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Prospective longitudinal assessment of sensorimotor gating as a risk/resiliency factor for posttraumatic stress disorder

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Little is understood about cognitive mechanisms that confer risk and resiliency for posttraumatic stress disorder (PTSD). Prepulse Inhibition (PPI) is a measure of pre-attentional response inhibition that is a stable cognitive trait disrupted in many neuropsychiatric disorders characterized by poor behavioral or cognitive inhibition, including PTSD. Differentiating between PTSD-related phenotypes that are pre-existing factors vs. those that emerge specifically after trauma is critical to understanding PTSD etiology and can only be addressed by prospective studies. This study tested the hypothesis that sensorimotor gating performance is associated with risk/resiliency for combat-related PTSD. As part of a prospective, longitudinal study, 1226 active duty Marines and Navy Corpsman completed a PPI test as well as a clinical interview to assess PTSD symptoms both before, and 3 and 6 months after a combat deployment. Participants that developed PTSD 6 months following deployment (N=46) showed lower PPI across pre and post-deployment time points compared to participants who did not develop PTSD (N=1182) . Examination of the distribution of PTSD across PPI performance revealed a lower than expected number of cases in the highest performing quartile compared to the rest of the distribution ($p < 0.04$). When controlling for other factors that predict PTSD in this population, those in the top 25% of PPI performance showed a >50% reduction in chance to develop PTSD (OR = 0.32). Baseline startle reactivity and startle habituation were not significantly different between PTSD risk and control groups. These findings suggest that robust sensorimotor gating may represent a resiliency factor for development of PTSD following trauma.

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INTRODUCTION

Development of posttraumatic stress disorder (PTSD) is a major public health concern. PTSD is associated with high levels of impairment across social and occupational domains [1], with impact on work loss and disability on par with neurological disorders and exceeding diabetes [2]. While the lifetime prevalence of exposure to traumatic events is high in the United States (~90%), only a subset of exposed individuals will go on to develop PTSD (~8%) [3, 4]. This disparity suggests that individual vulnerability and or protective factors play a role in the development of PTSD following trauma and may inform effective prevention and treatment efforts [5].

Prepulse inhibition is an operational measure of sensorimotor gating, a pre-attentional filtering mechanism. Presentation of a neutral acoustic "prepulse" 30–300 ms before a more intense, startling stimulus reduces startle magnitude, possibly via direction of cognitive resources toward the prepulse, inhibiting responses to the subsequent startle stimulus during this processing window [6]. PPI is a relatively heritable trait with high test-retest reliability and may be an endophenotype for a number of neuropsychiatric disorders [7–13]. PPI performance is reduced in a number of neuropsychiatric disorders including panic disorder, obsessive-compulsive disorder, schizophrenia, Tourette's disorder, and Huntington's disorder [14–18]. Just as some genetic mutations and brain injuries may confer risk across traditional psychiatric diagnoses [19–21], disruptions in fundamental cognitive processes such as stimulus processing and response inhibition may also confer risk across diagnoses, in particular diagnoses characterized by intrusive thoughts or images, sensations or movements [22]. The known neural substrates for PPI would also support its association with neuropsychiatric disorders characterized by abnormalities in cortical, striatal, and thalamic circuits [8, 23, 24].

For many of the disorders associated with PPI disruption, a defining feature is the inability to inhibit intrusive thoughts and behaviors (e.g. obsessive-compulsive disorder, Huntington's disorder, and Tourettes) [8, 25]. PTSD is characterized by the inability to inhibit trauma memories and fear responses to trauma cues [26]. PPI is modulated by multiple neural circuits involved in emotional regulation that are disrupted in PTSD, including prefrontal cortex, hippocampus, and amygdala [27], all of which modulate PPI performance [22–25]. PPI associations with PTSD however are inconsistent, with some cross-sectional studies showing significantly reduced PPI in PTSD patients [28–33] while others detected no differences or only marginal differences [34–37]. Animal models suggest that PPI may also be reduced

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after trauma or after activation of stress or threat-response circuits [38–41]. Thus, it remains unclear if PPI disruption is linked to PTSD, and if so, if this phenotype is a vulnerability factor present *before* trauma exposure and PTSD diagnosis or if PPI abnormalities manifest only after trauma exposure and PTSD symptom emergence. To test this question we examined sensorimotor gating and its relation to post-deployment PTSD as part of the Marine Resiliency Study, a prospective, longitudinal study of PTSD in Marines and Navy Corpsman deployed to Iraq or Afghanistan [42]. We examined sensorimotor gating both before and after deployment in participants who had no PTSD at pre-deployment, but who were grouped by development (or not) of PTSD 6 months after returning from deployment.

METHODS AND MATERIALS

Study design and participants

We extracted data from 4 infantry battalions (7/2008–5/2012) that participated in the Marine Resiliency Study. Participants were evaluated approximately 1 month ($N = 2582$) before a 7-month deployment to Iraq or Afghanistan, and 3 ($N = 1898$) and 6 ($N = 1643$) months after deployment. Detailed demographics for the MRS 1 sample are provided elsewhere [42]. The institutional review boards of the University of California San Diego, the Veterans Affairs San Diego Research Service, and the Naval Health Research Center approved this study. Written informed consent was obtained from all participants.

Of the original sample, 1498 participants were assessed for PTSD at 6 months post deployment and tested for PPI at all assessment periods (145 participants were not tested for PPI). Of those, 144 were excluded from the analysis due to poor hearing or unscorable startle responses at *all* assessment periods (see Supplementary methods for details). An additional 126 were excluded because they met DSM-IV diagnostic criteria for PTSD at the pre-deployment visit. Participants were included if they had interpretable startle data at any of the three assessment periods. This left a total of 1228 participants with interpretable startle data during at least one assessment period and no pre-deployment PTSD diagnosis (84% of the sample had usable data for at least two visits). Of these participants, 46 (4%) met diagnostic criteria for PTSD at the 6-month assessment period and 1182 (96%) did not. *N* varied slightly across assessment period depending on number of visits with scorable responses (e.g. PTSD group $N = 36–38$).

Measures

Participants completed a 4-h test battery including historical (e.g. self-report questionnaires), biological (e.g. blood collection, psychophysiology), neuropsychological, psychiatric/medical, and psychosocial assessments at each visit. Only measures used in the present study are described, for complete methods see [42].

Clinician-administered PTSD Scale (CAPS)

Posttraumatic stress disorder symptoms were assessed using the CAPS, a structured diagnostic interview administered before deployment, and again 3 and 6 months after deployment [43]. The outcome variable was diagnosis of PTSD at the 6-month post-deployment visit. The diagnosis was meeting criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (*DSM-IV*): a threat to life, injury, or physical integrity (Criterion A1) and the presence of at least one re-experiencing symptom, three avoidance symptoms, and two hyperarousal symptoms [44–46]. Symptoms must have occurred at least once within the past month (frequency ≥ 1) and caused a moderate amount of distress (intensity ≥ 2) [47]. CAPS score (intraclass correlation coefficient = 0.99) and PTSD diagnosis (Kappa = 0.714) inter-rater reliability was high. CAPS total score (0–136 range) served as a continuous measure of PTSD symptom severity.

Deployment trauma and stress exposure

To assess deployment stressors we administered 4 subscales of the Deployment Risk and Resilience Inventory (DRRI) [48] 1 week after return from deployment: Combat Experiences, Aftermath of Battle, Deployment Concerns about Life and Family Disruptions, and the Difficulty Living and Working Environments. Subscale scores were centered (subject score-group mean score) and averaged to produce one composite DRRI score. Positive and negative values represent higher and lower deployment stress, respectively.

Potential covariates

Tobacco and caffeine use, history of head injury and ancestry were examined as potential moderators of PPI and/or PTSD (see Supplementary methods for details). Only ancestry and deployment head injury were selected as variables in final statistical models. *Ancestry:* To control for the association of PPI with race/ethnicity we used ancestry identification using genetic markers as previously described (see Supplementary materials and [49]), which grouped subjects into 4 possible ancestry categories: African, Hispanic/Native American, European, and East Asian/other ancestry. *Traumatic Brain Injury (TBI)*: Because we previously found a strong association between deployment TBI and PTSD post-deployment in this population [50] this variable was included in our logistic regression models. Participants were queried about lifetime head injuries sustained before the index deployment and injuries sustained between the pre-deployment and 6-month post-deployment assessments (for details see [50]). TBI was defined as any head injury resulting in self-reported loss of consciousness (LOC) or altered mental status (i.e., dazed, confused, "seeing stars," and/or posttraumatic amnesia immediately afterward or upon regaining consciousness [51]) and treated as a categorical variable (0 = no TBI, 1 = one or more TBI). Pre-deployment lifetime trauma exposure was assessed using the Life Events Checklist (LEC)[52], which asks participants if they have experienced, directly or indirectly or learned about, any of 17 different traumatic experiences such as a natural disaster or assault. The number of traumatic events endorsed by either direct experience, indirect experience, or by learning about was summed to create a trauma exposure score.

Stimuli and apparatus

Acoustic stimuli were delivered and electromyography (EMG) was recorded using SR-HRLAB (San Diego Instruments, San Diego, CA, USA) as previously described [53, 54]. EMG signals were amplified (0.5 mV electrode input = 2500-mV signal output), band-pass filtered (100–1000 Hz), digitized, and recorded (1 kHz sampling rate). Electrode impedance was <10 kΩ.

Psychophysiology experimental procedures

To assess hearing, each participant was tested for detection of a 35-dB tone ranging from 500–3000 Hz (Grayson-Stadler Audiometer, see Supplementary materials). Subjects were seated in a comfortable chair and fitted with headphones. Two electrodes (Ag/AgCl) were placed at the left orbicularis oculi muscles. A reference electrode was placed on the left mastoid. The acoustic startle session consisted of a 5-min acclimatization period with a 70-dB broad-band background noise (continuous throughout the session), followed by a startle threshold test [55], an anxiety-potentiated startle test [56] and prepulse inhibition test [54]. Three min breaks were given between each test. Here we will discuss the PPI results only.

After a 1.5-min acclimation period participants were presented with the following trial types: a 40 ms, 114 dB startle pulse and three 20 ms prepulse + pulse combinations (86 dB prepulse preceding the 114 dB pulse at either a 30, 60, or 120 ms interval) with an average inter-trial interval of 15 s (range: 10–20 s) [18, 54]. A block of three 114 dB pulse-alone trials was presented at session start, followed by a block of mixed prepulse+pulse trials (6 each of 3 trial types) and 114-dB pulse-alone trials (10) presented in a pseudorandom order, and ending with a block of 3 114-dB pulse-alone trials. Pulse-alone trials were analyzed across the three blocks to test startle habituation [18, 54]. Only trials within block 2 were used to compute PPI. %PPI = 100 − [(startle response for PREPULSE + PULSE trial)/(startle response for PULSE-ALONE trial)] × 100.

EMG data preparation

EMG data were smoothed (5-ms rolling average) and responses were visually examined across each trial by a trained technician blind to symptom statsus to identify and remove artifact (e.g. voluntary blinks) that were not associated with the pulse onset (e.g. a response was not counted unless it was within 100 ms of pulse onset). Artifact not associated with pulse onset (e.g. a voluntary blink) or trials with exceptionally high noise levels at baseline were identified and removed by a blind rater according to standard methodology [53]. Subjects that did not have a detectable startle response (non-responder) or had poor hearing were excluded

Table 1. Demographics.

	Group (PTSD at 6 mo post deployment)	
	No PTSD ($n = 1182$)	**PTSD ($n = 46$)**
Pre-deployment age	22.35 (3.43)	22 (2.31)
Education		
<High school	4.9%	2.2%
High school	64%	67.4%
Some college	27.6%	21.7%
Bachelors	2.8%	6.5%
Post-Graduate	0.6%	0%
Ancestry (genetic)		
European	67%	54.3%
African	4.4%	10.9%
Hispanic/N.A.	18.3%	21.7%
Asian/Other	10.3%	13%
Pre-deployment trauma exposure	6.41 (3.96)	7.32 (3.74)
CAPS total score		
Pre-Deployment	12.82 (11.68)	20.93 (14.85)[a]
6 mo. post deployment	12.21 (12.89)	61.98 (15.26)[a]
DRRI Score (Z)	0.02 (0.76)	0.4 (0.79)[a]
Deployment TBI	18.3%	52.2%[a]
Lifetime Severe TBI	4%	7%

Data presented as mean (standard deviation) or percentages.
PTSD = PTSD diagnosis at 6 mo post deployment.
Lifetime severe TBI indicates self-report of TBI with loss of consciousness greater than 30 min.
NA Native American.
[a]$p < 0.05$ vs. Healthy.

(see Supplementary methods for details). Non-responders were removed due to potential floor effects of low startle reactivity and/or excessively high noise confounding PPI measures.

Statistical analysis

Covariate selection. Potential covariates based on past literature were examined for associations with PPI before final model building. We found no associations of self-reported caffeine and nicotine use on PPI, consistent with other studies [54]. Nor did we find an effect of specific Battalion to which each participant was assigned. Thus, these variables were not used in the final statistical models. Both groups exhibited similar levels of TBI exposure at pre-deployment thus this was not used as a factor in the models (Table 1, and Supplementary materials).

Mixed effects models. Linear mixed models were used to examine differences between participants with and without PTSD on PPI performance and baseline startle. For the PPI model, PTSD status, ISI, and Visit were entered as fixed factors (ISI and Visit as repeated measures). Testing Battalion and Subject ID were entered as nested random factors (Participants within Testing Battalion). For the baseline startle model, PTSD status, Startle Block, and Visit were entered as fixed factors (Startle Block and Visit repeated). Testing Battalion and Subject ID were again entered as nested random factors. In both cases, an unstructured covariance matrix was specified for repeated measures as suggested by model selection criteria. Restricted maximum likelihood estimation was employed for analysis of missing data. Significant effects ($\alpha = 0.05$) were explored using post-hoc simple effects tests with Tukey HSD adjustments. To investigate the relationship of combat experience and post-deployment PPI, Pearson correlations were conducted between each prepulse trial type and the DRRI score. Similarly, to investigate the relationship between PPI performance and PTSD symptom severity Pearson correlations were conducted between average PPI performance and CAPS total scores at 3 and 6 months post deployment.

Logistic regression model. According to the results of the linear mixed model, PPI was not significantly different across visits in line with multiple previous studies of consistent test-retest reliability [9–13]. Accordingly, for the logistic regression prediction of PTSD diagnosis, a "trait" PPI score for each individual was computed by averaging PPI across visits. A binary logistic regression model was then used to explore the extent of the influence of membership in the top quartile of the distribution of these PPI scores had on the probability of meeting criteria for PTSD at 6 months post deployment. We chose to focus on the 6-month time point to capture associations with more enduring PTSD diagnostic status.

Measures of pre-deployment PTSD symptoms, intensity of combat experience, and deployment-related traumatic brain injury were included in the model to assess the unique effect of PPI group membership in the context of other strong predictors of PTSD [55]. Battalion was not found to be a significant predictor and was thus removed from the analysis. History of lifetime severe TBI was not different across PPI performance groups (Top 25% vs. bottom 75% had 3 and 5% of subjects respectively endorsing a severe TBI) thus was not used in the model. African ancestry was found to significantly increase predicted PTSD probability relative to European Ancestry in this sample, however, inclusion or exclusion of this factor did not alter the overall effects of the other predictors (see Supplementary methods). Ancestry was also not associated with PPI performance, similar to other large studies of PPI [57, 58]. Thus, Ancestry was dropped from the logistic regression model for simplicity of interpretation and to avoid overfitting.

RESULTS

Demographics

Demographic information is in Table 1. Participants with PTSD at 6 months post deployment did not significantly differ in age from participants who did not develop PTSD. Participants with PTSD at 6 months post deployment also did not differ on pre-deployment exposure to traumatic events [$t = -1.64$, ns]. Participants with PTSD had significantly higher CAPS total scores at baseline [$t = -4.57$, $p < 0.0001$] and at 6-month [$t = -25.5$, $p < 0.0001$] assessments, as well as higher combat exposure [$t = -4.82$, $p < 0.0001$]. Significantly higher rates of deployment TBI were present in PTSD vs. healthy participants (52.2% vs.18.3%; Fisher's exact test = $p < 0.0001$). A Chi-Square test for Ancestry was invalid due to smaller than 5 expected frequencies in two PTSD group cells.

Linear mixed models

Prepulse inhibition. As expected, there was an overall main effect of ISI [$F(2,5563) = 178.05$, $p < 0.0001$] which did not vary across visits [ISIxVisit: $F(4,3615) < 1$, n.s.] such that PPI performance increased with each lengthening of the ISI (ps < 0.05). PPI performance remained stable across all visits [Main effect of Visit: $F(2,4809) < 1$, n.s.].

There was a significant main effect of PTSD status [$F(1,1358) = 6.83$, $p < 0.009$] such that participants with PTSD at 6 months post deployment overall showed reduced PPI across all visits relative to participants without PTSD (Fig. 1, top panel). The group difference in PPI performance was also dependent upon ISI [Fig. 1, bottom panel; $F(2,5563) = 3.72$, $p < 0.03$]. Post-hoc tests showed that the PTSD group at 6 months had reduced PPI at 30 ($p < 0.05$) and 60 ms trials ($p < 0.001$) relative to participants without PTSD. This effect did not vary across visits [ISI × PTSD × Visit: $F(4,3615) < 1$, n.s.].

Baseline startle. There was a main effect of Visit on startle [$F(2,7780) = 5.02$, $p < 0.007$] which trended toward varying by PTSD status [See Fig. 2, left panel; $F(2,7780) = 2.77$, $p < 0.07$]. This trend is due to slightly elevated startle responding at baseline in the PTSD group compared to those without PTSD, although no post-hoc comparisons were significant. All groups habituated

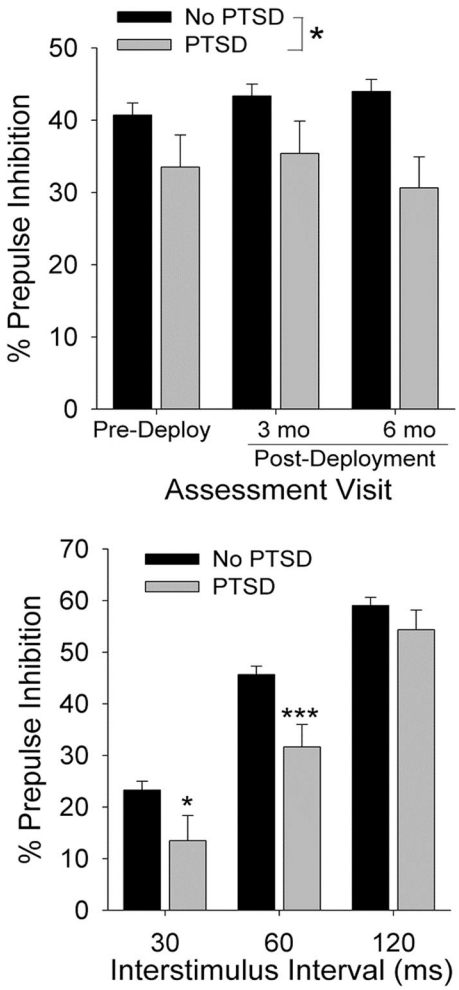

Fig. 1 PPI performance before and after deployment in those that did and did not go on to develop PTSD post-deployment. Top panel. Participants who went on to endorse PTSD at the 6 mo post deployment time point exhibited significantly reduced PPI independently of assessment period. *$p < 0.05$ Main effect of Group. See Results for details. Bottom panel. Participants who went on to develop PTSD at 6 months post deployment exhibited overall reductions in PPI at the 30 and 60 but not 120 ms ISI parameters *$p < 0.05$ ***$p < 0.001$ vs. No PTSD group, post hoc simple comparisons after ISI X group interaction. See "Results" for details.

similarly to the startle stimuli over time [Fig. 2, right panel; Main effect of block: $F(2,7780) = 264.04$, $p < 0.0001$, Main effect of group: $F(2,7780) < 1$, n.s.].

Logistic regression

To explore the difference in PPI across the two groups, we compared the distribution of PPI scores in participants with and without PTSD (Fig. 3, inset). PTSD cases were well represented across the lower three quartiles of the distribution, however, fewer PTSD cases overlapped with controls in the top quartile of PPI performers. Indeed, the top quartile of performers included only 10.9% of the PTSD cases whereas 89.1% of PTSD cases were located in the lower three quartiles (lower 75% of all performers). Fisher's exact test analysis confirmed that the uneven distribution of PTSD cases between the highest quartile and the lower 3 was significant ($p < 0.04$, Fig. 3; Top 25%: *N* subjects with PTSD = 5 out of 391, 1.7%; Bottom 75%: *N* subjects with PTSD = 41 out of 934, 4.4%). We then conducted a binary logistic regression to determine the risk scores for PTSD across the top 25% and bottom 75% groups (Table 2) in conjunction with known strong risk factors in this sample (deployment TBI, deployment trauma/stress, and pre-deployment symptoms [55]). All four variables included in the model were significant, unique predictors of post-deployment PTSD, with the total model producing a pseudo-R^2 of 0.16. Larger number of pre-deployment symptoms, deployment stressors, and incidence of deployment-related TBI all predicted a higher probability of PTSD. Membership in the top quartile of PPI performance significantly reduced the likelihood of meeting criteria for PTSD independent of the influence of the other variables (OR = 0.32, $p = 0.02$). To assess the contribution of PPI performance in relation to our covariates, a separate stepwise regression was conducted with all covariates entered at step one and PPI entered at step 2. At step one, all covariates remained significant predictors of PTSD status and the model produced a pseudo-R^2 of 0.135, indicating that PPI performance accounted for an additional 2.5% of the probability of developing PTSD (pseudo-R^2 of 0.16 for the full model).

Correlations

PPI and startle reactivity significantly correlated with deployment stress with trivial to small strength (rs = 0.07–0.13, see Supplementary materials for details). Neither PPI nor startle reactivity was associated with symptom severity at 3 or 6 months post deployment in the entire sample or within PTSD cases alone.

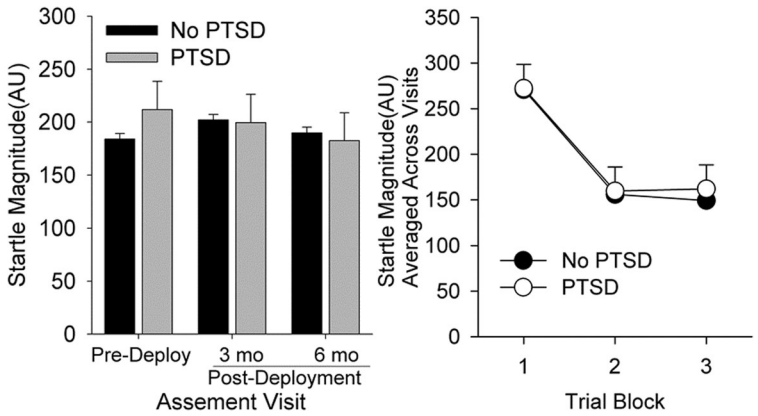

Fig. 2 Startle reactivity and habituation do not differ across those that did and did not go on to develop PTSD post deployment. Left panel. Average startle reactivity across the session at each assessment visit. Right panel. Startle habituation across 3 session blocks, averaged across all visits. AU arbitrary units.

DISCUSSION

The current study represents the first prospective, longitudinal test of PPI change in response to trauma exposure and development of PTSD. Development of PTSD 6 months following return from combat deployment was associated with significantly lower "trait" PPI, i.e. similar PPI scores across all assessment periods relative to participants who did not develop PTSD at 6 months. These effects were independent from general startle magnitude and habituation, which were not different across groups likely due to difficulty in detecting startle differences in individuals with PTSD when using high-intensity startle stimuli in neutral contexts [55, 59]. Furthermore, PPI performance did not strongly correlate with trauma exposure or symptom severity, suggesting that PPI performance may be a stable trait relatively impervious to long-term effects of trauma or PTSD diagnosis.

PTSD cases were least prevalent in the highest performing quartile of the PPI distribution, supporting the intriguing notion that relatively high PPI may be a PTSD resiliency factor, in contrast to low PPI being a risk factor. Logistical regression indicated that those scoring in the top 25% of the distribution had less than half of the risk for developing PTSD compared to participants scoring in the remaining 75% of the distribution. This pattern indicates high PPI performance specifically may play a role in resiliency to develop symptoms, but outside of this high performance group, PPI is not related to symptom severity. Whether high sensorimotor gating per se is an important mechanism for resiliency or if it is simply a marker for biological mechanisms (e.g. robust circuit function/connectivity) that confer resiliency is unclear.

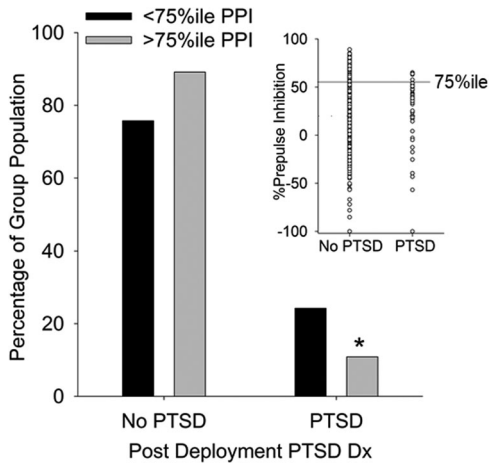

Fig. 3 Prevalence of PTSD in top PPI performers. Top 75th percentile of PPI performers across the sample exhibit a significantly lower rate of PTSD diagnosis relative to those in the lower range than would be expected by chance (Fishers exact test, $p < 0.05$). Inset: Scatter plot of PPI collapsed across 30 and 60 ms ISI trials and all visits for individuals who did and did not develop PTSD 6 mo after deployment illustrating lower membership in the top 75th performance percentile among those who developed PTSD.

Neural circuits that modulate PPI in humans are also strongly implicated in PTSD, and to some degree implicated in PTSD risk [60]. Imaging studies have shown consistent positive associations between prefrontal cortex activation, volume, white matter integrity and glucose metabolism with PPI performance [61–65]. These circuits are disrupted in PTSD patients after trauma [60], thus high PPI may reflect greater functionality and/or reserve to buffer stress-induced effects on this circuit. Hippocampal and amygdala circuits also modulate PPI, and these circuits have been linked to predisposition to develop PTSD [21, 60].

PPI is thought to measure a pre-attentional filtering mechanism that gates external and internal stimuli, and is positively correlated with some measures of executive function [66]. Thus, at a simple conceptual level a marked ability to gate or inhibit responses would not be a surprising resiliency factor for development of PTSD, as PTSD is characterized by intrusive thoughts and memories of the trauma as well as uncontrollable fear responses to external and internal stimuli. There is little information however about the overlap between PPI performance and emotion and fear regulation task performance that is associated with PTSD. PPI can be broken into both "automatic" and "controllable" components across different ISIs, with only ISI >100 ms modifiable by conscious attentional control (see Braff et al. [25] for review). In the present study, only PPI performance within the "automatic" spectrum (30 and 60 ms ISI) was significantly associated with PTSD diagnosis (schizophrenia is most consistently associated with deficits at the 60 ms ISI [58]). Thus, mechanisms that subserve "automatic" filtering performance may be important for this association with trauma resiliency. Finding that PPI performance at short but not long ISIs is associated with PTSD risk may explain why previous findings of PPI "deficits" are inconsistent in the literature, which have most typically used ISIs of 120 ms [26–32, 36, 37]. Given the present findings suggesting PPI performance is related to risk rather than modified by PTSD, may also explain why it may be more difficult to detect group differences consistently in smaller studies.

The present study and others have shown that PPI is a relatively stable trait (present results [67]), and that it has significant heritability [68]. Thus, future work of examining potential gene overlap between PTSD-associated risk and resiliency alleles and PPI-associated genes may prove fruitful in understanding pathways mediating stress resiliency [69]. It is not clear however if PPI is also "trainable", and if so, if increasing PPI performance generalizes to other cognitive and emotional functions or reduces psychiatric risk. "Bottom-up" training of acoustic discrimination has been shown to improve a wide range of cognitive and global functions in schizophrenia subjects [70], thus the idea that enhancement of relatively "simple" stimulus processing or inhibitory functions may confer therapeutic or even possibly prophylactic benefit is worth further research.

Strengths of this study include the very large sample size and the relatively rare prospective, longitudinal design to assess PPI

Table 2. Logistic regression predicting PTSD diagnosis at 6 months post deployment.

Predictor	β	Wald	p	Odds ratio	95% CI (LL – UL)	
Pre-deployment						
PTSD symptoms	0.04	12.8	<0.001	1.04	1.02	1.06
Deployment Trauma/Stress	0.55	6.93	0.008	1.73	1.5	2.6
Deployment TBI	1.24	12.68	<0.001	3.45	1.74	6.8
High PPI performance	−1.15	5.5	0.02	0.32	0.12	0.83

Pre-deployment symptoms as measured by total CAPS score. Deployment Trauma/Stress as measured by composite DRRI 1 week post deployment return. Deployment TBI indicates endorsed at least one head injury with altered mental state, loss of consciousness and/or post-injury amnesia. High PPI performance indicates representation in the top 25% of sample population distribution. PPI performance is defined as average PPI across 30 and 60 ms trials across all visits.

before trauma exposure and PTSD development. Limitations for this study include that the endorsement of PTSD at 6 months post deployment was relatively low (4%), which may have reduced our statistical power. Further, the was conducted only in men, as females did not at that time participate in Marine Infantry battalions, and represents a highly screened and relatively homogenous population. These factors may reduce generalizability of our results to more vulnerable and/or heterogeneous populations.

REFERENCES

1. Druss BG, Hwang I, Petukhova M, Sampson NA, Wang PS, Kessler RC. Impairment in role functioning in mental and chronic medical disorders in the United States: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2008;14:728–37.
2. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004;109:21–27.
3. Breslau N. The epidemiology of trauma, PTSD, and other posttrauma disorders. Trauma Violence Abuse. 2009;10:198–210.
4. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. J Trauma Stress. 2013;26:537–47.
5. Zhang L, Li H, Benedek D, Li X, Ursano R. A strategy for the development of biomarker tests for PTSD. Med Hypotheses. 2009;73:404–9.
6. Swerdlow NR, Braff DL, Geyer MA. Cross-species studies of sensorimotor gating of the startle reflex. Ann N Y Acad Sci. 1999;877:202–16.
7. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, et al. Initial heritability analyses of endophenotypic measures for Schizophrenia: the consortium on the genetics of schizophrenia. Arch Gen Psychiatry. 2007;64:1242–50.
8. Kohl S, Heekeren K, Klosterkötter J, Kuhn J. Prepulse inhibition in psychiatric disorders - apart from schizophrenia. J Psychiatr Res. 2013;47:445–52.
9. Flaten MA. Test-retest reliability of the somatosensory blink reflex and its inhibition. Int J Psychophysiol. 2002;45:261–5.
10. Abel K, Waikar M, Pedro B, Hemsley D, Geyer M. Repeated testing of prepulse inhibition and habituation of the startle reflex: a study in healthy human controls. J Psychopharmacol. 1998;12:330–7. 337
11. Schwarzkopf SB, McCoy L, Smith DA, Boutros NN. Test-retest reliability of prepulse inhibition of the acoustic startle response. Biol Psychiatry. 1993;34:896–900.
12. Ludewig K, Ludewig S, Seitz A, Obrist M, Geyer MA, Vollenweider FX. The acoustic startle reflex and its modulation: effects of age and gender in humans. Biol Psychol. 2003;63:311–23.
13. Francis DD, Szegda K, Campbell G, Martin WD, Insel TR. Epigenetic sources of behavioral differences in mice. Nat Neurosci. 2013;6:445–6.
14. Swerdlow NR, Light GA, Cadenhead KS, Sprock J, Hsieh MH, Braff DL. Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition, and level of function. Arch Gen Psychiatry. 2006;63:1325–35.
15. Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M. Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. Biol Psychiatry. 1996;39:33–41.
16. Perry W, Minassian A, Feifel D, Braff DL. Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. Biol Psychiatry. 2001;50:418–24.
17. Ahmari SE, Risbrough VB, Geyer MA, Simpson HB. Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. Neuropsychopharmacology. 2012;37:1216–23.
18. Ludewig S, Ludewig K, Geyer MA, Hell D, Vollenweider FX. Prepulse inhibition deficits in patients with panic disorder. Depress Anxiety. 2002;15:55–60.
19. Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen CY, Choi KW, et al. International meta-analysis of PTSD genome-wide association studies identifies sex and ancestry-specific genetic risk loci. Nat Commun. 2019;10:4558.
20. Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, et al. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the Million Veteran Program. Nat Genet. 2021;53:174–84.
21. Risbrough VB, Vaughn MN, Friend SF. Role of inflammation in traumatic brain injury–associated risk for neuropsychiatric disorders: state of the evidence and where do we go from here. Biol Psychiatry. 2022;91:438–48.
22. Swerdlow NR, Braff DL, Geyer MA. Sensorimotor gating of the startle reflex: What we said 25 years ago, what has happened since then, and what comes next. Psychopharmacology. 2016;30:1072–81.
23. Swerdlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology. 2001;156:194–215.
24. Naysmith LF, Kumari V, Williams SCR. Neural mapping of prepulse-induced startle reflex modulations as indices of sensory information processing in healthy and clinical populations: a systematic review. Hum Brain Mapp. 2021; 42:5495–518.
25. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology. 2001;156:234–58.
26. Acheson DT, Gresack JE, Risbrough VB. Hippocampal dysfunction effects on context memory: Possible etiology for posttraumatic stress disorder. Neuropharmacology. 2012;62:674–85.
27. Ressler KJ, Berretta S, Bolshakov VY, Rosso IM, Meloni EG, Rauch SL, et al. Posttraumatic stress disorder: clinical and translational neuroscience from cells to circuits. Nat Rev Neurol. 2022;18:273–88.
28. Ornitz EM, Pynoos RS. Startle modulation in children with posttraumatic stress disorder. Am J Psychiatry. 1989;146:866–70.
29. Grillon C, Morgan CA, Southwick SM, Davis M, Charney DS. Baseline startle amplitude and prepulse inhibition in Vietnam veterans with posttraumatic stress disorder. Psychiatry Res. 1996;64:169–78.
30. Grillon C, Morgan CA 3rd, Davis M, Southwick SM. Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. Biol Psychiatry. 1998;44:1027–36.
31. Echiverri-Cohen AM, Zoellner LA, Ho W, Husain J. An analysis of inhibitory functioning in individuals with chronic posttraumatic stress disorder. J Anxiety Disord. 2016;37:94–103.
32. Pineles SL, Blumenthal TD, Curreri AJ, Nillni YI, Putnam KM, Resick PA, et al. Prepulse inhibition deficits in women with PTSD. Psychophysiology. 2016;53:1377–85.
33. Butler RW, Braff DL, Rausch JL, Jenkins MA, Sprock J, Geyer MA. Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry. 1990;147:1308–12.
34. Lipschitz DS, Mayes LM, Rasmusson AM, Anyan W, Billingslea E, Gueorguieva R, et al. Baseline and modulated acoustic startle responses in adolescent girls with posttraumatic stress disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:807–14.
35. Holstein DH, Vollenweider FX, Jancke L, Schopper C, Csomor PA. P50 suppression, prepulse inhibition, and startle reactivity in the same patient cohort suffering from posttraumatic stress disorder. J Affect Disord. 2010;126:188–97.
36. Vrana SR, Calhoun PS, McClernon FJ, Dennis MF, Lee ST, Beckham JC. Effects of smoking on the acoustic startle response and prepulse inhibition in smokers with and without posttraumatic stress disorder. Psychopharmacology. 2013;230:477–85.
37. Meteran H, Vindbjerg E, Wiingaard Uldall S, Glenthoj B, Carlsson J, Orange B. Startle habituation, senory, and sensorimotor gating in trauma-affected refuges with posttraumatic stress disorder. Psychol Med. 2018;49:581–9.
38. Bakshi VP, Alsene KM, Roseboom PH, Connors EE. Enduring sensorimotor gating abnormalities following predator exposure or corticotropin-releasing factor in rats: a model for PTSD-like information-processing deficits? Neuropharmacology. 2012;62:737–48.
39. Risbrough VB, Hauger RL, Roberts AL, Vale WW, Geyer MA. Corticotropin-releasing factor receptors CRF1 and CRF2 exert both additive and opposing influences on defensive startle behavior. J Neurosci. 2004;24:6545–52.
40. Flandreau E, Risbrough V, Lu A, Ableitner M, Geyer MA, Holsboer F, et al. Cell type-specific modifications of corticotropin-releasing factor (CRF) and its type 1 receptor (CRF) on startle behavior and sensorimotor gating. Psychoneuroendocrinology. 2014;53C:16–28.
41. Rajbhandari AK, Baldo BA, Bakshi VP. Predator stress-induced CRF release causes enduring sensitization of basolateral amygdala norepinephrine systems that promote PTSD-like startle abnormalities. J Neurosci. 2015;35:14270–85.
42. Baker DG, Nash WP, Litz BT, Geyer MA, Risbrough VB, Nievergelt CM, et al. Predictors of risk and resilience for posttraumatic stress disorder among ground combat Marines: methods of the Marine Resiliency Study. Prev Chronic Dis. 2012;9:E97.
43. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8:75–90.
44. Blanchard EB, Hickling EJ, Taylor AE, Forneris CA, Loos W, Jaccard J. Effects of varying scoring rules of the Clinician-Administered PTSD Scale (CAPS) for the diagnosis of post-traumatic stress disorder in motor vehicle accident victims. Behav Res Ther. 1995;33:471–5.
45. Blanchard EB, Hickling EJ, Taylor AE, Loos W. Psychiatric morbidity associated with motor vehicle accidents. J Nerv Ment Dis. 1995;183:495–504.

46. Blanchard EB, Hickling EJ, Buckley TC, Taylor AE, Vollmer A, Loos WR. Psychophysiology of posttraumatic stress disorder related to motor vehicle accidents: replication and extension. J Consult Clin Psychol. 1996;64:742–51.
47. Weathers FW, Ruscio AM, Keane TM. Psychometric properties of nine scoring rules for the Clinician-Administered Post-traumatic Stress Disorder Scale. Psychological Assess. 1999;11:124–33.
48. King LA, King DW, Vogt DS, Knight J, Samper RE. Deployment Risk and Resilience Inventory: a collection of measures for studying deployment-related experiences of military personnel and veterans. Mil Psychol. 2006;18:89–120.
49. Nievergelt CM, Maihofer AX, Shekhtman T, Libiger O, Wang X, Kidd KK, et al. Inference of human continental origin and admixture proportions using a highly discriminative ancestry informative 41-SNP panel. Investig Genet. 2013;4:13.
50. Yurgil KA, Barkauskas DA, Vasterling JJ, Nievergelt CM, Larson GE, Schork NJ, et al. Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. JAMA Psychiatry. 2014;71:149–57.
51. von Holst H, Cassidy JD. Mandate of the WHO Collaborating Centre Task Force on mild traumatic brain injury. J Rehabil Med. 2004:43;8–10.
52. Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the life events checklist. Assessment. 2004;11:330–41.
53. Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry. 1992;49:206–15.
54. Acheson DT, Stein MB, Paulus MP, Geyer MA, Risbrough VB. The effect of pregabalin on sensorimotor gating in 'low' gating humans and mice. Neuropharmacology. 2012;63:480–5.
55. Glenn DE, Acheson DT, Geyer MA, Nievergelt CM, Baker DG, Risbrough VB. High and low threshold for startle reactivity associated with Ptsd symptoms but not Ptsd risk: evidence from a prospective study of active duty marines. Depress Anxiety. 2016;33:192–202.
56. Acheson DT, Stein MB, Paulus MP, Ravindran L, Simmons AN, Lohr JB, et al. Effects of anxiolytic treatment on potentiated startle during aversive image anticipation. Hum Psychopharmacol Clin Exp. 2012;27:419–27.
57. Swerdlow NR, Sprock J, Light GA, Cadenhead K, Calkins ME, Dobie DJ, et al. Multisite studies of acoustic startle and prepulse inhibition in humans: initial experience and methodological considerations based on studies by the Consortium on the Genetics of Schizophrenia. Schizophr Res. 2007;92:237–51.
58. Swerdlow NR, Light GA, Sprock J, Calkins ME, Green MF, Greenwood TA, et al. Deficient prepulse inhibition in schizophrenia detected by the multi-site COGS. Schizophr Res. 2014;152:503–12.
59. Acheson DT, Geyer MA, Risbrough VB. Psychophysiology in the study of psychological trauma: where are we now and where do we need to be? Curr Top Behav Neurosci. 2014;21:157–83.
60. Admon R, Milad MR, Hendler T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. Trends Cogn Sci. 2013;17:337–47.
61. Kumari V, Antonova E, Zachariah E, Galea A, Aasen I, Ettinger U, et al. Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans. Neuroimage. 2005;26:1052–8.
62. Hazlett EA, Buchsbaum MS, Haznedar MM, Singer MB, Germans MK, Schnur DB, et al. Prefrontal cortex glucose metabolism and startle eyeblink modification abnormalities in unmedicated schizophrenia patients. Psychophysiology. 1998;35:186–98.
63. Neuner I, Stöcker T, Kellermann T, Ermer V, Wegener HP, Eickhoff SB, et al. Electrophysiology meets fMRI: neural correlates of the startle reflex assessed by simultaneous EMG-fMRI data acquisition. Hum Brain Mapp. 2010;31:1675–85.
64. Kumari V, Fannon D, Geyer MA, Premkumar P, Antonova E, Simmons A, et al. Cortical grey matter volume and sensorimotor gating in schizophrenia. Cortex. 2008;44:1206–14.
65. Ota M, Sato N, Matsuo J, Kinoshita Y, Kawamoto Y, Hori H, et al. Multimodal image analysis of sensorimotor gating in healthy women. Brain Res. 2013;1499:61–68.
66. Swerdlow NR, Light GA. Neurophysiological biomarkers informing the clinical neuroscience of schizophrenia: mismatch negativity and prepulse inhibition of startle. Curr Topics Behav Neurosci. 2022, in press..
67. Light GA, Swerdlow NR, Rissling AJ, Radant A, Sugar CA, Sprock J, et al. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. PLoS ONE. 2012;7:e39434.
68. Greenwood TA, Light GA, Swerdlow NR, Calkins ME, Green MF, Gur RE, et al. Gating deficit heritability and correlation with increased clinical severity in schizophrenia patients with positive family history. Am J Psychiatry. 2016;173:385–91.
69. Quednow BB, Ejebe K, Wagner M. Meta-analysis on the association between genetic polymorphisms and prepulse inhibition of the acoustic startle response. Schizophr Res. 2018;198:52–59.
70. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology. 2012;37:43–76.

AUTHOR CONTRIBUTIONS

VBR, MAG, and DGB designed the study and supervised data collection and edited the manuscript, DTA contributed to data collection, conducted the analysis, and lead the manuscript preparation, CMN, KAY, and VBR aided data collection, processing, and analysis and edited the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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