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RESEARCH ARTICLE

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Fear learning alterations after traumatic brain injury and their role in development of posttraumatic stress symptoms

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Background: It is unknown how traumatic brain injury (TBI) increases risk for posttraumatic stress disorder (PTSD). One potential mechanism is via alteration of fear-learning processes that could affect responses to trauma memories and cues. We utilized a prospective, longitudinal design to determine if TBI is associated with altered fear learning and extinction, and if fear processing mediates effects of TBI on PTSD symptom change.

Methods: Eight hundred fifty two active-duty Marines and Navy Corpsmen were assessed before and after deployment. Assessments included TBI history, PTSD symptoms, combat trauma and deployment stress, and a fear-potentiated startle task of fear acquisition and extinction. Startle response and self-reported expectancy and anxiety served as measures of fear conditioning, and PTSD symptoms were measured with the Clinician-Administered PTSD Scale.

Results: Individuals endorsing "multiple hit" exposure (both deployment TBI and a prior TBI) showed the strongest fear acquisition and highest fear expression compared to groups without multiple hits. Extinction did not differ across groups. Endorsing a deployment TBI was associated with higher anxiety to the fear cue compared to those without deployment TBI. The association of deployment TBI with increased postdeployment PTSD symptoms was mediated by postdeployment fear expression when recent prior-TBI exposure was included as a moderator. TBI associations with increased response to threat cues and PTSD symptoms remained when controlling for deployment trauma and postdeployment PTSD diagnosis.

Conclusions: Deployment TBI, and multiple-hit TBI in particular, are associated with increases in conditioned fear learning and expression that may contribute to risk for developing PTSD symptoms.

KEYWORDS
biological markers, posttraumatic stress disorder, startle, trauma, traumatic brain injury

1 | INTRODUCTION

Posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) are "signature injuries" of recent U.S. military conflicts. Prevalence rates for veterans of these conflicts are estimated at 23% for PTSD (Fulton et al., 2015) and 10–23% for TBI (Hoge et al., 2008; O'Neil et al., 2013; Wilk et al., 2010). TBI has been associated with anxiety disorder symptomology in the general population (Moore, Terryberry-Spohr, & Hope, 2006), and recent longitudinal studies in military service members found that exposure to TBI increases risk for PTSD (Bombardier et al., 2010; Bryant et al., 2010; Carlson et al., 2011; Perry et al., 2016; Schneiderman, Braver, & Kang, 2008; Stein et al., 2015; Wisco et al., 2014; Yurgil et al., 2014). However, mechanisms through which TBI modifies risk for PTSD remain unknown. One potential mechanism is via disruption of neurocircuitry subserving fear responses to trauma memories and cues (Huang et al., 2014, 2016a). PTSD is consistently associated with alterations in fear-learning processes. Contemporary models of PTSD implicate elevated fear-memory acquisition, poor contextual gating of fear, and impaired learning and retention of fear

Abbreviations: CAPS, Clinician Administered PTSD Scale; CS, conditional stimuli; DRRI-2, Deployment Risk and Resilience Inventory-2; EMG, electromyography; FPS, fear-potentiated startle; LOC, loss of consciousness; MRS-II, Marine Resiliency Study II; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; US, unconditional stimulus

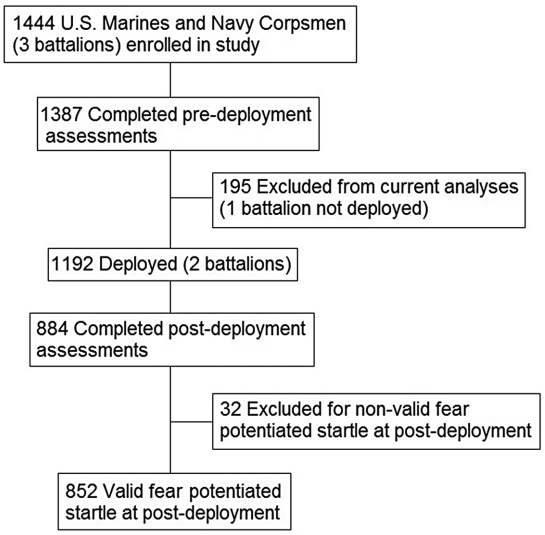

FIGURE 1 Participant flow and exclusion diagram

extinction in the development of exaggerated, enduring fear responses (Acheson et al., 2015; Briscione, Jovanovic, & Norrholm, 2014; Craske & Mystkowski, 2006; Grillon et al., 2009; Hermans, CRASKE, Mineka, & Lovibond, 2006; Lissek & van Meurs, 2015; Milad et al., 2009; Mineka & Zinbarg, 2006; Norrholm et al., 2011; Risbrough, Glenn, & Baker, 2016; VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014). Thus, head injuries affecting circuits involved with regulation of learned fear processes may increase risk for developing and maintaining PTSD symptoms (Yeh et al., 2016). In animals, brain injury is associated with enhanced fear acquisition (Reger et al., 2012; Schneider et al., 2016), impaired fear extinction (Schneider et al., 2016), and altered fear circuitry (Palmer, Metheny, Elkind, & Cohen, 2016) (but see (Sierra-Mercado et al., 2015)). However, specific effects appear to depend on methods used to model brain injury (Genovese et al., 2013; Logue, Cramer, Xu, Perl, & Galdzicki, 2015; Palmer et al., 2016) and it is unclear how accurately animal models reflect TBI in humans. Improved understanding of the effects of TBI on fear learning may facilitate treatment and prevention efforts for individuals recovering from head injury.

TBI is associated with performance deficits in memory, executive functioning, attention, and information processing that can persist for at least 1 year following injury (Carroll et al., 2014; 2004; Dikmen et al., 2009; Rabinowitz & Levin, 2014; Schretlen & Shapiro, 2009). It remains unknown if TBI impacts emotional learning processes related to PTSD. TBI is associated with disruption of neurocircuits mediating fear memory and its regulation, in particular cortical-limbic connectivity (Huang et al., 2014). Chronic traumatic encephalopathy (Gavett, Stern, & McKee, 2011; Stern et al., 2011) resulting from multiple concussions is associated with abnormal cortical and limbic circuit activation and morphology as well as symptoms of depression and emotional instability (Stern et al., 2011; 2013). In military samples, multiple blast exposures are associated with reduced cortical-limbic white matter integrity (Yeh et al., 2016), suggesting that "multiple hits" may particularly predispose subjects to abnormalities in fear circuit integrity and function.

Here, we tested the hypotheses that TBI alters fear conditioning and extinction, which in turn increases risk for postdeployment PTSD symptoms. We used data from the Marine Resiliency Study II (MRS-II; Acheson et al., 2015), a prospective, longitudinal study of active-duty service members assessed before and after combat deployment to Afghanistan. Participants completed a fear conditioning and extinction procedure, clinical interviews, and questionnaires at both assessments. We asked if deployment TBI is associated with postdeployment fear learning and extinction and if this effect is moderated by exposure to a previous recent TBI (i.e. "multi-hit" group). Finally, we conducted an exploratory mediation analysis to determine to what extent postdeployment fear learning mediates the association between deployment TBI and postdeployment change in PTSD symptoms.

2 | METHODS AND MATERIALS

2.1 | Study design and participants

MRS-II (Acheson et al., 2015) followed three battalions of U.S. Marines and Navy Corpsmen for 7 months. Two battalions were assessed on average 4 weeks (SD = 4.9) before deployment to Afghanistan and 22 weeks (SD = 22.4) after returning from deployment. The current analyses excluded the third battalion (n = 195), which was assessed at the same time points but was not deployed. Of 1,192 total individuals in the deployed battalions, 852 had valid fear-potentiated startle (FPS) measurement at postdeployment assessment (see Fig. 1). Postdeployment FPS data for 32 subjects were rendered nonvalid due to technical difficulties during testing. The institutional review boards of the University of California San Diego, VA San Diego Research Service, and Naval Health Research Center approved the study. Written informed consent was obtained from all participants.

2.2 | Fear conditioning and extinction procedure

Full details of FPS task methodology are previously reported in (Acheson et al., 2013, 2015; Norrholm et al., 2011).

2.2.1 | Apparatus and stimuli

A 250-psi air-puff delivered via a plastic tube positioned 2.5 cm from the center of the throat served as the unconditional stimulus (US). Colored geometric shapes (balanced across subjects) served as conditional stimuli (CS).

Acoustic startle was measured by electromyography (EMG) of the orbicularis oculi muscles in response to acoustic pulses (108 dB, 40 ms) delivered using a San Diego Instruments (SDI, San Diego, CA, USA) SR-HLAB EMG system. Sound levels were measured using continuous tones calibrated with a Quest Sound Level Meter on the A scale, coupled to the headphones with an artificial ear. EMG responses were recorded via Ag/Ag 3 M Red Dot electrodes placed at the orbicularis oculi muscles at the left eye connected to the SDI SR-HLAB EMG system. A reference electrode was placed on the mastoid bone behind the left ear. Prior to electrode placement, skin was cleaned with an alcohol swab and gently exfoliated with 3 M electrode prep tape. All elec-

trode resistances were <10 kΩ. EMG data were recorded at a sampling rate of 1 kHz, amplified (0.5 mV electrode input was amplified to 2500 mV signal output), band-pass filtered (100–1000 Hz), rectified, and then smoothed with a 5-point rolling average. Eyeblink responses were examined on a trial-by-trial basis at a window starting 100 ms before the startle pulse and ending 200 ms following the pulse. Only responses that peaked within 100 ms of pulse onset were scored as a startle response. Trials in which startle response was obscured by excessive baseline noise or artifact were removed and replaced with an imputed value based on the average of the immediately preceding and following trials.

Trial-by-trial US expectancy responses were recorded via participants' responses on a key pad linked to E- Prime software indicating whether they expected to receive an air-puff ("1" key), were unsure ("2" key), or did not expect to receive an air-puff ("3" key). Following the acquisition and extinction phases, self-reported anxiety was measured by participants using the keypad to rate how anxious they felt in the presence of the CS+ and CS−.

2.2.2 | Conditioning and extinction task

The fear conditioning protocol consisted of an acquisition and extinction phase. Each phase began with a blank screen and six pulses were presented to stabilize startle responding. Acquisition consisted of eight 6-s presentations of the reinforced conditional stimulus (CS+), eight 6-s presentations of the nonreinforced conditional stimulus (CS−), and eight startle pulses during a blank screen (noise alone or "NA" trials) to measure baseline startle. The US coterminated with the CS+ in 75% of the trials. Startle pulses were presented approximately 4 s following CS+ and CS− onset.

Extinction training began 5 min after the acquisition phase ended and consisted of 16 presentations of each stimulus type (CS+, CS−, and NA) but no US presentations. Startle pulse delivery was the same in extinction as during acquisition. The intertrial interval was 8–15 s in both phases.

2.2.3 | FPS and expectancy coding

Data were analyzed as previously described (Acheson et al., 2013, 2015). FPS and expectancy responses were averaged into blocks of four trials over the last half of acquisition and four blocks during extinction (early, early-middle, late-middle, late) for each stimulus type. FPS was operationalized as startle to the CSs (difference scores of average NA startle magnitude subtracted from average CS+ or CS− startle magnitude) calculated for each block. Expectancy responses were coded as: expect US = 1, unsure = 0, do not expect US = −1.

2.3 | Assessment of postdeployment PTSD symptoms, deployment stress, and TBI history

2.3.1 | Posttraumatic stress disorder

PTSD symptoms were assessed using the Clinician Administered PTSD Scale (CAPS (Blake et al., 1995; Weathers, Keane, & Davidson, 2001)). Interrater reliability between CAPS interviewers and trained observers making independent ratings was high (intraclass correlation coefficient = .99, $n = 76$). DSM- IV PTSD diagnostic criteria were defined as endorsing at least one criterion A event (event time frame not limited to during deployment), one cluster B symptom, two cluster C symptoms, and two cluster D symptoms (Blanchard et al., 1995).

2.3.2 | Deployment stress

Stressful experiences during deployment were assessed with a composite created from four scales of the Deployment Risk and Resilience Inventory-2 (DRRI-2; Vogt et al., 2013): postbattle experiences, combat experience, deployment concern, difficult living and working environment.

2.3.3 | TBI history

MRS methodology for TBI assessment has been previously reported (Yurgil et al., 2014; Yurgil et al., 2016). At pre-and postdeployment, history of head injury was assessed through structured interviews with high interrater reliability (Alosco et al., 2015). At predeployment, lifetime head injury (maximum 5) was assessed, while postdeployment assessment targeted head injuries sustained since the predeployment assessment. Any head injury resulting in loss of consciousness (LOC) and/or altered mental state (AMS; i.e., dazed, confused, "seeing stars," and/or posttraumatic amnesia [PTA]) was defined as TBI (National Center for Injury Prevention and Control, 2003; O'Neil et al., 2013). Individuals endorsing severe TBI (LOC > 30 min, $n = 1$) were excluded. Individuals were coded as having multi-hit TBI exposure if they reported multiple deployment TBIs and/or both a TBI during deployment and a prior "recent" TBI within 2 years prior to deployment. Based on two TBI factors (deployment TBI, recent TBI), four total TBI groupings were generated: "multi-hit TBI" (both deployment and recent TBI), "deployment TBI only" (deployment TBI, no recent TBI), "recent TBI only" (TBI within 2 years predeployment, no deployment TBI), and "no TBI" (no deployment or recent TBI). This grouping was made based on findings from sports research of associations between history of multiple head injuries with greater postconcussive symptoms and delayed recovery (Iverson, Echemendia, Lamarre, Brooks, & Gaetz, 2012; Wall et al., 2006; Zuckerman et al., 2016), and the expectation that more accurate TBI data would be obtained if self-report was limited to a relatively recent period before the assessment.

2.4 | Statistical analyses

For FPS and expectancy ratings, two primary measures were calculated: (1) fear acquisition (mean CS+ vs. CS− score across last half of acquisition phase), and (2) fear extinction (mean CS+ scores at each extinction block). Three-way mixed-design ANOVAs examined the effect of deployment TBI (multi-hit TBI and deployment TBI only) and recent TBI (multi-hit TBI and recent TBI only) as factors on postdeployment fear learning (CS+ and CS− trial type as a repeated subjects factor) and extinction (block of CS+ as repeated subjects factor). For self-reported anxiety ratings, three-way mixed-design ANOVAs examined the effect of recent TBI and deployment TBI as factors on postdeployment fear acquisition (CS+ and CS− ratings as repeated subjects factor) and extinction (postacquisition and postextinction rat-

TABLE 1 Predeployment and postdeployment psychiatric symptoms and demographics grouped by TBI history

	No TBI[a] (*n* = 570)	Recent TBI only[b,e] (*n* = 102)	Deployment TBI only[c,f] (*n* = 98)	Multi-hit TBI[d,e,f] (*n* = 82)	P value
Predeployment age[g]	21.55 (2.89)	20.82 (2.91)	21.27 (2.94)	20.74 (2.57)	.02[h], .49
Ancestry, %[i]					.43, .10
Caucasian	62.2	67.6	65.6	67.9	
African-American	6.2	4.9	4.2	1.2	
Hispanic/Native American	20.4	19.7	14.6	17.3	
Asian/other	11.2	7.8	15.6	13.6	
Predeployment PTSD diagnosis, %[i]	2.5	7.8	1.0	3.7	.009[j], .47
Total predeployment PTSD symptoms (CAPS)[g]	5.01 (9.44)	9.39 (13.64)	4.80 (9.08)	6.76 (10.67)	.001[k], .13
Postdeployment PTSD diagnosis, %[i]	4%	9%	13%	18%	<.001[l], .001[m]
Total postdeployment PTSD symptoms (CAPS)[g]	9.86 (13.94)	12.65 (17.29)	17.68 (17.11)	20.41 (17.91)	<.001[n], .049[o]
Deployment TBI severity, %[p]	*NA*	*NA*	AMS Alone = 81%, LOC<1 min = 15%, LOC 1–15 min = 4%, LOC 16–30 min = 0%	AMS Alone = 76%, LOC <1 min = 19%, LOC 1–15 min = 4%, LOC 16–30 min = 1%	.61
Deployment stress (DRRI-2)[g]	1.80 (.75)	1.83 (.69)	2.23 (.72)	2.46 (.72)	<.001 [n]

AMS, altered mental state; LOC, loss of consciousness.
[a]No deployment TBI or TBI within 2-years predeployment.
[b]TBI within 2-years predeployment, but no deployment TBI.
[c]Single deployment TBI, but no TBI within 2-years predeployment.
[d]Either multiple deployment TBI or single deployment TBI in addition to TBI within 2-years predeployment.
[e]In all analyses "Recent TBI" = Recent TBI only and multi-hit TBI groups.
[f]In all analyses "Deployment TBI" = Deployment TBI only and multi-hit TBI groups.
[g]Two-way ANOVA analyses performed for recent TBI × deployment. Values represent: Mean (SD).
[h]Main effect of recent TBI, individuals with recent TBI were younger.
[i]Chi-squared tests of distribution performed for percent with recent TBI and deployment TBI.
[j]The recent TBI group had a higher proportion of predeployment PTSD diagnosis.
[k]Main effect of recent TBI, higher scores in individuals with recent TBI.
[l]The groups with deployment TBI had a higher proportion of postdeployment PTSD diagnosis, both among individuals with recent TBI ($P = 0.05$) and among those without recent TBI ($P = 0.002$).
[m]The groups with recent TBI had a higher proportion of postdeployment PTSD diagnosis.
[n]Main effect of deployment TBI, higher scores in individuals with deployment TBI.
[o]Main effect of recent TBI, higher scores in individuals with recent TBI.
[p]Chi-squared test of distribution performed for percent of deployment TBI only and multi-hit TBI groups with different TBI severity.

ings as repeated subjects factor). Following all significant results, secondary analyses tested if associations were independent from postdeployment PTSD diagnosis and deployment stress (ANCOVAs with postdeployment PTSD diagnostic status and DRRI-2 composite as covariates). To determine if postdeployment TBI group differences in FPS were preexisting, all significant group differences were retested with the same groups for predeployment fear learning.

Mediation analyses separately tested if acquisition or extinction of FPS to the CS+ mediated the effect of deployment TBI on pre- to postdeployment change in PTSD symptoms. Moderated mediation analyses explored whether the indirect effect of deployment TBI on PTSD symptom change through fear-learning processes (acquisition, extinction) is conditional upon history of recent TBI. FPS acquisition and extinction values were standardized in mediation and moderated mediation models for easier interpretation. As recommended by Preacher, Rucker, and Hayes (2007), estimation of conditional indirect effects utilized a bias-corrected 5,000 bootstrap estimate of the 95% confidence interval (CI) to test whether indirect effects differ from zero at specific values of the moderator. Following significant results, secondary analyses examined the same mediation and moderated mediation models, except with DRRI-2 variance regressed out from PTSD symptom change in order to confirm that TBI associations with PTSD symptoms were independent from PTSD symptom change due to deployment stress.

All analyses were conducted in Statistical Package for the Social Sciences, SPSS version 21.0.0 (IBM Corp, 2012), with mediation and moderated mediation analyses conducted using MEDIATE (Hayes & Preacher, 2013) and MODMED procedures (Preacher et al., 2007).

TABLE 2 Symptom prevalence and loss of consciousness duration for recent predeployment and deployment TBI

	DCSS	PTA	Dizziness	Blurred vision	Loss of coordination	Ruptured ear drum
Prevalence of TBI altered mental state (AMS) symptoms (% of TBI with symptom[a])						
Recent predeployment	129 (92.8%)	139 (100%)[b]	89 (64.0%)	56 (40.3%)	56 (40.3%)	0 (0%)
Deployment	132 (73.3%)	154 (85.6%)[c]	78 (43.3%)	49 (27.2%)	50 (27.8%)	5 (2.8%)
	DCSS, PTA	**DCSS, PTA, dizziness, blurred vision, loss of coordination**	**DCSS, PTA, dizziness**	**DCSS, PTA, dizziness, blurred vision**	**DCSS, PTA, dizziness, loss of coordination**	**DCSS, PTA, blurred vision**
Most prevalent combinations of TBI AMS symptoms (% of TBI with symptom combination[a])						
Recent predeployment	31 (22.3%)	28 (20.1%)	18 (12.9%)	15 (10.8%)	20 (14.4%)	8 (5.8%)
Deployment	40 (22.2%)	24 (13.3%)	23 (12.8%)	13 (7.2%)	11 (6.1%)	6 (3.3%)
	AMS alone, No LOC	**LOC < 1 min**	**LOC between 1 and 15 min**	**LOC between 15 and 30 min**		
TBI loss of consciousness (LOC) severity (% of TBI with LOC duration[a])						
Recent predeployment	66 (47.5%)	39 (28.1%)	34 (24.5%)	0 (0%)		
Deployment	139 (77.2%)	32 (17.8%)	8 (4.4%)	1 (0.6%)		

DCSS, dazed, confused, or seeing stars; PTA, posttraumatic amnesia.

[a]Percentages calculated out of 139 total TBI in 2 years predeployment and out of 180 TBI experienced during deployment. For individuals with multiple recent or deployment TBI, only symptoms from most severe deployment TBI included.

[b]Duration of PTA associated with recent predeployment TBI was: less than 1 h ($n = 118$), 1 to 24 h ($n = 15$), longer than 24 h ($n = 3$), more than 7 days ($n = 1$) unknown duration ($n = 2$).

[c]Duration of PTA associated with deployment TBI was: less than 1 h ($n = 139$), 1 to 24 h ($n = 11$), longer than 24 h ($n = 3$), unknown duration ($n = 1$).

3 | RESULTS

3.1 | Sample characteristics

Demographics, pre- and postdeployment psychiatric symptoms, deployment-related trauma, number of incidents of deployment TBI, and recent predeployment TBI history are reported in Table 1. Overall, individuals that endorsed having at least a recent TBI before deployment were younger than those without recent predeployment TBI. There were no differences in ancestry based on TBI history. Predeployment PTSD diagnosis and PTSD symptoms were higher among individuals that reported recent predeployment TBI, while postdeployment PTSD diagnosis and PTSD symptoms were higher among individuals that endorsed having a recent predeployment TBI or a TBI during deployment. Deployment TBI but not recent TBI was associated with more severe deployment stress. Of the all-male sample 21.2% ($n = 180$) reported at least one deployment TBI (see Table 2 for severity details) and 44 participants (5.2%) reported multiple deployment TBI.

3.2 | Fear acquisition

3.2.1 | FPS

There was an interaction between recent TBI exposure, deployment TBI, and CS type on fear acquisition ($F(1, 848) = 5.58$, $P = .018$, partial $\eta^2 = .007$; Fig. 2A). During late acquisition, the multi-hit group had higher conditioned fear (CS+ response) than the single hit groups (recent TBI only group: $F(1, 848) = 5.36$, $P = .021$, partial $\eta^2 = .006$; deployment TBI only group: $F(1, 848) = 3.96$, $P = .047$, partial $\eta^2 = .005$). All groups showed significant discrimination between the CS+ and CS− (main effect of cue type $F(1, 848) = 121.60$, $P < .001$, partial $\eta^2 = .13$; post-hoc paired contrasts between CS+ and CS− trial for all groups $Ps = < .001$).

3.2.2 | Expectancy and self-report

All groups learned to accurately predict the air-puff US from the CS+ during late acquisition ($F(1, 835) = 1952.80$, $P < .001$, partial $\eta^2 = .70$; Table 3). Deployment TBI was associated with increased anxiety to the CS+ compared to those with no deployment TBI (deployment TBI × CS type: $F(1, 835) = 9.34$, $P = .002$, partial $\eta^2 = .01$; Table 3; simple main effect of deployment TBI: $F(1, 835) = 11.13$, $P = .001$, partial $\eta^2 = .01$). There were no differences across TBI groups in anxiety response to the CS−.

3.3 | Fear extinction

3.3.1 | FPS

As expected, conditioned fear was reduced over the extinction training session ($F(1, 839) = 85.37$, $P < .001$, partial $\eta^2 = .092$; post-hoc contrasts indicating CS+ decrease across extinction blocks in all groups $Ps < .001$). There was an interaction between recent TBI exposure, deployment TBI, and extinction block ($F(3, 839) = 3.22$, $P = .022$, partial $\eta^2 = .004$; Fig. 2B). During early extinction, the multi-hit group exhibited higher conditioned fear than the recent TBI only group ($F(1, 839) = 5.52$, $P = .019$, partial $\eta^2 = .007$). There was also a main effect of deployment TBI ($F(1, 839) = 4.18$, $P = .041$, partial $\eta^2 = .005$; Fig. 2C).

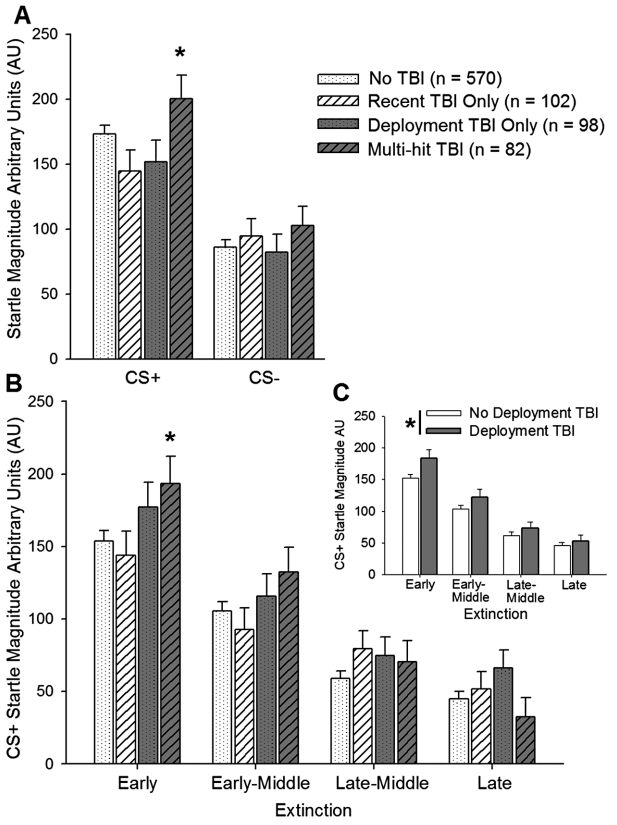

FIGURE 2 Effect of recent TBI and deployment TBI on postdeployment acquisition of conditioned fear Values represent fear-potentiated startle (FPS) magnitudes in arbitrary units (AU) with responding on noise alone trials subtracted from responding to CS+ and CS−, ±SEM. (A) Effect of recent TBI (recent TBI only and multi-hit TBI groups) and deployment TBI (deployment TBI only and multi-hit TBI groups) on postdeployment FPS to CS+ and CS− during late acquisition. *Higher CS+ responding during late acquisition in multi-hit TBI group than in recent TBI only group ($P = .021$) and deployment TBI only group ($P = .047$). (B) Effect of recent TBI (recent TBI only and multi-hit TBI groups) and deployment TBI (deployment TBI only and multi-hit TBI groups) on postdeployment FPS to CS+ during extinction. *Higher CS+ responding during early extinction in multi-hit TBI group than recent TBI only group ($P = .019$). (C) Effect of deployment TBI (deployment TBI only and multi-hit TBI groups) on postdeployment FPS to CS+ during extinction. *Higher overall CS+ responding in deployment TBI group than no deployment TBI group ($P = .041$)

3.3.2 | Expectancy and self-report

All groups showed declining expectancy of air-puff from the CS+ during extinction training ($F(3, 832) = 341.49$, $P < .001$, partial $\eta^2 = .29$; Table 3). There were no group differences in self-reported anxiety to the CS+ following extinction.

3.3.3 | Secondary analyses

When controlling for postdeployment PTSD diagnosis and deployment stress, significant interactions remained for acquisition of FPS ($P = .03$), self-reported anxiety following acquisition ($P = .03$), and for extinction of CS+ FPS ($P = .02$). Applying the same analyses to the predeployment acquisition and extinction data resulted in no group differences, suggesting the associations with TBI emerged after deployment (details in Supporting Information).

3.4 | Mediation/moderated mediation analyses

We first used mediation analyses to ask if fear responding (CS+ acquisition or CS+ extinction) mediated the association between deployment TBI and pre- to postdeployment change in CAPS, which it did not. We then used moderated mediation analyses to ask if prior TBI history moderated a fear responding mediation of deployment TBI associations with change in PTSD symptoms. The association of deployment TBI with fear acquisition was significantly moderated by recent TBI (standardized $\beta = .46$, $t(842) = 2.52$, $P = .012$; Fig. 3), and fear acquisition significantly predicted pre- to postdeployment increases in CAPS ($\beta = 1.27$, $t(842) = 2.34$, $P = .02$). Point estimates and 95% bias-corrected bootstrap CIs indicate significant indirect effects of deployment TBI on PTSD symptom change through FPS acquisition in the recent TBI group (.43, CI: 0.06–1.25), but nonsignificant indirect effects in the group without recent TBI (−.16, CI: −0.57 to 0.03).

3.4.1 | Secondary analyses

After regressing out deployment stress (DRRI-2) from change in CAPS, significant indirect effects remained for deployment TBI on PTSD symptom change through FPS acquisition in the recent TBI group (.31, CI: 0.001 to 1.16), but not in the group without recent TBI (−.12, CI: −0.51 to 0.03).

4 | DISCUSSION

This study examined the potential effect of TBI on fear learning and extinction, as well as association between TBI-related increases in fear conditioning and longitudinal increases in PTSD symptoms. Elevated fear during acquisition and early extinction was most strongly observed in subjects that experienced "multi-hit" TBI. Overall, subjects endorsing a deployment TBI had higher potentiated startle during extinction and reported more anxiety to the fear cue compared to those that did not experience TBI during deployment. Follow-up analyses showed that increased PTSD symptoms after deployment were significantly mediated by elevated cued fear only in the context of recent prior-TBI exposure. Overall, these results suggest that (1) TBI is associated with at least temporary alterations in fear learning and extinction, (2) experiencing multiple TBI within a 2- to 3-year time frame may exacerbate conditioned fear, and (3) elevated learned fear contributes to risk for PTSD after TBI.

The relative contribution of TBI versus PTSD to cognitive outcomes can be difficult to disentangle (Bombardier et al., 2010; Bryant et al., 2010; Carlson et al., 2011; Hoge, Goldberg, & Castro, 2009; Perry et al., 2016; Stein et al., 2015; Vasterling et al., 2012; Wisco et al., 2014; Yurgil et al., 2014). We and others have shown that PTSD is associated with increased fear learning and reduced extinction, however there is limited research on whether TBI affects these learning processes (Acheson et al., 2015; Norrholm et al., 2011; Risbrough

TABLE 3 Expectancy ratings and self-reported anxiety during acquisition and extinction across TBI groups

Measure	Conditioning phase/block	Stimulus type	No TBI[a] ($n = 570$)	Recent TBI only[b] ($n = 102$)	Deployment TBI only[c] ($n = 98$)	Multi-hit TBI[d] ($n = 82$)	*P* value
Expectancy ratings	Late acquisition	CS−	−0.74 (0.45)	−0.81 (0.37)	−0.76 (0.47)	−0.80 (0.41)	<.001[e]
		CS+	0.82 (0.36)	0.79 (0.42)	0.79 (0.36)	0.81 (0.38)	
	Early extinction	CS+	0.23 (0.60)	0.14 (0.63)	0.08 (0.61)	0.18 (0.67)	<.001 [f]
	Early-middle extinction	CS+	−0.24 (0.75)	−0.28 (0.75)	−0.36 (0.72)	−0.25 (0.79)	
	Late-middle extinction	CS+	−0.42 (0.77)	−0.51 (0.73)	−0.51 (0.71)	−0.42 (0.72)	
	Late Extinction	CS+	−0.51 (0.73)	−0.60 (0.72)	−0.58 (0.67)	−0.48 (0.71)	
Self-reported anxiety	Acquisition	CS−	1.69 (2.16)	1.35 (1.64)	1.54 (2.10	1.34 (1.78)	.002[g], <.001[e]
		CS+	5.14 (2.43)	4.89 (2.43)	4.31 (2.40)	4.22 (2.55)	
	Extinction	CS+	2.71 (2.45)	2.79 (2.68)	2.42 (2.54)	2.64 (2.52)	<.001[h]

[a]No deployment TBI or TBI within 2-years predeployment.
[b]TBI within 2-years predeployment, but no deployment TBI.
[c]Single deployment TBI, but no TBI within 2-years predeployment.
[d]Either multiple deployment TBI or single deployment TBI in addition to TBI within 2-years predeployment.
[e]Higher responding to CS+ than CS− across all groups.
[f]Decrease in CS+ ratings across extinction blocks in all groups.
[g]Higher anxiety ratings to the CS+ in the deployment TBI groups.
[h]Decrease in anxiety ratings to CS+ from end of acquisition to end of extinction in all groups .

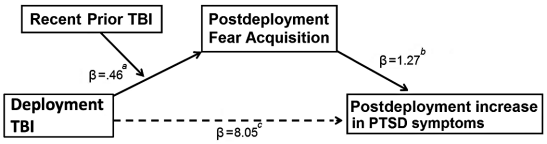

FIGURE 3 Indirect effect of deployment TBI on pre- to postdeployment change in CAPS total through postdeployment fear-potentiated startle acquisition is conditional on recent prior TBI (a) Recent TBI moderates effect of deployment TBI on standardized postdeployment FPS acquisition. β represents SD change in fear acquisition predicted by being in multi-hit group which experienced both deployment TBI and recent TBI. $P = .01$. (b) β represents increase in pre- to postdeployment CAPS total change predicted by 1 SD increase in postdeployment fear acquisition. $P = .02$. (c) β represents increase in pre- to postdeployment CAPS total change predicted by having experienced deployment TBI. $P < .001$

et al., 2016). Obvious potential confounders would be both trauma exposure and PTSD, as TBI (whether during deployment or prior to deployment) is associated with higher deployment stress and likelihood of meeting PTSD diagnostic criteria. However, findings were unchanged when accounting for either deployment stress or PTSD diagnosis, indicating that this phenotype cannot be attributed simply to these other factors. Additionally, lack of preexisting group differences in fear learning processes at predeployment suggest that altered patterns of fear conditioning were related to deployment TBI specifically. That is, past TBI exposure itself is not sufficient for increased fear conditioning, only the combination of prior TBI with a second hit was sufficient.

This pattern of results is similar to elevated fear responding during acquisition and extinction seen in individuals with PTSD (Norrholm et al., 2011). However, we did not detect alterations in extinction rate (Acheson et al., 2015; Milad et al., 2008; Orr et al., 2000; Wessa & Flor, 2007), nor did we observe changes in safety-signal learning after TBI which have also been reported in individuals in PTSD (Acheson et al., 2015; Norrholm et al., 2011). This more limited pattern suggests that TBI mimics some but not all of the fear-learning abnormalities observed in PTSD. The observed elevations in fear responding suggest that TBI may contribute to at least temporary alterations in the neural circuitry underlying fear acquisition and expression. TBI and chronic traumatic encephalopathy have been associated with disruption of cortical and limbic structures that make up the same fear circuit implicated in PTSD (Gavett et al., 2011; Huang, Risling, & Baker, 2016b; Stern et al., 2011). Another potential mechanism through which TBI may increase risk for PTSD is the postconcussive inflammatory cascade (Gyoneva & Ransohoff, 2015; Prasad & Bondy, 2015; Signoretti, Lazzarino, Tavazzi, & Vagnozzi, 2011). Immunoinflammatory markers are elevated in PTSD patients (Baker, Nievergelt, & O'Connor, 2012; Pace & Heim, 2011; Passos et al., 2015) and modulate stress response (Goshen & Yirmiya, 2009) and fear conditioning (Davies et al., 2016; Genovese et al., 2013). Chronic neuroinflammation may prolong and exacerbate negative sequelae of head injury (Faden & Loane, 2014), potentially resulting in increased stress response (Jones, Lebonville, Barrus, & Lysle, 2015; Wohleb et al., 2014) and likelihood of pathological outcomes.

The current findings add to extant research suggesting that multiple mild TBI (LOC < 30 min) may result in more significant neurocognitive disruption than a single head injury. Research on sports-related head injury suggests that history of "multiple" or "recurrent" TBI may be associated with greater postconcussive symptoms and delayed recovery (Covassin, Stearne, & Elbin, 2008; Guskiewicz et al., 2003; Iverson et al., 2012; Matser, Kessels, Lezak, Jordan, & Troost, 1999; Morgan et al., 2015; Ponsford et al., 2012; Wall et al., 2006; Zuckerman

et al., 2016). Preclinical research also suggests that recurrent TBI may increase risk for negative neurocognitive outcomes through white matter and microvascular disruption, increased neuroinflammation, astrogliosis, and p-Tau immunoreactivity (Donovan et al., 2014; Fidan et al., 2016; Fujita, Wei, & Povlishock, 2012; Luo et al., 2014; Mannix et al., 2013; Mouzon et al., 2014), although numerous questions related to the pathophysiology of recurrent head injury remain unanswered (Brody et al., 2015). Future study of peripheral immune markers within the MRS-II sample may help identify immune pathways associated with TBI-related increases in fear conditioning.

Several limitations of this study should be noted. First, all information regarding TBI history was based on self-report, and recall of TBI experienced during deployment may have low reliability (Alosco et al., 2015). Hence, assessment of TBI history was limited to a relatively recent period (2 years) to improve self-report accuracy. Second, the all-male sample limits generalizability to females, particularly given known sex differences in both fear learning and TBI response (Inslicht et al., 2013; Laker, 2011; Maeng & Milad, 2015; Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009; Shvil et al., 2014). Third, altered fear learning only partially accounted for the relationship between deployment TBI and PTSD symptom changes, suggesting other important factors also contribute to TBI-linked risk for PTSD.

The main findings support the hypothesis that deployment TBI and multi-hit TBI in particular are associated with alterations in learned-fear processes, which are considered central to the etiology of PTSD. Potential mechanisms of TBI-induced alterations include decreased cortical inhibition of limbic responses via loss of white matter integrity or increased neuroinflammation, thereby heightening risk for PTSD and other psychiatric disorders. Identifying effects of TBI on fear learning and stress-related neurobiological processes may facilitate improved psychiatric treatment and prevention efforts for individuals recovering from head injury.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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