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https://escholarship.org/uc/item/77s696sk

Journal

Depression and Anxiety, 33(3)

ISSN

1091-4269

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Publication Date

2016-03-01

DOI

10.1002/da.22475

Peer reviewed

Research Article

HIGH AND LOW THRESHOLD FOR STARTLE REACTIVITY ASSOCIATED WITH PTSD SYMPTOMS BUT NOT PTSD RISK: EVIDENCE FROM A PROSPECTIVE STUDY OF ACTIVE DUTY MARINES

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Background: *Heightened startle response is a symptom of PTSD, but evidence for exaggerated startle in PTSD is inconsistent. This prospective study aimed to clarify whether altered startle reactivity represents a trait risk-factor for developing PTSD or a marker of current PTSD symptoms.* **Methods:** *Marines and Navy Corpsmen were assessed before (n = 2,571) and after (n = 1,632) deployments to Iraq or Afghanistan with the Clinician-Administered PTSD Scale (CAPS). A predeployment startle-threshold task was completed with startle probes presented over 80–114 dB[A] levels. Latent class mixture modeling identified three growth classes of startle performance: "high," "low," and "moderate" threshold classes. Zero-inflated negative binomial regression was used to assess relationships between predeployment startle threshold and pre- and postdeployment psychiatric symptoms.* **Results:** *At predeployment, the low-threshold class had higher PTSD symptom scores. Relative to the moderate-threshold class, low-threshold class membership was associated with decreased likelihood of being symptom-free at predeployment, based on CAPS, with particular associations with numbing and hyperarousal subscales, whereas high-threshold class membership was associated with more severe predeployment PTSD symptoms, in particular avoidance. Associations between low-threshold membership and CAPS symptoms were independent from measures of trauma burden, whereas associations between high-threshold membership and CAPS were not. Predeployment startle threshold did not predict postdeployment symptoms.* **Conclusions:** *This study found that both low startle threshold (heightened reactivity) and high startle threshold (blunted reactivity) were associated with greater current PTSD symptomatology, suggesting that startle reactivity is associated with current PTSD rather than a risk marker for developing PTSD. Depression and Anxiety*

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PTSD is common in veterans across war eras; current prevalence estimates include 12.2% (Vietnam War),[1] 10.1% (Persian Gulf War),[2] and 23% (Operation Enduring Freedom/Operation Iraqi Freedom)[3] and are higher for combat veterans, who have a 1.5–3.5-fold increased risk for PTSD relative to nondeployed veterans.[4] Although evidence-based treatments for PTSD exist, only 40–50% of patients are treatment responsive.[5–8] Mixed treatment response rates may be partly due to heterogeneity of symptoms and underlying pathology.[9] Both treatment and prevention strategies might be improved by identifying biomarkers associated with specific symptom domains and with prospective risk for PTSD development, enabling more efficient targeting of interventions.[10] The startle response might be such a candidate biomarker, but it is unknown whether altered startle responding represents a "trait" or "state" biomarker for PTSD.

The startle response is an operational measure of threat anticipation linked to fear circuit activation in humans and animals (e.g.,[11,12]). Heightened startle responding is a commonly endorsed symptom of PTSD that has been a long-standing criterion within the evolving versions of the DSM including DSM-5.[13,14] Empirical evidence for exaggerated startle magnitude in PTSD is mixed, however,[15,16] with a meta-analysis indicating only modest increases in baseline startle reactivity.[17] There are several potential reasons for modest associations. Startle hyperreactivity and hyporeactivity may be experienced by different subgroups of PTSD patients with distinct trauma-related pathology or trauma histories (e.g.,[18]). For example, PTSD resulting from a single trauma may be characterized by elevated startle reactivity whereas PTSD following multiple traumas is characterized by diminished physiological reactivity.[19] Furthermore, startle reactivity differences may not reflect current PTSD symptom state, but instead indicate increased risk of developing PTSD. There is circumstantial evidence for an association of startle reactivity with anxiety disorder risk: (1) offspring of anxiety disorder patients have increased startle reactivity compared to offspring of nonanxious parents[20–22] and (2) increased startle is linked to childhood trauma, a strong PTSD risk factor.[17] Two prospective studies were contradictory in supporting increased baseline startle reactivity as a PTSD risk factor,[23,24] although these studies were relatively small (*n* = 99 and 138) and had few subjects with a diagnosis of PTSD. Thus, it remains unclear if startle reactivity is a marker of state PTSD symptoms or a trait marker of PTSD risk.

Self-reported "increased startle" in PTSD subjects may refer to elevated probability of having a startle response under subthreshold conditions rather than simply heightened startle magnitude (e.g.,[25]). Patients may report elevated startle because the stimulus intensity needed to induce startle responding is lower, thus increasing the probability of startle across a wider range of stimuli rather than showing greater response magnitude per se. Thus, to parse out differences between startle threshold versus response magnitude, we examined startle reactivity across a range of intensities to identify overall magnitude differences and changes in the threshold to induce a response. We examined data extracted from the Marine Resiliency Study (MRS),[26] a large prospective study of active duty service members to test the hypotheses that (1) startle reactivity is associated with current PTSD symptoms and other stress-related symptoms and (2) predeployment startle reactivity predicts postdeployment symptom development. Since PTSD is a heterogeneous condition,[27,28] we examined associations of startle with overall PTSD symptoms and DSM-IV symptom clusters using a 4-factor model[29] (re-experiencing, avoidance, numbing, hyperarousal), and with general anxiety and depression symptoms.

METHODS

STUDY DESIGN AND PARTICIPANTS

MRS[26] is a longitudinal study of 2,600 U.S. Marines and Navy Corpsmen (typically treating/aiding combat wounded) around combat deployments to Iraq or Afghanistan (1-month predeployment, immediately postdeployment, and ∼3- and ∼6-months postdeployment). Institutional review boards of the University of California San Diego, VA San Diego Research Service, and Naval Health Research Center approved the study, and written informed consent was obtained from all participants.

Of the 2,592 participants with valid predeployment startle reactivity, 2,571 completed predeployment psychiatric measures and 1,632 completed psychiatric measures at 6-month postdeployment. To test both hypotheses, we used predeployment startle data (largest N). To predict PTSD-risk, we used predeployment startle to predict symptoms at the 6-month time point (reflecting greatest chronicity after trauma).

MEASURES

Complete MRS methods are described elsewhere[26]; only measures relevant to the present study are presented here.

STARTLE THRESHOLD TEST

Stimuli and Apparatus. Startle pulses were delivered using a San Diego Instruments (San Diego, CA, USA) SR-HRLAB EMG system as previously described.[30–32] EMG data (1-KHz sampling rate) were amplified, rectified, band-pass filtered (100–1,000 Hz), and smoothed (5-point rolling-average). All trials were reviewed by trained technicians using standard methods to remove artifact (e.g., responses that began before or 100 ms after probe onset were removed). Details are in supplementary materials.

Experimental Procedure. Prior to startle testing, hearing threshold was examined using 100, 500, 3,000, and 6,000 Hz tones at 35 dB[A] via a Grason–Stadler Audiometer (Eden Prairie, MN, USA). The startle threshold task was modeled after prior research.[25] After a 5 min acclimation, four 114-dB[A] broadband pulses were presented to assess "maximal" startle reactivity scores. Startle probes were then presented in pseudo-random order across six intensities: 80, 85, 90, 95, 100, and 105 dB[A] (5 pulses/trial-type). Probes had instantaneous rise/fall time, were 40 ms in duration, with intertrial interval average of 15 s. A 70 dB[A] broadband background noise was continuous.

ASSESSMENT OF PSYCHIATRIC SYMPTOMS

Posttraumatic Stress Disorder. Predeployment and 6-month postdeployment PTSD symptom severity was assessed using the Clinician-Administered PTSD Scale (CAPS),[33] a structured diagnostic interview designed to assess DSM-IV PTSD symptoms[34–36] with high convergent and divergent validity.[37] Interrater reliability was high between CAPS interviewers and trained observers making independent ratings, with an intraclass correlation coefficient = 0.99 ($n = 261$). CAPS was scored as zero if participants did not endorse any criterion A traumatic events according to DSM-IV on the Life Event Checklist (LEC),[38] a survey of criterion A events experienced or witnessed (0–16 range). CAPS total score (0–136 range) served as a continuous measure of PTSD symptoms. Four CAPS subscales were also calculated[29]: re-experiencing (B1-5), hyperarousal (D1-5), avoidance (C1-2), and numbing (C4-6). DSM-IV PTSD diagnostic criteria were defined as endorsing at least one criterion A event, one cluster B symptom, three cluster C symptoms, and two cluster D symptoms whereas "subthreshold" PTSD was defined as endorsing at least one criterion A event, one cluster B symptom, and either three cluster C or two cluster D symptoms.[39, 40]

Anxiety. Predeployment and 6-month postdeployment anxiety symptoms were assessed with the Beck Anxiety Inventory (BAI),[41] a 21-item questionnaire (0–63 range) of general cognitive and somatic anxiety symptoms experienced within the past week with divergent and discriminant validity.[42] BAI cognitive (items 4, 5, 9, 10, 14, 16, 17) and somatic (items 1–3, 6–8, 11–13, 15, 18–21) subscales were also calculated.

Depression. Predeployment and 6-month postdeployment depressive symptoms within the past 2 weeks were assessed with the Beck Depression Inventory II (BDI-II),[43] a 21-item questionnaire (0–63 range) with strong discriminant, convergent, and content validity.[44]

Childhood Trauma. Traumatic experiences during childhood were assessed at predeployment with a modified Childhood Trauma Questionnaire (CTQ),[45] a 34-item questionnaire (25–170 range) with strong discriminant and convergent validity.[46, 47]

Deployment Stress and Combat Exposure. Stressful experiences during combat and deployment were assessed at 6-months postdeployment with four scales from the Deployment Risk and Resilience Inventory-2 (DRRI-2; Postbattle Experiences, Combat Experience, Deployment Concern, Difficult Living and Working Environment), with high criterion validity and internal consistency (0.92).[48]

ANCESTRY

To control for associations of race with startle reactivity (e.g., [49]), we used a genetically derived ancestry variable as a covariate.[50] Participants were placed into four groups: Caucasian ($N = 1,588$); African-American ($N = 161$); Hispanic and Native American ($N = 459$); and Asian/Other ($N = 363$; details in supplementary materials).

STATISTICAL ANALYSIS

Analyses were conducted using statistical software package R, version 3.1.1,[51] and Statistical Package for the Social Sciences, SPSS version 21.0.0.[52] To best analyze curvilinear response differences in predeployment startle magnitude as startle stimulus intensity increased, a Latent Class Mixture Model (LCMM; R package lcmm)[53] was used. This approach enables identification of homogenous subgroups of participants within the full cohort that followed unique trajectories of startle magnitude increases across stimulus intensities. Group membership classifications were then used as an independent variable to indicate participant startle tendency across stimulus intensities. The model was constructed iteratively, with curvilinear trajectory being specified and additional groups being added until model fit either no longer improved or membership in any class dropped below 10% of the sample.

MRS measures of psychiatric symptoms (CAPS, BAI, BDI-II) at predeployment and 6-month postdeployment were positively skewed, overdispersed, and had an excess of zero scores, as previously reported.[54] Hence, zero-inflated negative binomial regression (ZINBR) was the appropriate analytic method. ZINBR uses maximum likelihood to model outcomes via two component models: logistic regression (zero model) predicting probability of a zero score, and negative binomial regression (count model) predicting total score.

Predeployment startle threshold class was included as a factor in ZINBR analyses to predict symptoms at

TABLE 1. Comparisons of characteristics and psychiatric symptoms between startle threshold classes

Predeployment characteristic	High-threshold ($n = 1,318$)	Moderate-threshold ($n = 987$)	Low-threshold ($n = 266$)	P-value
Age[a]	22.69 (3.62)	22.88 (3.42)	22.93 (3.20)	.33
Ancestry[b], %				**<.001**[c]
Caucasian	55.3	68.9	68.0	
African-American	8.5	4.2	2.6	
Hispanic/Native American	18.2	17.0	19.2	
Asian/Other	17.9	9.9	10.2	
Marital status[b], %				.26
Never Married	62.3	61.2	59.0	
Married	35.1	34.4	36.8	
Divorced	1.5	3.0	2.6	
Separated	1.1	1.5	1.5	
CTQ[a]	40.65 (14.15)	40.12 (13.59)	39.05 (12.59)	.22
Childhood Physical abuse	8.8 (4.1)	8.8 (4.0)	8.6 (3.7)	.76
Childhood sexual abuse	5.6 (2.2)	5.6 (2.2)	5.5 (2.0)	.87
Lifetime trauma (LEC)[a]	4.96 (3.23)	5.11 (3.26)	5.44 (3.24)	.08
Months spent in military[a]	36.28 (36.08)	35.60 (34.40)	37.54 (31.72)	.70
Months remaining in enlistment[a]	27.67 (13.31)	27.74 (13.26)	26.59 (13.87)	.43
Any previous deployment[b], %	**49.5**	**51.7**	**58.6**	**.03**[d]
Total previous deployments[a]	0.84 (1.1)	0.86 (1.1)	0.97 (1.2)	.20
Total lifetime TBI with LOC[a]	0.59 (0.99)	0.64 (0.94)	0.53 (0.85)	.18
CAPS[a]	**7.02 (12.94)**	**6.03 (10.80)**	**8.68 (13.84)**	**.005**[e]
BAI[a]	5.99 (5.71)	5.99 (5.81)	6.82 (6.15)	.09
BDI-II[a]	6.47 (7.74)	6.61 (7.77)	7.45 (7.94)	.17
PTSD diagnosis, traditional[f], %[b]	3.8	3.1	5.6	.15
PTSD diagnosis, subsyndromal[g], %[b]	**7.8**	**6.5**	**11.3**	**.03**[h]
Postdeployment characteristic	High-threshold ($n = 835$)	Moderate-threshold ($n = 632$)	Low-threshold ($n = 165$)	
DRRI-2[a]	0.1 (0.80)	−0.03 (0.81)	0.07 (0.85)	.17
Combat and postbattle experience[a]	0.30 (0.23)	0.29 (0.23)	0.32 (0.24)	.34
CAPS[a]	9.67 (16.12)	9.37 (15.57)	9.73 (14.80)	.94
BAI[a]	4.79 (7.84)	4.77 (8.09)	4.89 (7.04)	.98
BDI-II[a]	5.37 (7.20)	4.85 (6.74)	5.86 (6.56)	.11
PTSD diagnosis, traditional[f], %[b]	5.6	5.2	5.3	.95
PTSD diagnosis, subsyndromal[g], %[b]	10.4	10.6	11.8	.87

[a]One-way ANOVA analyses performed.
[b]Chi-squared test of distribution performed.
[c]Post hoc tests indicate lower proportion of high-threshold participants were Caucasian and a higher proportion were African-American and Asian/Other ($P < .001$), higher proportion of moderate-threshold participants were Caucasian and a lower proportion were African-American and Asian/Other ($P < .001$), and higher proportion of low-threshold participants were Caucasian ($P = .03$) and a lower proportion were African-American ($P = .01$).
[d]Post hoc tests indicate a higher percentage of participants in the low-threshold than high-threshold class with previous deployment experience ($P = .023$).
[e]Post hoc tests indicate lower score in moderate-threshold class than low-threshold class ($P = .005$).
[f]Traditional PTSD criteria: criterion A event, at least 1 cluster B symptom, 3 cluster C symptoms, and 2 cluster D symptoms, with minimum frequency ratings of 1 and minimum intensity ratings of 2 on CAPS.
[g]Subsyndromal PTSD criteria: criterion A event, at least 1 cluster B symptom, 3 cluster C or 2 cluster D symptoms, with minimum frequency ratings of 1 and minimum intensity ratings of 2 on CAPS.
[h]Post hoc tests indicate higher proportion of participants in the low-threshold class than moderate-threshold class met subsyndromal PTSD criteria ($P = .02$).
Significant associations are highlighted in bold.

either predeployment or 6-month postdeployment. Because the moderate-startle class displayed the lowest predeployment CAPS scores (Table 1), it was chosen as the referent group in ZINBR analyses to detect symptom increases in the other classes. Ancestry and deployment history differed between startle threshold classes (Table 1), thus these variables were included in the model. Number of correct responses on the hearing test was included to account for hearing differences potentially affecting startle reactivity. A composite of DRRI-2 scales was included to account for differences in combat and deployment experience. An interaction between

DRRI-2 and startle class was examined but it did not improve the model. Multiple other potential confounders were evaluated, including predeployment depression (via BDI-II), sleep quality, caffeine and tobacco use, and traumatic brain injury (TBI), but none improved the model.

Startle threshold class membership at predeployment was the primary predictor variable. The zero and count models were primarily used to predict responses on CAPS and CAPS subscales (re-experiencing, avoidance, numbing, hyperarousal) at both predeployment and 6-month postdeployment. Secondary ZINBR models including trauma history variables (CTQ and LEC) were conducted to examine effects of childhood and lifetime trauma burden on the relationship between startle threshold and PTSD symptoms. Additional secondary analyses predicted predeployment and 6-month postdeployment responses on BAI, BAI subscales (somatic, cognitive), and BDI-II.

ZERO MODEL: PREDICTING ABSENCE OF PSYCHIATRIC SYMPTOMS

Exponentiated coefficients of the zero model were interpreted as odds of a zero score. The zero model intercept reflects the base probability of having a zero score given that a participant was in the moderate-threshold class, Caucasian, never before deployed, with average hearing. Average DRRI-2 and PTSD symptom scores at predeployment were also referents when predicting 6-month postdeployment scores.

COUNT MODEL: PREDICTING TOTAL PSYCHIATRIC SYMPTOMS

Exponentiated coefficients of the count model represent multiplicative change in predicted measure score per unit change in a given predictor. The count model intercept reflects a predicted symptom score given the same referents as described for the zero model.

RESULTS

STARTLE THRESHOLD CLASS

The LCMM showed three distinct classes of growth across stimulus intensity levels (Fig. 1). The high-threshold class (51.3% of participants) was characterized by relatively flat trajectory, only rising in magnitude at the highest dB[A] levels. The moderate-threshold class (38.4% of participants) was characterized by a slope of increasing startle magnitude across dB[A] levels. The low-threshold class (10.3% of participants) was characterized by an abruptly steep slope, distinguishable even at low dB[A] levels.

SAMPLE CHARACTERISTICS BY STARTLE THRESHOLD CLASS

Overviews of pre- and postdeployment MRS cohort characteristics have been reported previously.[25,45] Predeployment demographic and descriptive data are presented for each startle threshold class (Table 1). Chi-squared tests indicated significant predeployment
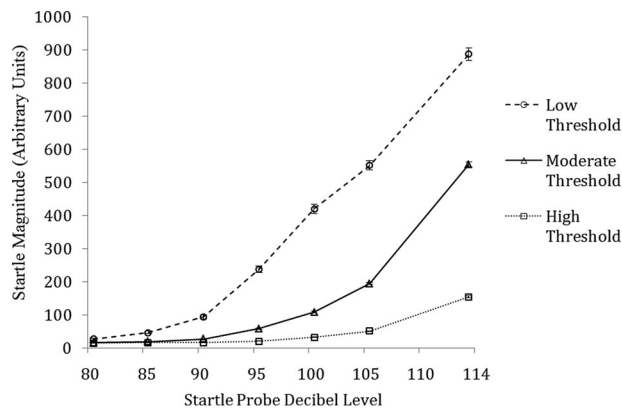

Figure 1. Mean startle threshold class response across decibel level, ±1 SEM. Startle class trajectories identified using Latent Class Mixture Model.

differences between startle threshold classes in racial ancestry (χ^2 (6, $n = 2{,}592$) = 72.95; $P < .001$). More participants in the low-threshold class had been previously deployed compared to other classes (χ^2 (2, $n = 2{,}585$) = 6.96; $P = .03$). Startle threshold classes did not differ at predeployment in age, marital status, total number of prior deployments, total months spent in the military, total months remaining in military enlistment, total lifetime TBI with loss of consciousness, or childhood trauma measures. The low-threshold class tended to have more lifetime trauma ($P < .08$).

Pre- and postdeployment measures of psychiatric symptoms are presented for each threshold class (Table 1). One-way analysis of variance (ANOVA) indicated significant threshold class differences in CAPS at predeployment (F (2, 2,586) = 5.31; $P = .005$) but not postdeployment. Deployment trauma did not differ across classes. Although classes did not differ in the percent meeting DSM-IV PTSD diagnostic criteria at predeployment (3.7% of participants), significantly more participants met subthreshold PTSD in the low-threshold compared to moderate-threshold class (χ^2 (2, $n = 2{,}592$) = 6.84; $P = .03$). There were no class differences in full or subthreshold PTSD at postdeployment. Threshold classes did not differ on BAI or BDI-II.

ZERO-INFLATED NEGATIVE BINOMIAL REGRESSION

For clarity, we have only depicted ZINBR results for threshold class as a predictor of PTSD at predeployment (Table 2) and postdeployment (Table 3) in the body of the paper. Full models with all predictors are included as supplementary materials.

RELATIONSHIP BETWEEN STARTLE THRESHOLD AND CURRENT PTSD SYMPTOMS

Count Model. In participants endorsing PTSD symptoms, high-threshold class membership increased predeployment predicted CAPS score by a factor of 1.14 (14%; $P = .04$), CAPS-reexperiencing by a factor of

TABLE 2. Zero-inflated negative binomial regression predicting predeployment CAPS total score and subscales

Outcome measure	Model	Variable[a]	Estimate (SE)	P-value	Predicted measure total[b,c]	Ratio (95% CI)[d]
CAPS total	Count	(Intercept)	2.90 (0.21)	<.001	9.96	(8.07–12.29)
		High-threshold*	**0.14 (0.06)**	**.04**		**1.14 (1.01–1.29)**
		Low-threshold	0.17 (0.10)	.08		1.18 (0.98–1.43)
	Zero	(Intercept)	−0.63 (0.35)	.07	53.05%	(44.32–61.59%)
		High-threshold	0.03 (0.09)	.76		1.02 (0.86–1.23)
		Low-threshold*	**−0.38 (0.15)**	**.01**		**0.68 (0.50–0.92)**
CAPS-reexperiencing	Count	(Intercept)	2.17 (0.21)	<.001	5.17	(4.19–6.38)
		High-threshold*	**0.18 (0.07)**	**.01**		**1.20 (1.05–1.36)**
		Low-threshold	0.14 (0.11)	.17		1.15 (0.59–2.26)
	Zero	(Intercept)	0.14 (0.34)	.68	64.36%	(56.25–71.73%)
		High-threshold	0.12 (0.10)	.22		1.13 (0.93–1.36)
		Low-threshold	0.02 (0.15)	.88		1.02 (0.76–1.39)
CAPS-avoidance	Count	(Intercept)	1.36 (0.24)	<.001	4.20	(3.30–5.34)
		High-threshold*	**0.16 (0.07)**	**.02**		**1.17 (1.02–1.35)**
		Low-threshold	0.10 (0.11)	.38		1.10 (0.89–1.36)
	Zero	(Intercept)	0.74 (0.39)	.06	79.28%	(72.14–84.96%)
		High-threshold	0.06 (0.11)	.57		1.06 (0.86–1.32)
		Low-threshold	−0.11 (0.17)	.52		0.89 (0.63–1.26)
CAPS-numbing	Count	(Intercept)	1.87 (0.22)	<.001	6.02	(4.83–7.50)
		High-threshold*	**0.21 (0.08)**	**.01**		**1.24 (1.06–1.44)**
		Low-threshold	0.08 (0.11)	.46		1.08 (0.88–1.33)
	Zero	(Intercept)	0.89 (0.40)	.03	89.74%	(85.43–92.88%)
		High-threshold	0.06 (0.13)	.60		1.06 (0.83–1.36)
		Low-threshold*	**−0.58 (0.18)**	**<.001**		**0.56 (0.40–0.79)**
CAPS-hyperarousal	Count	(Intercept)	2.29 (0.16)	<.001	7.31	(6.23–8.58)
		High-threshold	0.02 (0.05)	.73		1.02 (0.91–1.13)
		Low-threshold	−0.03 (0.08)	.72		0.97 (0.84–1.13)
	Zero	(Intercept)	0.33 (0.34)	.33	79.94%	(73.93–84.85%)
		High-threshold	−0.12 (0.19)	.21		0.88 (0.73–1.07)
		Low-threshold*	**−0.57 (0.15)**	**<.001**		**0.57 (0.42–0.76)**

[a]Moderate-threshold membership used as referent group for high-threshold and low-threshold class membership.
[b]Estimate for participant who is Caucasian, never before deployed, with average hearing.
[c]For the zero model, base probability of a predicted score of 0.
[d]95% confidence interval for predictor coefficient. Count model coefficients indicate multiplicative change in predicted measure score per unit change in predictor. Zero model coefficients indicate predicted factor change in odds of a zero score for measure per unit change in predictor.
*Predictor P-value <.05
Significant associations are highlighted in bold.

1.20 (20%; $P = .01$), CAPS-avoidance by a factor of 1.17 (17%; $P = .02$), and CAPS-numbing by a factor of 1.24 (24%; $P = .003$), but was not associated with CAPS-hyperarousal. Low-threshold class membership did not significantly predict CAPS.

Zero Model. High-threshold class membership did not significantly affect predeployment odds of a zero score on CAPS or CAPS-subscales. Low-threshold class membership decreased predeployment odds of a zero score on CAPS by a factor of 0.68 (32%; $P = .01$), CAPS-numbing by a factor of 0.56 (44%; $P < .001$), and CAPS-hyperarousal by a factor of 0.57 (43%; $P < .001$), but did not affect odds of zero scores on CAPS-reexperiencing or CAPS-avoidance.

RELATIONSHIP BETWEEN STARTLE THRESHOLD AND FUTURE PTSD RISK

Neither high-threshold nor low-threshold class membership at predeployment were significantly associated with postdeployment CAPS in the count or zero models.

Secondary Analyses. For full results of secondary models see supplementary materials. When trauma-burden measures were included in ZINBR models, associations between low-threshold class and PTSD symptoms remained significant (Ps = <.001–.01). High-threshold class association with CAPS-avoidance also remained significant ($P = .04$) whereas associations with CAPS-total, CAPS-reexperiencing and CAPS-numbing did not. Removing participants that denied ever experiencing a category A event ($N = 80$, 3%) from the analyses did not change the findings (data not shown). For predicting anxiety and depression, low-threshold class membership decreased the odds of a zero score for BAI-somatic by a factor of 0.64 (36%; $P < .04$) whereas class membership was not associated with BDI-II. To examine if trauma burden is related to startle threshold among individuals with PTSD, we examined class differences in CTQ and LEC among PTSD cases. Individuals meeting predeployment diagnosis for PTSD endorsed more childhood trauma

TABLE 3. Zero-inflated negative binomial regression predicting 6-months postdeployment CAPS total score and subscales

Outcome measure	Model	Variable[a]	Estimate (SE)	P-value	Predicted measure total[b,c]	Ratio (95% CI)[d]
CAPS total	Count	(Intercept)	2.56 (0.26)	<0.001	12.00	(9.25–15.56)
		High-threshold	0.04 (0.07)	0.53		1.04 (0.91–1.20)
		Low-threshold	−0.05 (0.11)	0.66		0.95 (0.767–1.18)
	Zero	(Intercept)	0.80 (0.48)	0.10	43.71%	(32.46–55.66%)
		High-threshold	−0.03 (0.14)	0.78		0.97 (0.75–1.24)
		Low-threshold	−0.12 (0.22)	0.59		0.89 (0.58–1.35)
CAPS-reexperiencing	Count	(Intercept)	1.81 (0.29)	<0.001	5.67	(4.24–7.57)
		High-threshold	0.04 (0.08)	0.56		1.04 (0.90–1.21)
		Low-threshold	−0.12 (0.12)	0.29		0.88 (0.70–1.11)
	Zero	(Intercept)	1.46 (0.48)	0.002	68.64%	(57.52–77.96%)
		High-threshold	−0.06 (0.13)	0.63		0.94 (0.73–1.21)
		Low-threshold	−0.38 (0.21)	0.07		0.68 (0.45–1.03)
CAPS-avoidance	Count	(Intercept)	1.72 (0.30)	<0.001	4.46	(3.30–6.02)
		High-threshold	0.04 (0.08)	0.63		1.04 (0.88–1.23)
		Low-threshold	−0.09 (0.13)	0.49		0.92 (0.71–1.18)
	Zero	(Intercept)	2.08 (0.52)	<0.001	86.46%	(79.16–91.49%)
		High-threshold	−0.21 (0.15)	0.15		0.81 (0.61–1.08)
		Low-threshold	−0.37 (0.23)	0.10		0.69 (0.44–1.08)
CAPS-numbing	Count	(Intercept)	2.09 (0.36)	<0.001	6.45	(4.50–9.25)
		High-threshold	0.15 (0.10)	0.13		1.16 (0.96–1.40)
		Low-threshold	0.01 (0.15)	0.96		1.01 (0.75–1.35)
	Zero	(Intercept)	3.36 (0.63)	<0.001	89.06%	(81.02–93.77%)
		High-threshold	−0.14 (0.15)	0.37		0.87 (0.64–1.18)
		Low-threshold	0.00 (0.25)	0.99		1.00 (0.61–1.65)
CAPS-hyperarousal	Count	(Intercept)	2.26 (0.20)	<0.001	8.24	(6.75–10.07)
		High-threshold	0.02 (0.06)	0.76		1.02 (0.91–1.14)
		Low-threshold	−0.05 (0.09)	0.61		0.96 (0.80–1.14)
	Zero	(Intercept)	0.92 (0.47)	0.05	59.71%	(48.09–70.34%)
		High-threshold	0.17 (0.12)	0.17		1.18 (0.93–1.51)
		Low-threshold	0.02 (0.20)	0.94		1.02 (0.68–1.51)

[a]Moderate-threshold membership used as referent group for High-threshold and Low-threshold class membership.
[b]Estimate for participant who is Caucasian, never before deployed, with average hearing and DRRI, and with zero scores on measures at predeployment.
[c]For the zero model, base probability of a predicted score of 0.
[d]95% confidence interval for predictor coefficient. Count model coefficients indicate multiplicative change in predicted measure score per unit change in predictor. Zero model coefficients indicate predicted factor change in odds of a zero score for measure per unit change in predictor.

(P < .001) and physical abuse (P = .001) in the high-threshold class, but there were no class differences for LEC.

DISCUSSION

This study examined if differences in startle threshold are associated with PTSD symptom severity (PTSD state) and/or are predictive of trait risk for developing PTSD after deployment. Startle responses were fitted into three distinct growth classes across stimulus intensity levels, with classes defined by high, moderate, and low thresholds. ZINBR models indicated that relative to moderate-threshold, high-threshold class membership at predeployment was associated with more severe predeployment symptoms on CAPS-total, CAPS-reexperiencing, CAPS-avoidance, and CAPS-numbing. Relative to moderate-threshold, low-threshold class membership was associated with decreased likelihood of

being symptom-free at predeployment on CAPS-total, CAPS-numbing, CAPS-hyperarousal, and BAI-somatic. These findings suggest that low startle threshold may be associated with increased likelihood of endorsing current PTSD and anxiety symptoms, whereas high-threshold responding is associated with increased PTSD severity once symptoms emerge. Previous research supports that "baseline" EMG startle reactivity is associated with PTSD symptom state that can remit after treatment,[55] although there are some inconsistencies likely due to methodological differences.[56] Predeployment startle threshold class did not predict postdeployment psychiatric symptoms, suggesting that startle threshold does not represent a trait risk-factor for developing PTSD or anxiety. The large cohort size and pre- and postdeployment assessments used here build on previous prospective research finding that startle sensitization develops along with PTSD symptoms rather than representing a preexisting risk factor.[57] PTSD risk has been asso-

ciated, however, with startle in response to conditioned fear-cues or aversive stimuli,[24] suggesting that EMG responses during threat may probe different mechanisms of PTSD risk than "baseline" startle tasks. Neither current depression nor development of depression symptoms were predicted by threshold class, consistent with previous findings that altered startle response is associated with fear and anxiety but not depression.[58–60]

The association of current PTSD symptoms with both low and high startle thresholds is consistent with findings that many PTSD patients show exaggerated startle reactivity similar to other fear-based disorders, whereas PTSD patients with particularly severe trauma histories demonstrate blunted startle similar to disorders of pervasive apprehension and negative affect.[18, 19] Our finding that low-threshold responding was associated with PTSD and somatic anxiety symptoms is consistent with a fear-based PTSD presentation. That high-threshold reactivity was associated with more severe PTSD symptoms but not anxiety symptoms is consistent with the idea that a subset of PTSD patients show diminished defensive responding. In secondary analyses, low-threshold startle was associated with CAPS-total, -numbing, and -hyperarousal symptoms above and beyond variance accounted for by childhood and lifetime trauma, suggesting that elevated startle reactivity develops independently from trauma exposure. Alternatively, when accounting for trauma burden high-threshold startle only remained predictive for avoidance, but not CAPS-total or re-experiencing symptoms. There were no differences between threshold classes on measures of lifetime trauma burden or depression, although among the 96 individuals who met DSM-IV criteria for PTSD at predeployment, those with high startle threshold had greater history of childhood trauma and physical abuse. Together, these results suggest that PTSD following high childhood and lifetime trauma burden may be characterized by diminished physiological reactivity, with trauma burden accounting for much of the association between blunted startle and PTSD severity, whereas elevated startle may be associated with PTSD symptoms independent from trauma history.

These findings suggest that a moderate startle-threshold may indicate minimal current PTSD symptomatology relative to high or low startle thresholds, and may have important implications regarding the relationship between PTSD and abnormalities in startle response neurocircuitry. Startle reactivity is modulated by the amygdala and bed nucleus of the stria terminalis, via projections to nodes of the primary startle circuit in the brainstem that mediate startle.[61] Exaggerated startle reactivity is putatively related to amygdala hyperactivity in PTSD (e.g., [62]), but several different neurobiological processes might contribute to low startle being associated with increased psychiatric symptoms. During severe stress, the periaqueductal gray (PAG) inhibits startle in favor of other defensive behaviors resulting in an inverted-U shaped dose-response function

between stressor intensity and startle response.[63, 64] Signaling pathways linked to inverted U-shaped effects on startle reactivity that are abnormal in PTSD include corticotropin releasing factor (CRF) and glucocorticoid signaling. PTSD patients exhibit increased CRF levels in cerebrospinal fluid[65–68] and increased glucocorticoid sensitivity.[69] Moderate CRF and glucocorticoid levels induce increased startle whereas high doses induce reduced startle reactivity[70–73] CRF-induced inhibition or potentiation of startle also depend on neural sources of CRF hypersignaling.[74] Future research is needed to determine if these neural circuits and signaling pathways are linked to different startle thresholds. Understanding the neurobiological mechanisms influencing startle threshold might help identify separate functional pathologies across PTSD and other anxiety disorders.

This study has important limitations. First, this cohort was entirely male so it is unknown if the findings are applicable to females, particularly given recent gender differences found in the relationship between startle reactivity and PTSD.[75] Second, this cohort was young, generally healthy, and highly screened, all of which may limit generalizability. Third, the types of traumas faced by this military cohort may differ from traumas experienced by civilians. Fourth, participants developing symptomatology postdeployment may have been less likely to remain in the military until postdeployment assessment. Few study participants met PTSD diagnostic criteria at pre- or postdeployment, thus this study may have been underpowered to detect the relationship between startle threshold and severe PTSD symptoms.

Overall, these findings indicate that distinct patterns of startle reactivity across high and subthreshold stimulus intensity are associated with current PTSD symptom "state," but not with trait risk for developing psychiatric symptoms. Moderate startle-threshold was associated with fewer current PTSD symptoms relative to low- and high-thresholds. Future research should investigate the relationship between lifetime trauma burden and PTSD symptom severity with blunted startle responding. Additionally, future research should examine the biological underpinnings of startle threshold as an intermediate phenotype for PTSD state. Improved understanding of startle and other PTSD-related biomarkers may facilitate targeting of treatment and prevention strategies.

Conflict of Interest Disclosures. Dr. Risbrough reports personal fees from Sunovion, and grants from Johnson and Johnson, outside of the submitted work. Dr. Geyer reports support from San Diego Instruments, personal fees from Otsuka, personal fees from Lundbeck, personal fees from Omeros, personal fees from Dart, personal fees from Sunovion, and personal fees from Neurocrine, outside the submitted work. Drs. Acheson, Baker, Glenn, and Nievergelt have nothing to disclose.

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