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COMTval158met polymorphism links to altered fear conditioning and extinction are modulated by PTSD and childhood trauma

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Abstract

Background—Risk for posttraumatic stress disorder (PTSD) is thought to be mediated by gene × environment (G×E) interactions that affect core cognitive processes such as fear learning. The catechol-*O*-methyltransferase (*COMT*) val158met polymorphism has been associated with risk for PTSD and impaired fear inhibition. We used a large, relatively homogenous population to: (1) replicate previous findings of poor fear inhibition in *COMT* Met/Met carriers with PTSD; (2) determine if *COMT* association with fear inhibition is moderated by childhood trauma (CT), an environmental risk factor for PTSD; and (3) determine if *COMT* is associated with altered fear processing after recent exposure to combat trauma.

Methods—Male Marines and Navy Corpsmen of European-American ancestry were assessed prior to (n = 714) and 4–6 months after deployment to Afghanistan (n = 452). Acquisition and extinction of fear-potentiated startle, childhood and combat trauma history, and PTSD diagnosis were assessed at both time points.

Results—Before deployment, Met/Met genotype was associated with fear inhibition deficits in participants with current PTSD; however this association was dependent on CT exposure. After deployment, combat trauma was associated with a modest reduction in fear extinction in Met/Met compared to Val/Val carriers. There were no associations of *COMT* genotype with fear extinction within healthy and non-traumatized individuals.

Conclusions—These findings support the hypothesis that G×E interactions underlie associations of *COMT*val158met with fear inhibition deficits. These studies confirm that Met/Met carriers with PTSD have poor fear inhibition, and support further research in understanding how this polymorphism might impact response to extinction-based therapies.

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Keywords

COMT polymorphism; PTSD; trauma; childhood trauma; fear extinction; Marines

Introduction

Posttraumatic stress disorder (PTSD) affects 7–8% of the American population and up to 20% of military veterans (Pace & Heim, 2011). The risk of developing PTSD, which is characterized by intrusive re-experiencing of a traumatic event, avoidance of trauma-related stimuli and hyperarousal, is close to 40% in individuals who endorsed a sufficiently high number of traumatic events (Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Neuner et al., 2004). In the US, 61% of men and 51% of women endorsed at least one trauma in their lifetime (Kessler, Ruscio, Shear, & Wittchen, 2010; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Because only a fraction of those that experience trauma go on to develop chronic PTSD symptoms, understanding the biological risk factors that contribute to PTSD is important and may lead to development of novel prophylactic and treatment targets.

In humans, a commonly carried single nucleotide polymorphism (SNP) in the coding sequence for *COMT*, with valine (Val) being substituted by methionine (Met) at amino acid residue 158, results in a 40% reduction in COMT enzymatic activity in Met/Met carriers, leading to increased catecholamine tone in Met/Met carriers, particularly in the cortex (Chen et al., 2004). This SNP (rs4680) has been associated with risk for several neuropsychiatric disorders, although these associations are controversial and inconsistent (Almli, Fani, Smith, & Ressler, 2013; Clark et al., 2013; Goenjian et al., 2014). Some human studies reported that Met/Met carriers are at higher risk to develop PTSD by exhibiting impaired affective function, reduced fear extinction, and exaggerated potentiated startle reflex and anxiety (Enoch, Xu, Ferro, Harris, & Goldman, 2003; Lonsdorf et al., 2009; Montag et al., 2008; Zubieta et al., 2003). Nevertheless, the relationship between *COMT*val158met polymorphism and PTSD remains inconclusive (Li et al., 2016), suggesting the importance of gene × environment interactions in the development of PTSD. Although several studies have shown *COMT*val158met polymorphism × trauma interactions on risk for PTSD, it remains unclear how the SNP interacts with other PTSD risk factors such as early life stress or recent trauma (Boscarino, Erlich, Hoffman, & Zhang, 2012; Kolassa et al., 2010; Valente et al., 2011).

PTSD is associated with increased fear responding, reduced safety signal learning, and poor fear extinction (Acheson et al., 2015b; Jovanovic & Norrholm, 2011). Although previous studies have indicated that homozygous Met carriers similarly exhibit increased conditioned fear, reduced safety signal learning, and/or impaired fear extinction (Lonsdorf et al., 2009; Norrholm et al., 2013; Wendt et al., 2015), the results are inconsistent as to whether these alterations are found in healthy subjects or in subjects with current PTSD symptoms only. Childhood trauma is a strong predictor of PTSD in adulthood, and is well known to interact with genes to modulate PTSD risk (Mehta & Binder, 2012). However, it is not clear how early life stress may modify *COMT* associations with fear learning processes or if these

processes are altered by recent trauma exposure. In the present study we used a large, relatively homogenous population to: (1) replicate previous findings of altered fear processes in *COMT* Met/Met carriers with and without PTSD; (2) determine if *COMT* associations with fear learning and inhibition are moderated by childhood trauma, a strong environmental risk factor for PTSD; and (3) determine if *COMT* is associated with altered fear processing after exposure to recent combat trauma.

Methods

Study design and participants

The second phase of the Marine Resiliency study (MRS-II; Baker et al., 2012) involved a prospective longitudinal study of ≈ 1200 U.S. Marines and Navy Corpsmen that were deployed to Afghanistan. The U.S. Marines were from infantry battalions tested between October 2011 and October 2013, at bases in Southern California. Participants of European-American ancestry were assessed prior to (n = 714) and approximately 4–6 months after deployment to Afghanistan (n = 452) (see below for exclusion details). The study, for which all participants provided written informed consent, was approved by the institutional review boards of the University of California San Diego, Veterans Affairs San Diego Research Service, and Naval Health Research Center. Only males were included in the study, since infantry battalions did not include females at the time of assessment.

Genotyping

*COMT*val158met SNP (rs4680) was genotyped as previously described (Nievergelt et al., 2015). Briefly, blood samples were collected at the first visit and blood leukocytes were isolated. Genomic DNA was prepared from blood leukocytes at the Biomedical Genomics Microarray (BioGeM) Core facility (University of California San Diego, La Jolla, CA, USA) using the automated AutoGenFlex Star System, quantified with the Nanodrop 1000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA). Genotyping was performed by RUCDR Infinite Biologics (Piscataway, NJ, USA) with the human OmniExpress Exome array (Illumina Inc., San Diego, CA, USA). The assay call and reproducibility rates were > 99%. SNPs for control samples (identified as those with no PTSD diagnosis) respected the Hardy-Weinberg Equilibrium ($p < 5 \times 10^{-8}$). To control for race/ethnicity we used ancestry identification using genetic markers as previously described (Nievergelt et al., 2013), to identify 4 possible ancestry categories: African-American, Hispanic/Native American, European-American and East Asian/other. All ancestries other than European-American were excluded to reduce population stratification. Within European-Americans a principal component analysis (PCA) (Nievergelt et al., 2015), implemented in EIGENSTRAT (Price et al., 2006) was performed to control for additional genetic background heterogeneity. PCAs were then used as covariates in all statistical models.

Childhood Trauma Questionnaire

Before deployment, participants completed a modified 34-item (25–170 range) Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) to assess traumatic experiences (emotional, physical and sexual abuse and emotional and physical neglect) during childhood. Presence of childhood trauma was determined based on cut-off scores as previously

described (Agorastos et al., 2014): emotional abuse: ≥13; physical abuse: ≥10; sexual abuse: ≥8; emotional neglect ≥15; physical neglect: ≥10. It has been shown that risk for PTSD and depression symptoms were similar for both single and multiple childhood traumatic event type (Agorastos et al., 2014). Therefore, we divided the childhood traumatic experiences in two categories: 0 (no childhood trauma) or 1 (at least one type of childhood trauma).

Combat experiences and stress

After deployment, combat trauma and stress during deployment were measured using the Deployment Risk and Resilience Inventory-2 (DRRI-2), with high criterion validity and internal consistency (0.92) (Vogt et al., 2013). From the questionnaire, a total Combat Experience Score (CES) was calculated that encompassed all the traumatic and stressful events during deployment. To determine the role of trauma exposure (CES, 0–56 possible score), we used a validated approach (Collings, Valjee, & Penning, 2013; DeSantis et al., 2011): a median was calculated and the CES was divided in two groups: low (CES score ≤ 12) and high (CES score > 12).

Assessment of psychiatric symptoms

As previously described (Baker et al., 2012; Glenn et al., 2016), the Clinician-Administered PTSD Scale (CAPS), an interview designed to assess DSM-IV PTSD symptoms, was administered (Blake et al., 1995; Smith, Redd, DuHamel, Vickberg, & Ricketts, 1999; Weathers, Keane, & Davidson, 2001). Four CAPS subscales were assessed based on symptoms: re-experiencing (B1–5); avoidance (C1–2); numbing (C4–6); and hyperarousal (D1–5). PTSD symptom severity was measured by the CAPS total score (0–136 range). PTSD diagnosis was defined based on modified “subthreshold” guidelines, specifically at least one criterion A event, one cluster B symptom, and either three cluster C or two cluster D symptoms (Blanchard et al., 1996). Depression symptoms were assessed via self-report using the Beck Depression Inventory (BDI-II), which scores depressive symptoms as moderate to severe (> 19) within the past two weeks (Beck, Steer, Ball, & Ranieri, 1996).

Fear conditioning protocol

Fear conditioning was performed as previously described (Acheson, Eyler, Resovsky, Tsan, & Risbrough, 2015a; Orcutt et al., 2016). Briefly, a SR-HLAB Electromyography (EMG) system (San Diego Instruments, San Diego, CA, USA) was used to deliver startle pulses (108 dB, 40 ms). The air puff (250 psi) was delivered through a plastic tube positioned 2.5 cm from the center of the throat and stimuli were presented to the participant using E-Prime Software (Psychology Software Tools Inc., Sharpsburg, PA, USA). Eyeblink EMG responses were recorded through Ag/Ag 3 M Red Dot electrodes (resistance < 10 kΩ) placed on the *orbicularis oculi* muscle at the left eye. A reference electrode was placed at the mastoid bone behind the left ear.

The fear conditioning task was divided in two sessions: acquisition and extinction phases. Before the acquisition phase, each participant was instructed that one of two colored symbols presented was associated with an air puff. For stabilization of startle responding, each phase began with 6 startle pulses without stimuli. During the acquisition phase, 8 conditioned stimuli (CS+; danger signal; either a blue or yellow circle or square) were

presented for 6 s followed by an air puff in 75% contingency (previously measured and described; Acheson et al., 2015b), and 8 non-reinforced stimuli (CS-; safety signal; either a blue or yellow circle or square) were never paired with an air puff, and 8 startle stimuli were presented in the absence of any stimuli (noise-alone trial). The noise-alone trials were used as an index of baseline startle across the phase. The startle pulses were presented 4 s after the onset of CS+ or CS- signal, and the stimuli (blue or yellow circles or squares) paired with the CS+ and CS- signals were randomly assigned across subjects. After the acquisition phase, participants rested for 5 min and were then told to remember the associations they have learned before starting the extinction phase. During the extinction phase, each stimulus (CS+, CS- and noise-alone) was presented 16 times, but no air puff was presented. Fear extinction learning in this task is relatively similar after both short (less than 10 min) or long delays (72 hrs) after fear acquisition learning (Norrholm et al., 2008).

Statistical analysis

A total of 1134 U.S. Marines were assessed at pre-deployment. Only participants of European-American ancestry (EA; $n = 714$) were included in the study due to potential population stratification (Met allele is less frequent in African American, Hispanic, and Asian populations) (DeMille et al., 2002; Palmatier, Kang, & Kidd, 1999). Data on 7 participants were excluded from analysis due to technical difficulties during testing that resulted in low signal/noise ratio that precluded accurate signal measurement. Of the 714 EA participants analyzed in the pre-deployment phase, 524 completed all the questionnaires and fear conditioning testing at post-deployment, and 2 participants were excluded from analysis due to technical difficulties. Among the 522 participants from whom all the parameters were successfully obtained after deployment, 70 participants were excluded from the post-deployment analysis because they had been diagnosed with PTSD before deployment which could have confounded interpretation of deployment effects on fear processing (Figure 1).

Fear conditioning data were analyzed as previously described, standard for this FPS protocol (Acheson et al., 2015b). Within each block, the noise-alone startle averages were subtracted from the CS+ and CS- averages to adjust for changes in baseline startle across the session. As in past studies using this task, to assess fear acquisition we collapsed the last half of the trials in the acquisition phase (Acheson et al., 2015b). To assess fear extinction, we followed the statistical conventions described by our group and others for this task (Acheson et al., 2015b; Norrholm et al., 2011) by collapsing each trial type into 4 equal blocks, the first block (early) consisting of the first 4 trials of the phase, the second block (mid 1) trials 5–8, the third block (mid 2) trials 9–12, and the last block (late) trials 13–16.

We first determined if our study replicated previous reports of Met/Met increases in FPS during acquisition and extinction in subjects with PTSD, using the pre-deployment data set. Repeated measures two-way (Genotype × PTSD diagnosis) analysis of variance (ANOVA), with block as within-subjects factor and childhood trauma (total CTQ score), lifetime trauma burden (Life Event Checklist, LEC; Gray, Litz, Hsu, & Lombardo, 2004), CAPS score, and 4 ancestry PCAs as covariates, was used for each CS trial separately, followed by Sidak *post hoc* tests, as appropriate. We separated the CS trial types because of the difficulty in interpreting and powering analyses with >3-way interactions, and because previous studies

suggest that CS- responses are strongly associated with *COMT* val158met genotype (Norrholm et al., 2013). We next asked if childhood trauma moderates the relationship between *COMT* genotype and PTSD on FPS acquisition and extinction. Therefore, repeated measures three-way ANOVA (Genotype × PTSD diagnosis × childhood trauma), with block as within-subjects factor, and LEC, CAPS score and ancestry PCAs as covariates, was conducted, followed by Sidak *post hoc* tests. Finally, to investigate the effect of recent combat trauma exposure on FPS, repeated measures two-way ANOVA (Genotype × CES), with block as within-subjects factor, and childhood trauma, LEC, CAPS score, and ancestry PCAs as covariates, was performed, followed by Sidak *post hoc* tests. Interactions with block were followed by separate ANOVAs at each block.

Results

Demographic and trauma history of participants

Demographic and descriptive information of participants in MRS-II have been described previously (Acheson et al., 2015b; Minassian et al., 2015). Pre-deployment demographic and trauma information are described for each *COMT* genotype (Table 1). Following one-way ANOVA, no differences in age, months spent in military, childhood or lifetime trauma history (CTQ and LEC, respectively), or BDI-II score were found across *COMT* genotype groups before deployment (Table 1) and Chi-square test revealed no difference in marital status, education, or PTSD diagnosis (Table 1). However, a non-parametric Kruskal-Wallis test revealed a main effect of genotype was observed on CAPS score ($p < 0.01$), with Met/Met carriers showing higher CAPS score before deployment compared to Met/Val carriers ($p < 0.01$, following Dunn's comparison test) (Table 1). In Marines not diagnosed with PTSD, a main effect of genotype was still observed before deployment on CAPS score (Kruskal-Wallis test, $p = 0.01$), with Met/Met carriers showing higher CAPS score compared to Met/Val carriers ($p < 0.01$ following Dunn's comparison test) (data not shown). After deployment, no change was observed on combat experience score (CES), CAPS and BDI-II score, or in the percentage of participants diagnosed with PTSD across *COMT* genotype groups (Table 2).

Met/Met genotype is associated with increased fear-potentiated startle in individuals with PTSD and childhood trauma exposure

We first determined if our study replicated previous reports of Met/Met increases in FPS during acquisition and extinction in participants with PTSD when controlling for trauma burden and childhood trauma. In the acquisition phase, genotype was not associated with differences in FPS during either the CS+ or CS- (no main effects or interactions with PTSD group, Figure 2, for Table of means ± SEM see Supplementary Table 1). PTSD participants exhibited increased FPS to the CS- ($F_{1,701} = 8.85$; $p < 0.01$) regardless of genotype (Figure 2b). During extinction, main effects of block ($F_{3,701} = 10.83$; $p < 0.001$ and $F_{3,701} = 11.07$; $p < 0.001$) were observed on CS+ and CS- signal, respectively, but did not interact with other factors (Figure 3a–f, for Table of means ± SEM see Supplementary Table 1). There were no significant associations of genotype or PTSD with CS+ responding (Figure 3g). Across the CS- trials however, Met/Met carriers diagnosed with PTSD had increased FPS compared to Met/Met carriers without PTSD (genotype: $F_{2,701} = 4.48$, $p < 0.05$; genotype × PTSD: $F_{2,701}$

= 3.21, $p < 0.05$, followed by *post hoc* test $p < 0.05$) (Figure 3h). These results replicate previous findings that Met/Met carriers with PTSD exhibit increased responses to safety signals compared to Met/Met carriers without PTSD (Norrholm et al., 2013).

We next asked if childhood trauma moderates the relationship between *COMT* genotype and PTSD on FPS acquisition and extinction. In the acquisition phase, three-way ANOVA (Genotype × PTSD diagnosis × childhood trauma) showed no main effects of childhood trauma or interactions with the other factors during the CS+ or CS- trials (see above). During the extinction phase, all groups showed significant reductions in potentiation to both the CS + and CS- trials (main effects of block: $F_{3,696} = 10.82$; $p < 0.001$ and $F_{3,696} = 9.51$; $p < 0.001$) (Figure 4a–f). Whereas no genotype associations were observed with FPS during the CS+ trials (Figure 4g), a genotype × PTSD diagnosis × childhood trauma interaction was observed ($F_{2,696} = 3.50$, $p < 0.05$; genotype: $F_{2,696} = 3.80$, $p < 0.05$; genotype × PTSD: $F_{2,696} = 2.96$, $p = 0.05$) on FPS across the CS- trials (Figure 4h). *Post hoc* comparisons indicated that high FPS during the safety signal in Met/Met carriers with PTSD was primarily found in participants that endorsed childhood trauma ($p < 0.05$, compared to Met/Met carriers not diagnosed with PTSD, but with at least one childhood trauma) (Figure 4h), while Met/Met carriers with PTSD but without childhood trauma were not different than carriers without PTSD.

Increased fear-potentiated startle in Met/Met carriers after deployment is moderated by combat trauma

We next investigated the effect of deployment-related combat trauma exposure on FPS after return from deployment. To assess combat trauma effects, we grouped subjects into high and low trauma exposure via a median split of combat experience scores (CES) assessed by the DRRI post-deployment. To control for chronic PTSD, we excluded participants who were already diagnosed with PTSD at pre-deployment. In the acquisition phase, neither genotype nor combat trauma was associated with FPS during the CS+ and CS- signals. During the extinction phase, a main effect of block ($F_{3,439} = 7.59$; $p < 0.001$) and a block × genotype × CES interaction ($F_{6,439} = 2.14$; $p < 0.05$) were found during the CS+ trials. Thus, ANOVAs (Genotype × CES) were conducted for each block separately (Figure 6). Within the mid 2 extinction block, a strong trend for a genotype × CES interaction was observed ($F_{2,439} = 3.28$; $p < 0.05$). High combat exposure increased fear-potentiated response during the mid 2 CS+ trials only in Met/Met carriers, compared to Met/Val or Val/Val carriers (Figure 6a–c). During the CS- signal, a main effect of block was found ($F_{3,439} = 5.73$; $p < 0.001$), but no effect of either genotype or combat trauma was found on FPS (Figure 6d–f).

Discussion

The present study aimed to verify whether *COMT*val158met polymorphism moderated impaired fear processes observed in PTSD, if these associations were further moderated by childhood trauma, and if genotype was associated with recent trauma effects on learned fear processes. We replicated previous findings that homozygous Met carriers diagnosed with PTSD displayed greater FPS to the CS- (safety signal) compared to Val carriers before deployment. Importantly, childhood trauma significantly moderated this association, since

only Met/Met carriers with PTSD who endorsed childhood trauma, as compared to those who did not endorse childhood trauma, had a higher fear-potentiated response to the safety signal during extinction. After deployment, Met/Met carriers reporting high, not low, combat trauma showed modest elevations in fear-potentiated response to the CS+ (danger signal) during extinction compared to Val carriers when controlling for PTSD symptoms.

Here, the increased FPS found in Met/Met carriers diagnosed with PTSD replicated previous studies reporting poor safety signal learning and reduced fear extinction in the same genotype group (Norrholm et al., 2013). However, we showed that the elevated FPS in homozygous Met carriers was moderated by childhood trauma history, such that Met/Met carriers diagnosed with PTSD who endorsed at least one category of childhood abuse/neglect showed the lowest safety signal learning (i.e. high FPS to CS-). This pattern of results supports the theory that gene × environment interactions are important factors in the risk of PTSD development, perhaps via alterations in core fear learning processes such as fear cue generalization. Although childhood trauma has widely been described as a risk factor for PTSD in U.S. troops (Agorastos et al., 2014; Cabrera, Hoge, Bliese, Castro, & Messer, 2007; Van Voorhees et al., 2012) and has been suggested to predict impaired fear extinction in PTSD patients (Stevens et al., 2016), the development of PTSD and the severity of its symptoms have been strongly associated with gene × environment interactions (Koenen, 2007; Nievergelt et al., 2015; Norrholm & Ressler, 2009; Skelton, Ressler, Norrholm, Jovanovic, & Bradley-Davino, 2012). Among the genes that have been linked to PTSD, the *COMTval158met* SNP interacts with traumatic load and urban violence, with Met/Met genotype showing a higher risk of PTSD (Boscarino et al., 2012; Kolassa et al., 2010; Valente et al., 2011). To our knowledge, the findings presented here are the first to report gene × environmental risk factor interactions in disruption of fear inhibition, a behavioral characteristic linked to the fear-related symptoms of PTSD (Acheson et al., 2015b; Jovanovic & Norrholm, 2011; Jovanovic et al., 2010).

Marines with no history of PTSD symptoms before deployment, who carried the Met/Met genotype and endorsed high combat trauma showed modest increases in FPS to the CS+ during extinction compared to Met/Met carriers who experienced low trauma or were Val/Val carriers. These findings suggest that acute trauma exposure, and more importantly, current PTSD symptoms are necessary to observe *COMT*val158met associations with altered fear processes. Two other studies have reported modulation of fear extinction by the *COMT*val158met polymorphism in healthy controls (Lonsdorf et al., 2009; Wendt et al., 2015), but those studies did not control for lifetime trauma. In sum, our finding that *COMT* SNP-modulated response to severe combat trauma (Nievergelt et al., 2015) is in agreement with the gene × environment hypothesis of PTSD. Interestingly, impaired fear extinction has been specifically associated with PTSD, not depression or anxiety, in active-duty Marines (Acheson et al., 2015b; Jovanovic et al., 2010), suggesting that impaired fear conditioning before deployment might be a predictor of higher PTSD risk after combat.

Altogether, our data support the conclusion that the COMTval158met SNP may contribute to disrupted fear inhibition in the context of severe trauma exposure and PTSD symptom burden. Dopamine transmission in the prelimbic and infralimbic cortex in rodents (dorsal anterior cingulate cortex and ventromedial prefrontal cortex in humans) modulates fear

response by maintaining and inhibiting fear response, respectively (Abraham, Neve, & Lattal, 2014; Quirk & Mueller, 2008). Although COMT is mainly expressed in the PFC, the involvement of other brain regions, such as hippocampus, should not be excluded. The hippocampus modulates contextual fear learning through dopaminergic activity (Abraham et al., 2014; Phillips & LeDoux, 1992). Interestingly, *COMT*val158met polymorphism has been associated with changes in hippocampal CA2/3 volumes, which is negatively correlated with trauma exposure in Met/Met (Rabl et al., 2014). Decreased hippocampal volume has been reported in civilian trauma-related PTSD (Smith, 2005; Villarreal et al., 2002; Woon, Sood, & Hedges, 2010) and combat-related PTSD (Gurvits et al., 1996), and has been shown to predict vulnerability to psychological trauma (Gilbertson et al., 2002). Therefore, *COMT*val158met polymorphism could alter contextual fear inhibition through changes in hippocampal function. Additionally, COMT may affect fear inhibition via modulation of norepinephrine signaling (Chen et al., 2004; Mier, Kirsch, & Meyer-Lindenberg, 2010). The COMT enzyme catabolizes norepinephrine (Tunbridge, 2010), and elevated plasma concentrations are reported in Met carriers (Jung et al., 2012). PTSD patients have higher stress-induced norepinephrine release compared to healthy individuals (O'Donnell, Hegadoren, & Coupland, 2004). The noradrenergic signaling modulates fear memory consolidation by enhancing fear response in humans (Soeter & Kindt, 2011; Visser, Kunze, Westhoff, Scholte, & Kindt, 2015), suggesting a potential role of COMT-mediated fear extinction through noradrenergic as well as dopaminergic mechanisms.

Despite the large sample size of this study (714 participants), a limitation is that women were not included, because they were not part of infantry battalions at the time of assessment. Women show lower COMT activity than men, due to its estrogen-modulated downregulation (Chen et al., 2004; Hassan, Salama, Arafa, Hamada, & Al-Hendy, 2007; Tunbridge, 2010). Furthermore, sex-dependent associations between *COMT* polymorphism and anxiety-related traits have been reported (Stein, Fallin, Schork, & Gelernter, 2005). A previous large study showed no sex-dependent effect of *COMT*val158met polymorphism on impaired fear inhibition found in PTSD patients (Norrholm et al., 2013). However, further investigation will be necessary to assess the potential gene × trauma interactions in women.

These findings replicate previous studies showing that the Met/Met carriers with PTSD are more likely to show increased fear responding compared to Met/Val or Val/Val carriers with PTSD, and extend this finding to show that this association is modulated by early life trauma exposure. This study supports the suggestion that *COMT* could be a potential biomarker of treatment response to exposure-based cognitive-behavior therapy (CBT). Here, Met/Met carriers that endorsed a childhood or combat trauma exhibited resistance to extinction, suggesting that these individuals may show reduced response to therapy targeting the behavioral patterns associated with fear symptoms, such as exposure-based CBT (Lonsdorf & Kalisch, 2011). In addition, Met/Met carriers also exhibit increased fear responding after combat trauma, regardless of PTSD diagnosis, suggesting some acute loss of fear regulation after trauma in Met/Met carriers as a whole. These results support a role of COMT gene-environment interactions in the development of psychiatric-relevant phenotypes. Further work will be necessary to understand the mechanisms underlying the modulation of cortical signaling by the *COMT*val158met polymorphism and fear extinction memory impairments in PTSD pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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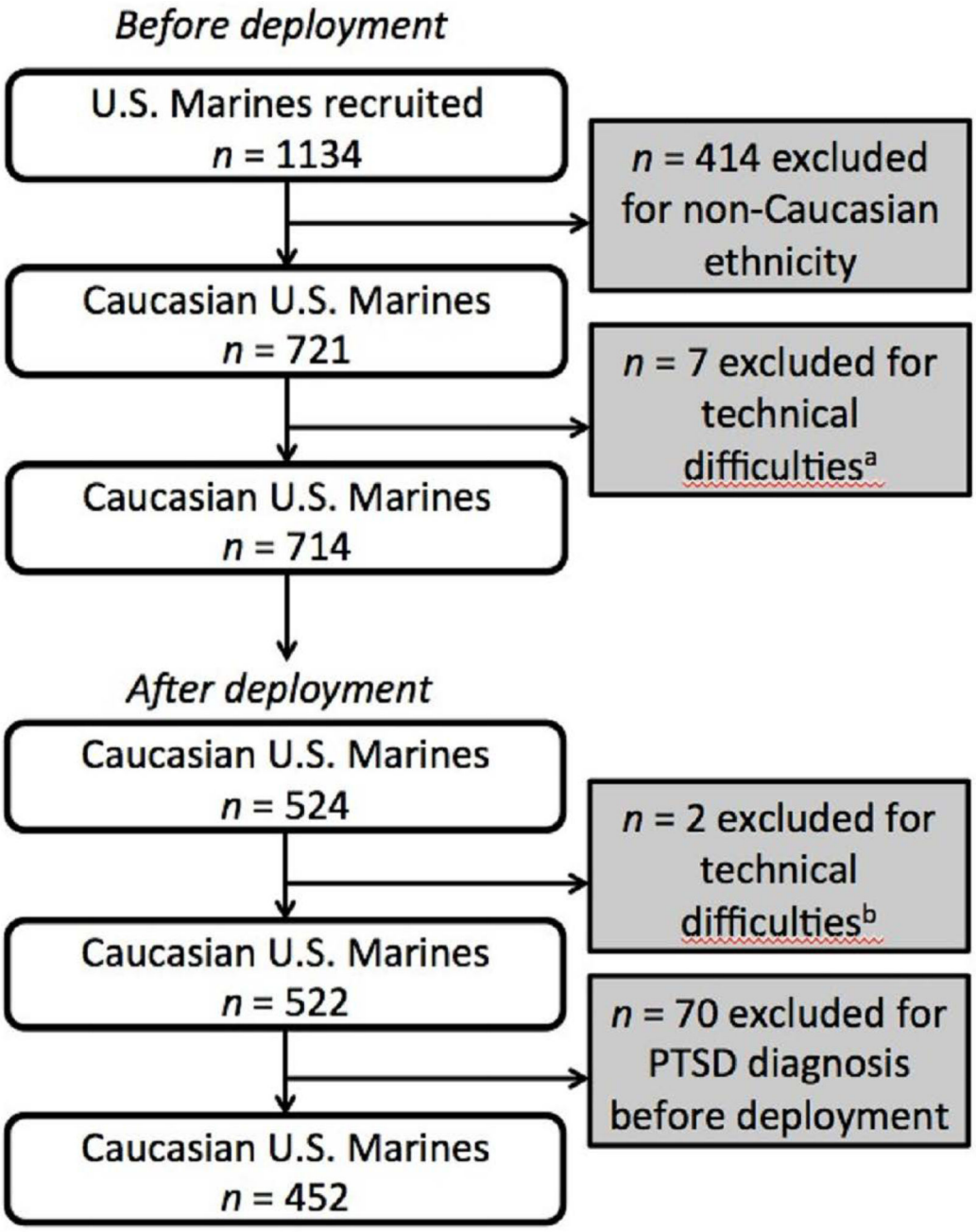

Figure 1.
Chart indicating the number of participants recruited and excluded from the final analysis.

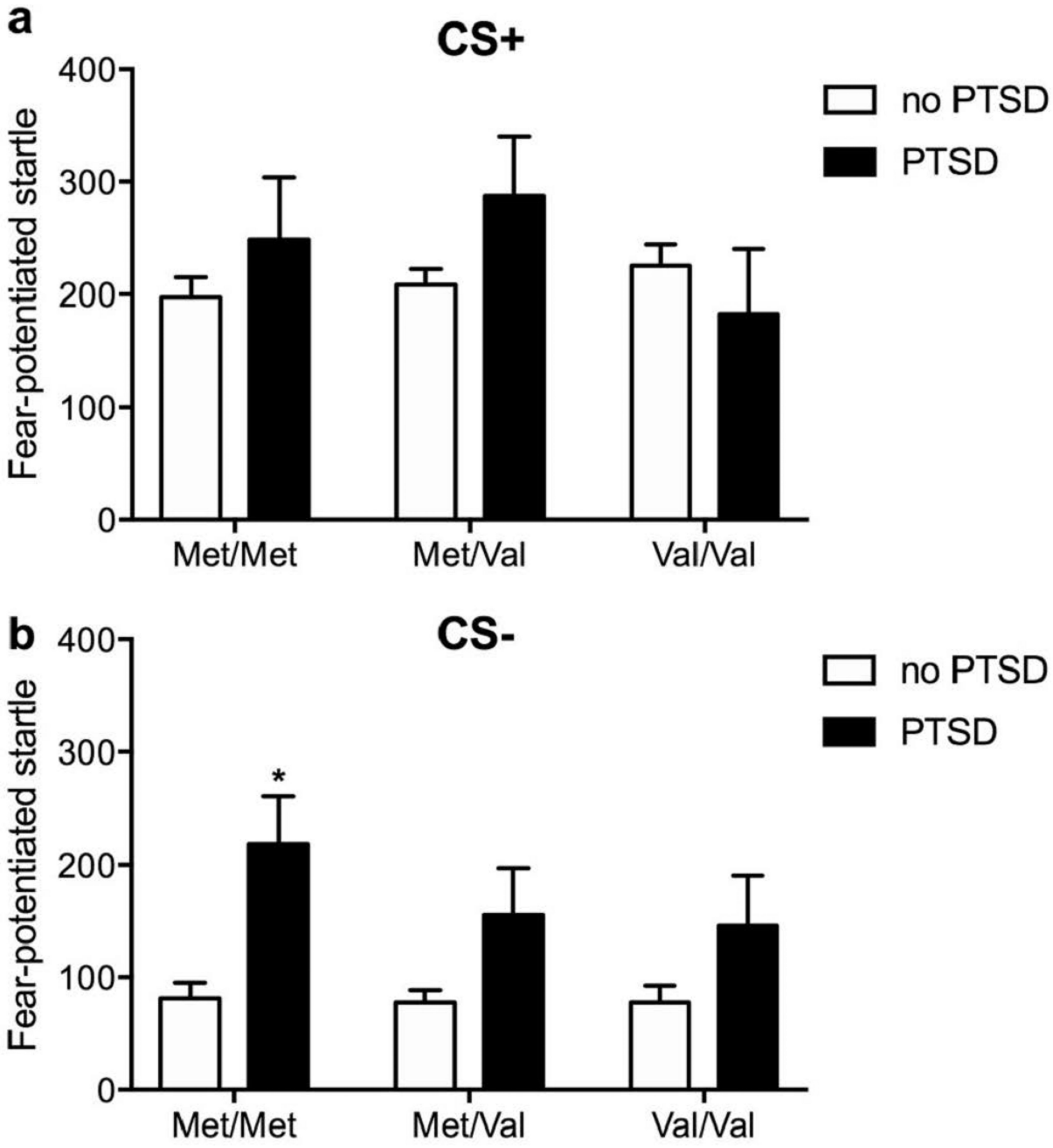

Figure 2.
Effect of COMT genotype and PTSD diagnosis on fear-potentiated startle during late acquisition before deployment.

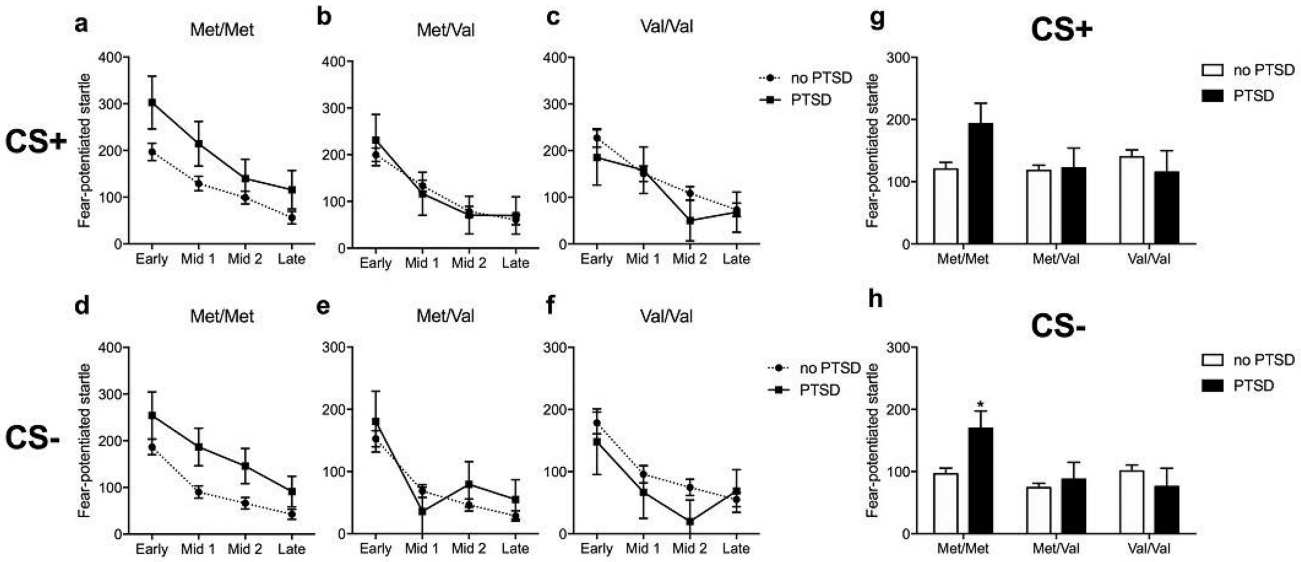

Figure 3.

Effect of COMT genotype and PTSD diagnosis on fear-potentiated startle during extinction before deployment.

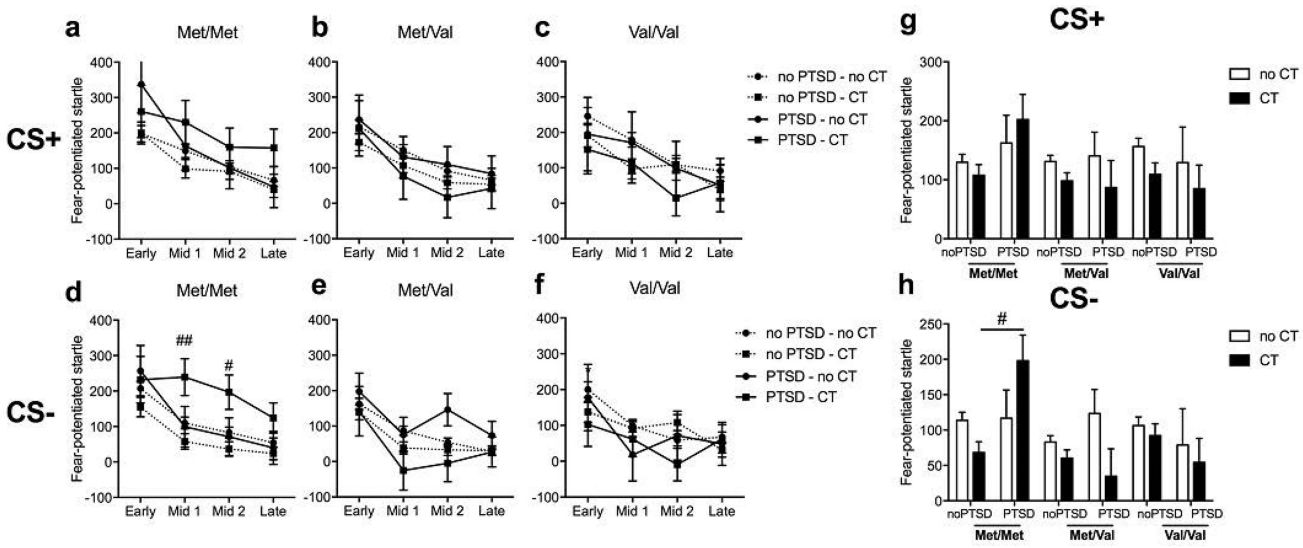

Figure 4.

Modulation by childhood trauma (CT) of the effect of COMT genotype and PTSD diagnosis on fear-potentiated startle during extinction before deployment.

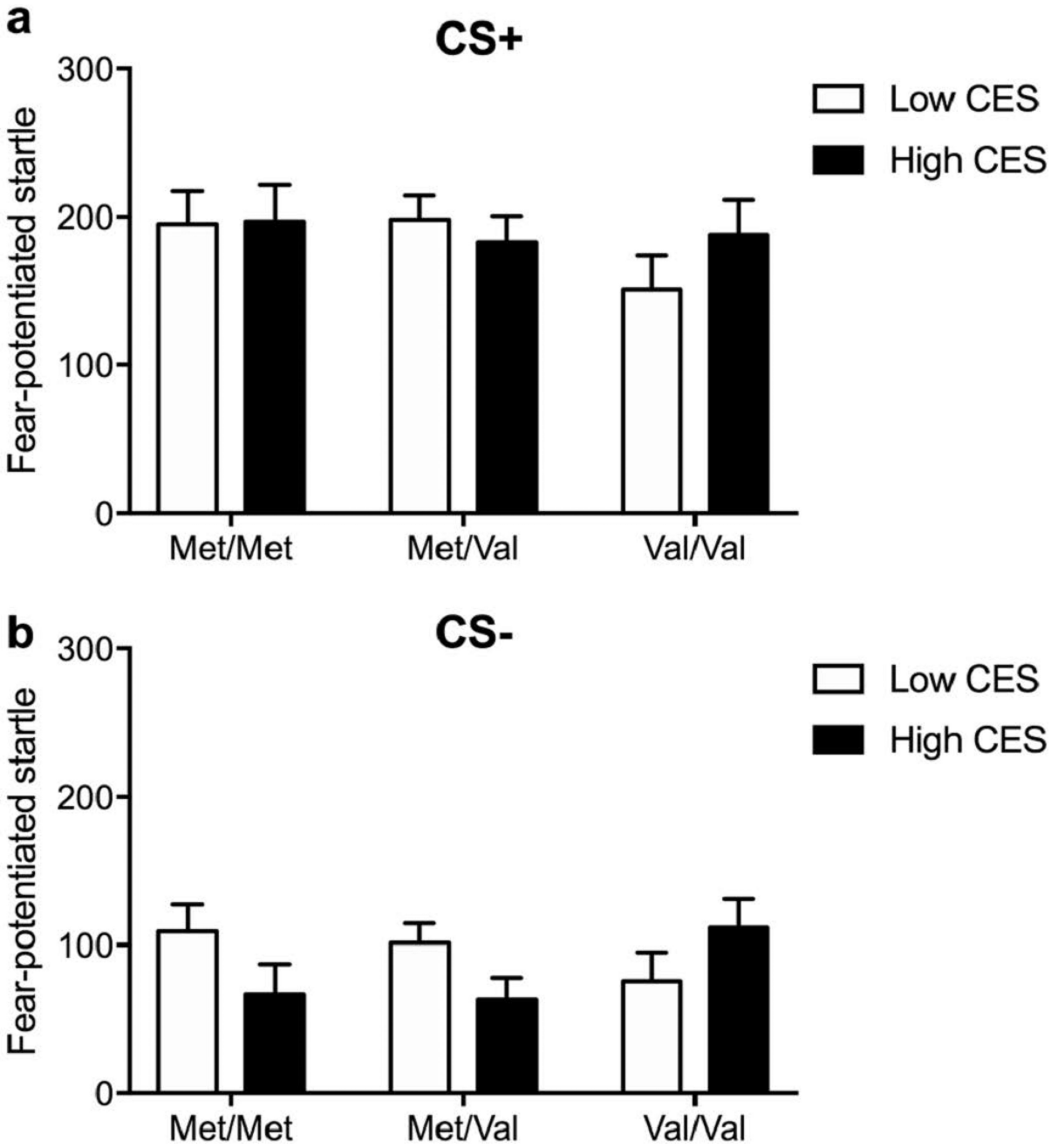

Figure 5.
Effect of COMT genotype and combat trauma on fear-potentiated startle during late acquisition after deployment.

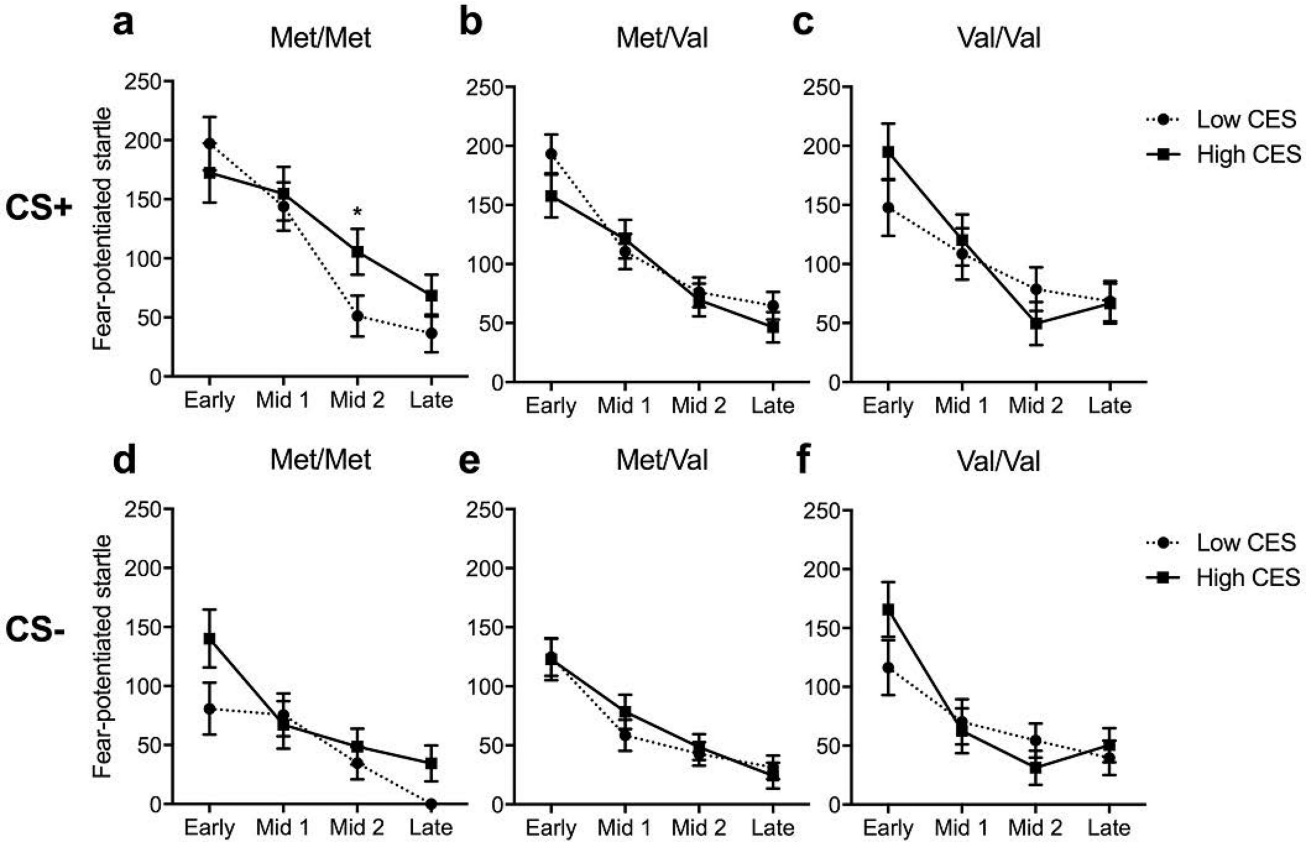

Figure 6.

Effect of COMT genotype and combat trauma on fear-potentiated startle during extinction after deployment.

Table 1

Demographic characteristics, trauma history and psychiatric symptoms scores across *COMT* genotype groups before deployment

	COMT **Met/Met**	***COMT*** **Met/Val**	***COMT*** **Val/Val**	***p*** **value**
Demographics				
n	201	332	181	N/A
Age (M, SD) [a]	22.30 (2.89)	22.11 (2.77)	22.04 (2.61)	0.54
Marital status % [b]				0.63
Never married	68.66	71.69	69.61	
Married	28.85	26.51	29.83	
Divorced	1.00	1.20	0.56	
Separated	1.49	0.60	0.00	
Higher education % [b]				0.65
Masters or Doctorate Degree	0.00	0.30	0.00	
College	24.38	24.40	28.73	
High school diploma	74.13	72.29	66.85	
Other	1.49	3.01	4.42	
Months spent in military (M, SD) [a]	31.77 (25.44)	29.36 (24.82)	29.06 (24.87)	0.46
Months left in enlistment (M, SD) [a]	27.19 (12.96)	27.32 (13.48)	26.84 (13.54)	0.95
Trauma history				
Childhood trauma (CTQ) (M, SD)[a]	36.75 (12.91)	36.68 (11.61)	38.08 (14.81)	0.46
Lifetime trauma (LEC) (M, SD) [a]	4.60 (3.17)	4.32 (2.82)	4.28 (2.77)	0.44
Psychiatric symptoms				
CAPS score (M, SD) [b]	**14.11 (13.62)** **	11.01 (12.68)	12.36 (12.90)	< **0.01**
BDI-II (M, SD) [a]	5.95 (7.04)	4.72 (5.90)	5.14 (6.06)	0.09

	COMT Met/Met	*COMT* Met/Val	*COMT* Val/Val	*p* value
PTSD diagnosis (%) [c]	11.44	7.83	11.60	0.26

BDI-II, Beck Depression Inventory II; CAPS, Clinician-Administered PTSD Scale.

[a] One-way ANOVA performed followed by Tukey's *post hoc* test;

[b] non-parametric Kruskal-Wallis test;

[c] Chi-squared test performed;

** $p < 0.05$ following Dunn's comparison test, compared to COMT Met/Val genotype

Table 2

Combat trauma history and psychiatric symptoms across COMT genotype groups after deployment

	COMT **Met/Met**	***COMT*** **Met/Val**	***COMT*** **Val/Val**	***p*** **value**
n	127	236	124	N/A
Combat experience score (M, SD) [a]	11.64 (7.60)	13.29 (8.52)	13.45 (9.90)	0.18
CAPS score (M, SD)[b]	16.91 (17.36)	14.00 (15.69)	15.22 (16.75)	0.19
BDI-II (M, SD) [a]	3.56 (5.92)	3.42 (5.56)	3.24 (4.32)	0.37
PTSD diagnosis (%)[c]	17.32	18.64	18.55	0.95

BDI-II, Beck Depression Inventory II; CAPS, Clinician-Administered PTSD Scale.

[a]One-way ANOVA performed followed by Tukey's *post hoc* test;

[b]non-parametric Kruskal-Wallis test;

[c]Chi-squared test performed