4. Discussion

The present meta-analysis aimed at investigating the current evidence regarding the ability of veterans with PTSD to inhibit fear in safety situations and at exploring a potential association of fear inhibition in veterans with early life trauma. Data from 4 studies were analysed and no significant effect was found over those studies, rejecting the hypothesis that veterans with PTSD exhibit impaired fear inhibition. In addition, early life trauma was reported in 2 out of 4 studies and no significant effect was found, therefore there is no evidence to support the assumption that early life trauma influences veterans' ability to inhibit fear. Because of the small number of studies and high heterogeneity, the results should be interpreted with great precision.

To our knowledge, this is the first meta-analysis on fear inhibition and early life trauma in veterans with PTSD. Our results are compatible with the study of Burriss et al., (2007) who investigated fear inhibition in civilians and found that patients with PTSD were as able as the control group to respond differentially to reinforced and non-reinforced conditioned stimuli and that extinction of fear was successful. Similarly, Orr et al., (2000) found that PTSD patients could discriminate better between dangerous and safe conditions, although they used a different way to measure fear inhibition, including heart rate, skin conductance and face electromyogram. This could mean that combat trauma may not be different from other types of trauma experienced by civilians as it seems that there are no differences between veterans with PTSD and the general population. However, the current study is in contrast with previous research supporting that individuals with PTSD have deficits in inhibiting fear under safe conditions, suggesting differences in fear processing between healthy and PTSD populations (Jovanovic et al., 2013; Norrholm et al., 2011).

Prior-to-combat trauma has been found to increase the risk for developing PTSD in veterans (Armenta et al., 2018; King et al., 1996; Reisman, 2016), therefore, a regression analysis was performed to investigate whether early life trauma affects negatively veterans' ability to inhibit fear, but no significant effect was found. Results from the current analysis revealed two studies in which early life trauma was measured, thus evidence to support our assumption is scarce. For example, our results

were different from the studies of Birn et al., (2014) and Bremner et al., (1993) who argued that the majority of veterans with PTSD have been previously abused, sexually or physically. In addition, the current meta-analysis contradicts results from the meta-analysis of Xue et al., (2015) who explored risk factors for combat-related PTSD in veterans and found that early trauma before deployment were associated with combat-related PTSD. The main reason for these divergent results could be that most studies on early trauma focused on specific traumatic events, such as childhood maltreatment, sexual trauma, accidents, death witness or disasters, whereas the two studies included in the analysis measured prior exposure to traumatic events in general, indicating that the type of trauma experienced before combat may play a significant role in veterans' ability to inhibit fear.

The current analysis revealed a large number of heterogeneity which caused ambiguity and mixed results among the included studies. A possible explanation for the heterogeneity observed could be the differences in methodology. For example, one of the most important aspects that might have caused this variance could be the difference in the time-point of measurement. Specifically, only the study of Deslauriers et al., (2017) measured fear inhibition before and after deployment. Also, Sijbrandij et al., (2013) used a different diagnostic assessment tool for PTSD (PSS-SR) compared to the rest of the studies that used the CAPS, which might have influenced the measurement of symptom severity. Finally, findings of Straus et al., (2018) contradicted findings from the other studies of the current analysis. It was argued that veterans are able to inhibit fear, however, this study had the smallest sample size of all the included studies and therefore, conclusions cannot be drawn with great certainty unless results are replicated with larger population.

The present meta-analysis has implications for the understanding of learning theories of PTSD in the veteran population. The theory of fear inhibition and early life trauma are not indicatives of why veterans continue to show persistent symptoms of PTSD after treatment. Therefore, it is important to investigate further which learning mechanism explains better combat-related PTSD in order to provide them with the most appropriate treatment plan. Also, these results may help in exploring more in depth other pre-deployment factors, such as comorbidty, that may influence learning mechanisms. As a result, combat-related PTSD can be predicted and prevented with pre-deployment assessments based on learning mechanisms and risk factors. Finally,

researchers should use a specific way to measure fear inhibition in order to avoid getting mixed results.

4.1 Limitations

Although this study was carefully prepared, shortcomings were met and, therefore, need to be acknowledged. First of all, the screening included articles retrieved only from PubMed database and if additional databases were searched it could be possible that more studies would come up that are missed in our search. Moreover, other searching strategies, such as retrieving articles from the reference lists, could result in more studies. The presence of significant heterogeneity because of methodological differences may have affected the outcome of this study and thus, results cannot be generalized. Also, because early life trauma was measured by self-report questionnaires, participants' responses could have been biased and incidents such as childhood abuse may not have been reported. However, it is worth to mention that in case of prior exposure it is difficult to determine the nature of the trauma as it could be assumed as combat-related. Finally, co-morbidity could influence the ability to inhibit fear as it may have been present in participants but not assessed in the included studies, leaving it sub-threshold.

5. Conclusion

In conclusion, this meta-analysis did not give evidence to argue that veterans with PTSD have impaired fear inhibition and that other traumatic events before combat influence this ability. Data were obtained from 4 studies including 1378 participants. Despite some limitations, the present study could be a springboard for investigating other fear-learning theories and develop more effective interventions for veterans with PTSD. Moreover, it is important to exploring further the effect of other risk factors in relation to learning theories. As a result, a better understanding will be achieved which may add in predicting the risk of developing PTSD after deployment and increase treatment responses.

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Appendices

Appendix 1

Search terms

Veteran OR army OR armed OR military OR deployed OR Combat OR soldier

AND posttraumatic* OR PTSD OR shell-shock OR “combat neurosis” OR “battle fatigue” OR “survivor guilt”

AND Context* OR situational OR “Hyper-Conditionability” OR “hyper-conditioning” OR condition* OR “two-stage learning” OR incubation OR “associative learning” OR extinction OR generalization OR generalisation OR “fear inhibition” OR inhibition OR “safety cues” OR habituat* OR sensitisation OR sensitization OR amygdala

AND (English[lang] NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms]))

Appendix 2