ORIGINAL ARTICLE

Attention to Threats and Combat-Related Posttraumatic Stress Symptoms

Prospective Associations and Moderation by the Serotonin Transporter Gene

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Importance: Combat places soldiers at risk for posttraumatic stress disorder (PTSD). The excessive rates of PTSD and other adjustment disorders in soldiers returning home make it imperative to identify risk and resilience factors that could be targeted by novel therapeutic treatments.

Objective: To investigate the interplay among attention to threat, combat exposure, and other risk factors for PTSD symptoms in soldiers deployed to combat.

Design and Setting: Longitudinal prospective study of Israeli Defense Force infantry soldiers carried out in 2008 through 2010. Repeated measurements during a 1-year period included baseline and predeployment data collected in training camps and deployment data collected in the combat theater.

Participants: Infantry soldiers (1085 men; mean age, 18.8 years).

Main Outcome Measures: Postcombat PTSD symptoms.

Results: Soldiers developed threat vigilance during combat deployment, particularly when they were exposed to high-intensity combat, as indicated by faster response times to targets appearing at the location of threat relative to neutral stimuli ($P < .001$). Threat-related attention bias also interacted with combat exposure to predict risk for PTSD ($P < .05$). Bias toward threat at recruitment ($P < .001$) and bias away from threat just before deployment ($P < .05$) predicted postcombat PTSD symptoms. Moreover, these threat-related attention associations with PTSD were moderated by genetic and environmental factors, including serotonin transporter (5-HTTLPR) genotype.

Conclusions and Relevance: Combat exposure interacts with threat-related attention to place soldiers at risk for PTSD, and interactions with other risk factors account for considerable variance in PTSD vulnerability. Understanding these associations informs research on novel attention bias modification techniques and prevention of PTSD.

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Combat exposure confers risk for posttraumatic stress disorder (PTSD) and other forms of psychopathology. However, soldiers' psychiatric responses to combat stress vary markedly between individuals, and the basis for this variability remains poorly understood. Most work on PTSD examines diagnosed patients displaying concurrent symptoms. Such research designs preclude definitive examination of premorbid vulnerability factors owing to biases associated with retrospective reports.[1,2] The current longitudinal study examined the interplay between environmental risk, created by deployment to combat zones, and threat-related attention in predicting PTSD symptoms in infantry soldiers.

Ample evidence indicates that attention is deployed in a biased, maladaptive pattern in PTSD and anxiety disorders,[3] that such threat-related attention biases are plastic,[4] shifting after exposures to danger,[5,6] and that such biases predict PTSD symptoms in soldiers exposed to warzone stress.[7] The primary goal of the current study was to examine the predictive relations between pretraumatic attention bias and PTSD symptoms, using multiple assessments of PTSD and attention bias over time.

Prior research on the attention-anxiety interplay also suggests that other risk factors may moderate the association between threat-related attention patterns and PTSD. Accordingly, the secondary goal of the current study was to consider the manner in which other risk factors moderate the

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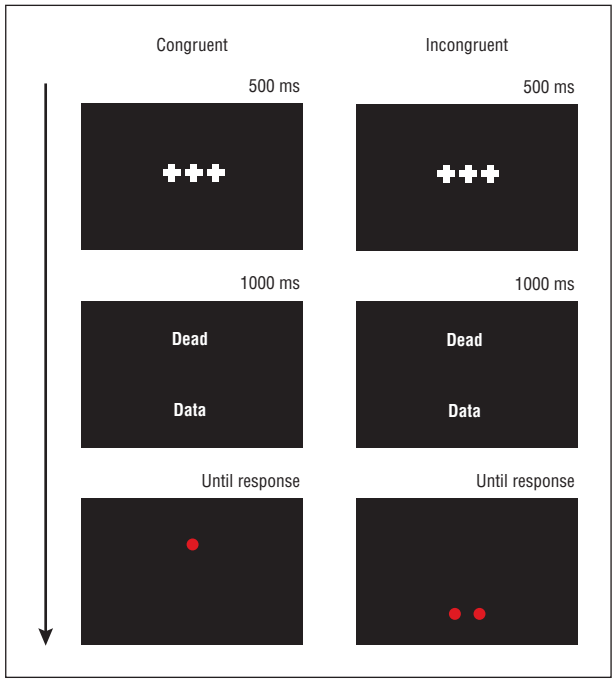

Figure 1. Sequence of events in a dot-probe trial. Left panels represent a threat-congruent trial; right panels, a threat-incongruent trial.

attention-PTSD association. Specifically, a gene polymorphism appearing in the promoter region of the serotonin transporter gene SLC6A4 variant (alternate name used here: serotonin transporter gene-linked polymorphic region [5-HTTLPR])[8-10] is particularly relevant for attention-PTSD associations.[11] The low-transcription genotype (SS, SL_G, L_GL_G) may interact with environmental risk to shape either adaptive or dysfunctional outcomes. Carriers of low-transcription variants, unlike carriers with the high-transcription variant (L_AL_A), typically display vigilance toward threats,[12-15] a profile that might increase risk for PTSD.[16,17] However, recent research findings also suggest that the low-transcription genotype may confer adaptive cognitive advantages under stressful conditions.[17]

Soldiers are taught to selectively attend to potential threats in order to enhance military performance in combat. Because deployed soldiers confront dramatic changes in environmental threat conditions, ranging from safety to acute danger, considerable plasticity in various aspects of threat-related attention is required. Insufficient plasticity in threat processing may hinder military performance and confer risk for psychological maladjustment. The current study prospectively examines the interplay among threat-related attention plasticity as measured with a computerized dot-probe task[4] and other risks for PTSD in Israeli Defense Force (IDF) soldiers during their first combat deployment. Specifically, the study charts changes in threat-related attention at 3 points along the soldiers' deployment cycle and the relation of threat-related attention to PTSD symptoms after combat exposure. Based on prior findings,[5-7] we expected greater attentional threat avoidance before and during combat exposure to predict greater PTSD symptoms. Furthermore, we examined how threat-related attention and serotonin-related gene polymorphism (5-HTTLPR) interact with combat exposure to predict PTSD symptoms.

METHODS

PARTICIPANTS

Male soldiers (n=1085; mean [SD] age,18.8 [1.0] years; range,18-24 years) were recruited from 1160 eligible soldiers (7% declined participation); 99% were Jewish (25% Ashkenazi, 27% Sephardic, 44% mixed, and 3% of African-Ethiopian origin). Because of high troop mobility and operational demands, we were able to study only subsamples of the full cohort at each data collection point. Baseline assessment occurred within 2 weeks of recruitment (n=890). Predeployment assessment occurred 24 weeks later, after training but before deployment to a combat zone (n=927). The postcombat assessment occurred in the combat theater, 1 year after recruitment and after 6 months of deployment (n=749). A complete repeated-measures data set (ie, all 3 time points) was obtained for 487 soldiers.

Written informed consent was obtained from all participants at each of the data collection time points. Given the sensitivity of research in military settings, research staff worked with the IDF to empower participants to decline participation. The study was approved by the Tel Aviv University Institutional Review Board, the IDF Medical Corps Ethics Committee, and the Israeli Ministry of Health High Ethics Committee.

THREAT BIAS ASSESSMENT

Threat-related attention bias was evaluated with a dot-probe task, fully described elsewhere.[5,6,18] The task consisted of 152 threat-neutral trials that began with a fixation display, followed by a word pair, and then a target in either of the 2 locations vacated by the words (**Figure 1**). Participants had to identify the target type as quickly as possible without compromising accuracy. Threat bias was calculated as the difference between mean reaction time to targets at neutral-word locations and targets at threat-word locations, thus providing a snapshot of participants' attention to threats. Positive bias scores reflect faster mean reaction time to targets appearing at the location of threat stimuli; such a positive bias is termed *attention toward threat* or *threat vigilance*. Negative bias scores reflect the opposite pattern, which is termed *attention away from threat* or *threat avoidance*.

PTSD AND TRAUMA

Symptoms of PTSD during the most recent month were evaluated with the PTSD Checklist (PCL, specific stressor version).[19,20] Clinically significant symptoms required 1 intrusion symptom, 3 avoidance symptoms, 2 hyperarousal symptoms, and a total score of at least 50. This combination was considered the clinical cutoff for PTSD in the current study. The primary outcome measure was postcombat symptoms measured in the combat theater after 6 months of deployment. Baseline and predeployment PTSD symptoms were also measured but were low in frequency.

Premilitary trauma was assessed on a 6-item questionnaire, inquiring whether participants had been present and/or injured in a terrorist attack or a motor vehicle crash or exposed to sexual or physical assault.

The primary index of combat-exposure was each unit's military operational assignment taken from official military records and rated as either high or low exposure. By definition, some op-

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Table 1. Soldiers' Self-reported Combat Experiences After 6 Months of Combat Deployment[a]

Combat Experience	Soldiers Reporting Experience, %[b]			*P* Value[c]
	Full Sample (N = 722)	Low Exposure (n = 317)	High Exposure (n = 405)	
Being attacked or ambushed	2.5	1.1	3.5	.01
Receiving incoming artillery, rocket, or mortar fire	10.1	7.5	12.0	.005
Being shot at or receiving small-arms fire	3.4	1.9	4.6	.01
Shooting or directing fire at the enemy	7.9	0.9	13.1	.001
Seeing dead or seriously injured Israelis	6.9	4.3	8.9	.001
Knowing someone seriously injured or killed	22.7	20.5	24.4	.05
Seeing ill or injured women or children whom you were unable to help	4.8	2.8	6.3	.005
Had a close call, was shot or hit, but protective gear saved you	1.7	0.6	2.5	.05
Clearing or searching homes or buildings	10.6	1.3	17.6	.001
Being at a place where stones or explosive devices were thrown	23.2	9.2	33.7	.001
Arresting wanted individuals	19.2	3.8	30.7	.001

[a] This table shows experiences with rates that differed significantly between the high- and low-exposure groups. Additional reported combat experiences in which the exposure groups did not differ included the following: being responsible for the death of an enemy combatant, being responsible for the death of a noncombatant, seeing dead bodies or human remains, handling or uncovering human remains, participating in demining operations, being wounded or injured, had a buddy shot or hit who was next to you, engaging in hand-to-hand combat, and/or saved the life of a soldier or civilian.

[b] Percentages are given for the full sample and as a function of exposure intensity. Low exposure was defined as second-line deployment and high exposure as first-line deployment. Data exclude missing values because not all respondents answered every question.

[c] *P* values were determined with 2-tailed Fisher exact test for contrast between the low- and high-exposure groups.

erational posts involve higher combat intensity than others (eg, guarding a large military base near the front line vs conducting reconnaissance patrols beyond the area occupied by friendly forces). Thus, by noting the geographic location and nature of operational commands for each soldier's platoon, we were able to objectively estimate the geo-operational exposure as high or low. The geo-operational index provides a unique observation on the actual exposure environment than that of self-reports, which is of utmost relevance to the study of gene × environment interactions.[16] Furthermore, the use of an objective index of exposure addresses potential confounds between personal vulnerability and self-reports on combat exposure.

We also obtained a secondary measure of combat exposure using soldiers' self-reports on the Combat Experiences Scale.[21] The original scale consisted of 18 yes-or-no questions concerning various combat events. We added 2 event types specifically relevant to the IDF deployment context (see 2 last items in **Table 1**). Both measures are important in the context of the current study. Geo-operational exposure is particularly relevant to analyses concerning gene × environment interactions because it objectively quantifies combat-zone environments. However, despite the potential confound between personal vulnerability and subjective self-reports on combat exposure, this measure still provides an index of an individual's combat exposure, regardless of the geo-operational assignment of his platoon.

GENETICS

DNA was isolated from saliva samples by using Oragene-DNA kits (DNA Genotek). Genotyping was performed in 2 stages for the S (103–base pair [bp]), L (146-bp), L_A (146 bp), and L_G (61-bp) alleles. The 5-HTTLPR region was amplified in a 20-μL reaction with 10 ng of DNA with 1× Optimized Buffer A, 1× polymerase chain reaction (PCR) enhancer, 0.25-μmol/L primers (FAM-ATCGCTCCTGCATCCCCCATTAT [forward], GAGGTGCAGGGGGATGCTGGAA [reverse]), 0.125-μmol/L deoxyribonucleotide triphosphate, and 1.25 U of Platinum Taq polymerase (all from Invitrogen). The PCR conditions were as follows: 95°C (5 minutes), 40 cycles at 94°C (30 seconds), 52°C (30 seconds), 68°C (1 minute), and a final elongation at 68°C (10 minutes). S and L genotypes were discriminated directly from the PCR reaction products, and the rs25531 genotypes (L_A and L_G) were determined by digesting 10 μL of PCR mix with 100 U of MspI (New England Biolabs; 37°C, 1 hour, 1× restriction buffer). Amplicons were visualized with GeneScan 500 ROX Size Standard (Applied Biosystems) and analyzed with a 3730 DNA Analyzer (Applied Biosystems); allele sizes were determined by using GeneMapper software (version 4.0; Applied Biosystems). Genotyping accuracy was determined empirically by duplicate genotyping of 25% of the samples selected randomly. The error rate was less than 0.005, and the completion rate more than 0.95. The 5HTTLPR allele frequency was 172 (26%) for SS (SS, SL_G, L_GL_G), 315 (48%) for SL (SL_A, L_AL_G), and 174 (26%) for LL (L_AL_A), in Hardy-Weinberg equilibrium ($\chi^2 = 1.45$; $P = .23$).

Studies[22,23] have shown that 3 relatively common functional alleles at the HTTLPR locus affect 5-HTT transcription, acting codominantly. Compared with the L_A allele, the S and L_G alleles lead to lower rates of transcription and are functionally equivalent such that the L_G and S alleles have similar transmission efficacy profiles.[23] Therefore, it is logical to group the 6 common genotypes into 3 functionally defined categories as follows: low (SS, SL_G, and L_GL_G), intermediate (SL_A and L_AL_G), and high (L_AL_A). Thus, 5-HTTLPR polymorphism was grouped based on presumed efficacy of serotonin neurotransmission: low (SS/SL_G; 26% of the sample), intermediate (SL_A/L_AL_G; 48% of the sample), and high (L_AL_A; 26% of the sample). The allelic frequency was 46% for S, 50% for L_A, and 4% for L_G. Greater efficacy denotes greater reuptake of serotonin, leading to lower levels of serotonin in the synapse as well as decreased duration and magnitude of serotonergic signaling. The potential effect of population origin was estimated via self-reports on the geographic origins of each participant's 4 grandparents and 2 parents. Participants were classified on an ethnicity index as Ashkenazi, Sephardi, mixed, or African-Ethiopian.

PROCEDURE

Soldiers were tested 3 times during a 1-year period. The dot-probe task was administered first, followed by questionnaires and collection of saliva samples. Baseline and predeployment data were collected in training camps. Deployment data were collected in the combat theater.

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STATISTICAL ANALYSIS

Our primary prediction was of changes in attention bias from baseline through deployment, with differences between soldiers who ultimately manifested high relative to low levels of in-theater PTSD symptoms; this prediction was tested in a 3 × 2 × 2 analysis of covariance. Time (baseline, predeployment, and in deployment) served as a within-subject variable; geo-operational exposure (low or high) and clinical-cutoff PTSD in deployment (yes or no) served as between-subject variables. Precombat PCL score and self-reported combat exposure were entered as covariates. This type of analysis is limited by including only participants with complete data. Nevertheless, this approach best illustrates time-related changes in a dependent measure while modeling effects of independent measures on those longitudinal patterns. In this analysis, we did not include 5-HTTLPR status owing to small cell sizes. The effects of 5-HTTLPR status are treated in depth in the context of the following regression and mixed-models analyses.

To complement the aforementioned analytic approach, we used regression analyses to predict in-deployment PTSD symptoms, including 5-HTTLPR status as well as many other relevant predictors. We first entered each of these primary predictors (high school completion, predeployment PTSD symptoms, traumatic history, predeployment threat bias, self-reported combat experience, geo-operational combat exposure index, and 5-HTTLPR status). We then entered the following interaction terms: predeployment threat bias × 5-HTTLPR, geo-operational combat exposure index × 5-HTTLPR, predeployment threat bias × geo-operational combat exposure index, and predeployment threat bias × geo-operational combat exposure index × 5-HTTLPR (3-way interaction). We repeated these analyses using self-reported combat experiences rather than the geo-operational combat exposure index in the interaction terms.

Finally, we applied an approach that includes subjects irrespective of missing data, a linear regression, structural equation modeling framework with maximum-likelihood estimation, including data from any participant with at least 1 variable at 1 time point. This second model tested the prediction that attention bias shapes risk for PTSD in the context of other risks (education level, precombat PTSD symptoms, premilitary trauma, 5-HTTLPR genotype, and level of combat exposure). Specifically, attention bias, 5-HTTLPR genotype, and combat exposure were expected to modulate one another, in relation to PTSD symptoms. This hypothesis was tested in a bias × 5-HTTLPR × exposure interaction.

Data were analyzed by using Mplus software (version 6.1)[24] and assuming data were missing at random. This analysis estimates the log likelihood of each model for the outcome, conditional on the covariates. As in conventional regression analysis, all covariates were assumed to be correlated. Finally, means and variances of all continuous covariates were estimated in the model to allow for missing data among these measures. Most missing data were missing at random, but participants with greater predeployment PTSD symptoms were less likely to continue in the study after deployment. Therefore, predeployment PTSD symptoms were included as a covariate in all analyses. Before all regression analyses, continuous covariates and predictors were mean centered, and the interactions of the predictors were computed as the product of the 2 mean-centered variables. The 5-HTTLPR genotype was effect coded; −1, 0, and 1 indicated low, medium, and high functionality, respectively.

The focus of these analyses was moderation of risk for combat-related PTSD. Therefore, hypothesis tests relied primarily on tests of interaction, performed within the structural equation modeling framework. Level of combat exposure (high vs low) was tested as a moderator through the use of multigroup regressions, and a χ^2 difference test was applied to test for significant differences between models with and without group differences. The multigroup model tested moderation of PTSD risk by attention bias, 5-HTTLPR status, and the 2-way attention × 5HTTPLR interaction, within each exposure group. This provided a test of a 3-way exposure × attention × 5-HTTLPR interaction. In addition, standardized coefficients from the parallel models were used to calculate a χ^2 difference test of effects between exposure groups. All significant interactions were probed and plotted according to standards outlined elsewhere by Aiken and West.[25] Specifically, interaction effects involving 5-HTTLPR were probed further in post hoc analyses using scores relabeled to denote either low functionality as 0 (medium, 1; high, 2) or high functionality as 0 (low, −2; medium, −1) and performing the multigroup regression analysis again for each relabeled score. The estimated attention bias effects from each analysis (with low, medium, or high 5-HTTLPR functionality labeled as 0) were then compared with each other by using additional beta difference tests.

RESULTS

COMBAT EXPERIENCES

A mean of 2.03 combat events per soldier (range, 0-13 events) was reported after deployment. Of 722 deployed soldiers, 405 were assigned to high- and 317 to low-exposure regions, with classifications based on units' objective operational assignments (geo-operational exposure index). As expected, soldiers in high-exposure units reported more combat-related events than those in low-exposure units (t_{720} = 10.73; $P < .001$). Similar associations arose in an analysis considering only the 487 soldiers with no missing data (t_{485} = 9.12; $P < .001$; see Table 1 for details about types and frequencies of combat events experienced).

CHANGE OVER TIME IN THREAT-RELATED ATTENTION BIAS AND PTSD SYMPTOMS

The primary analysis examined changes in attention bias across the 3 data collection waves (**Table 2**) as a function of in-theater PTSD status and geo-operational exposure. Both hypothesized interactions emerged as predictors of changes in threat vigilance: time × geo-operational exposure ($F_{2,479}$ = 5.15; $P < .006$) and time × PTSD ($F_{2,479}$ = 4.52; $P < .01$). No other main or interaction effects were significant.

To explicate the interaction between time and geo-operational exposure, follow-up comparisons were conducted (**Figure 2**A). For the groups with high or low geo-operational exposure, no between-group differences in threat bias were found at baseline or before deployment. These emerged only after combat exposure, when the high-exposure group manifested greater threat vigilance than the low-exposure group (t_{485} = 3.46; $P < .001$).

To explicate the time × PTSD interaction, follow-up comparisons were conducted (Figure 2B). At baseline, participants who ultimately would score above the PTSD cutoff after deployment had greater threat bias than those who would score below the cutoff (t_{483} = 2.05; $P < .05$). After training but before deployment, the PTSD group showed attentional threat avoidance, in contrast to the

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Table 2. Posttraumatic Stress Disorder Symptoms and Attention-Related Indices by Time in the Deployment Cycle and Combat Exposure Intensity

Index	Baseline (n = 487)	Before Deployment (n = 487)	During Deployment: High Exposure (n = 270)	During Deployment: Low Exposure (n = 217)
Posttraumatic stress disorder symptoms, PCL				
Scale score, mean (SD)	24.86 (8.69)	25.37 (9.56)	25.56 (11.44)	24.15 (8.85)
Above clinical cutoff, %	2.6	4.5	8.1	5.1
Attention dot-probe task				
RT for threat stimuli, mean (SD), ms	498 (84)	519 (106)	429 (89)	437 (83)
RT for neutral trials, mean (SD), ms	498 (85)	516 (104)	449 (86)	441 (82)
Threat bias score, mean (SD), ms	−1 (21)	−3 (30)	21 (50)	4 (57)
Accuracy for threat stimuli, mean (SD), %	98 (2)	99 (2)	92 (8)	93 (8)
Accuracy for neutral trials, mean (SD), %	98 (2)	98 (2)	96 (6)	94 (7)

Abbreviations: PCL, PTSD Checklist; RT, reaction time.

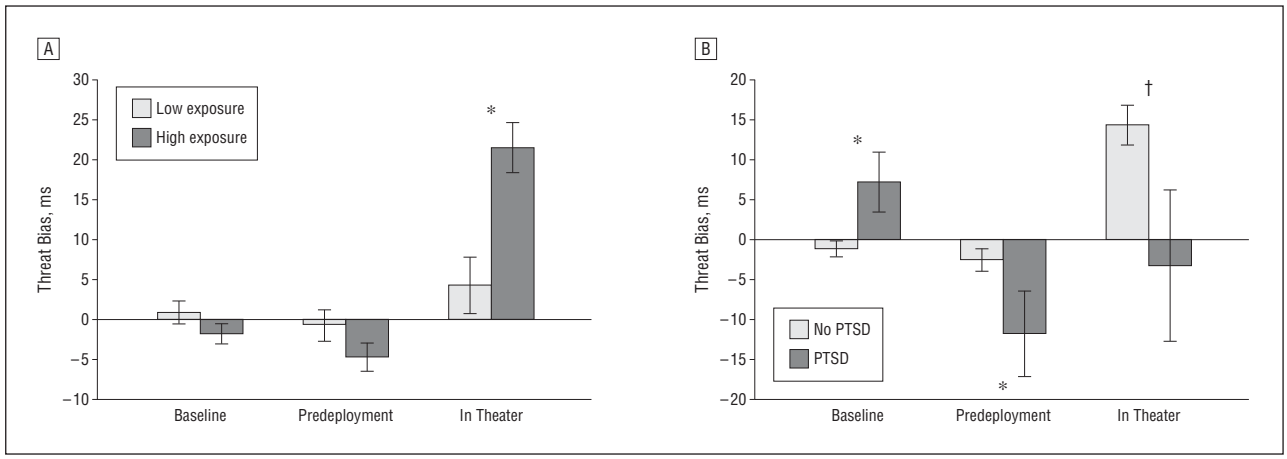

Figure 2. Means and standard error bars for effects of combat exposure on threat vigilance as a function of time in the deployment cycle (A) and changes over time in threat-related attention bias as a function of posttraumatic stress disorder (PTSD) symptoms during deployment (B). *$P < .05$; †$P = .08$.

no-PTSD group, which showed no bias ($t_{483} = 1.98$; $P < .05$). Finally, a nonsignificant trend level difference was manifested in deployment ($t_{485} = 1.77$; $P = .08$).

PREDICTING PTSD SYMPTOMS FROM THREAT BIAS, 5-HTTLPR STATUS, AND COMBAT EXPOSURE

Preliminary Analysis of Sample Characteristics and PTSD

Correlation or *t* tests were conducted to examine bivariate relations. Soldiers who did not complete high school had more PTSD symptoms in combat during deployment than those who did ($t_{718} = 3.88$; $P < .001$). In addition, predeployment PTSD symptoms and trauma history were positively correlated with PTSD symptoms during deployment ($P < .05$ for all). Thus, high school completion (0, no; 1, yes), predeployment PTSD symptoms, and baseline trauma history were included in the predictive model. The ethnicity indices were not related to any of the outcome measures and thus were not included in the predictive models.

Finally, allele frequencies of the L and S forms vary among different populations. The S form is relatively uncommon among sub-Saharan African populations (11%) relative to white Europeans (50%) and Asians (70%). This race-related variability in frequencies suggests differing susceptibilities to the effects of the S allele in different ethnic groups.[26] We therefore repeated the analyses, excluding the soldiers of African-Ethiopian origin. This omission did not change any of the reported findings. More important, because these models include predeployment PTSD symptoms, they predict changes in PTSD, over and above any symptoms present before deployment.

Predicting PTSD Symptoms During Deployment in Linear Regression Model Using Participants With Full Data Sets

The model significantly predicted 34% of the variance in PTSD symptoms, a large, statistically significant effect ($F_{11,440} = 19.90$; $P < .001$). Significant single predictors included predeployment threat bias ($\beta = -.10$; $P < .01$; 95% CI, −0.06 to −0.007), and predeployment PTSD symptoms ($\beta = .52$; $P < .001$; 95% CI, 0.48 to 0.65). High school completion marginally predicted in-deployment PTSD symptoms ($\beta = -.07$; $P = .06$; 95% CI, −4.43 to 0.09). In addition, 2 significant interaction terms emerged: predeployment threat bias × geo-

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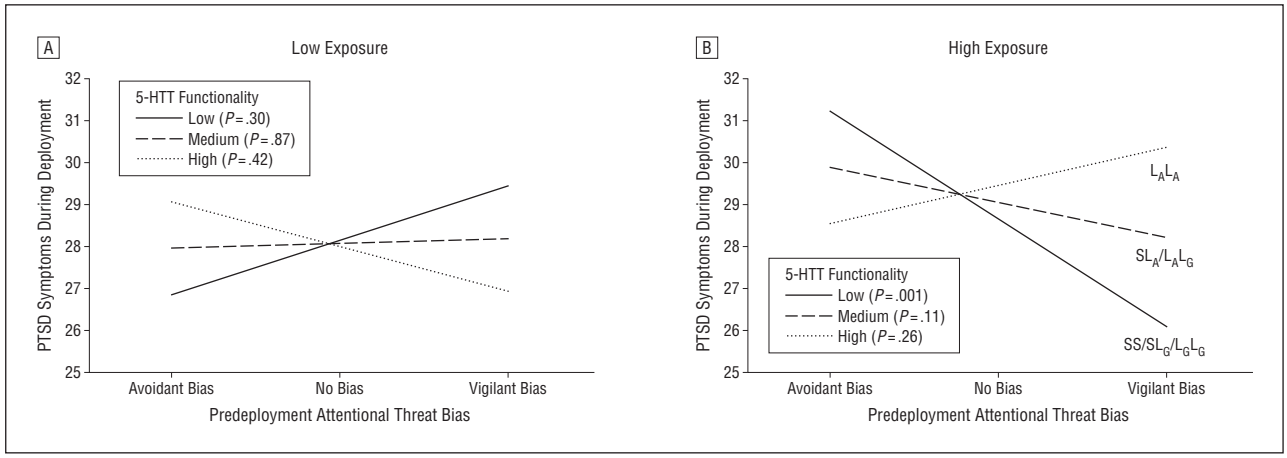

Figure 3. Predeployment threat-related attention biases, 5-HTTLPR functionality, and combat exposure intensity predict posttraumatic stress disorder (PTSD) symptoms during deployment.

operational exposure index ($\beta = -.73$; $P < .004$; 95% CI, −0.45 to −0.08), which was subsumed under the 3-way interaction term of predeployment threat bias × geo-operational combat exposure × 5-HTTLPR interaction ($\beta = .62$; $P < .01$; 95% CI, 0.02 to 0.19). None of the other single predictors or interaction terms was significant.

Repeating this analysis using self-reported combat experiences rather than the geo-operational combat exposure index in the interaction terms revealed the same pattern of results. The model significantly predicted 35% of the variance in PTSD symptoms ($F_{11,440} = 19.18$; $P < .001$). Significant predictors were predeployment threat bias ($\beta = -.10$; $P < .01$; 95% CI, −0.06 to −0.007) and predeployment PTSD symptoms ($\beta = .52$; $P < .001$; 95% CI, 0.48 to 0.65). High school completion marginally predicted in-deployment PTSD symptoms ($\beta = -.07$; $P = .06$; 95% CI, −4.43 to 0.09). Similarly, 2 significant interaction terms emerged: predeployment threat bias × self-reported combat experiences ($\beta = -.33$; $P < .02$; 95% CI, −0.06 to −0.005), subsumed under the 3-way interaction term of predeployment threat bias × self-reported combat experiences × 5-HTTLPR ($\beta = .40$; $P < .002$; 95% CI, 0.009 to 0.04). None of the other single predictors or interaction terms was significant.

Predicting PTSD Symptoms During Deployment in the Full Sample

Within a structural equation modeling framework, multigroup linear regression analyses were conducted to test the effects of the geo-operational exposure index (high vs low), predeployment attentional threat bias, and 5-HTTLPR functionality, as individual predictors and through interactions with each other, on the level of PTSD symptoms (PCL score) during deployment in the combat theater. High school completion (0, no; 1, yes), predeployment PTSD symptoms, baseline trauma history, and self-reported combat experience in deployment were included as covariates in the predictive model. This analysis included all 1085 participants. The model allowing for group (high vs low exposure) differences ($\chi^2_{12} = 10.15$; $P = .60$; Comparative Fit Index [CFI], 1.00; Root Mean Square Error of Approximation [RMSEA], 0.00; Standardized Root Mean Residual [SRMR], 0.02) had significantly better fit than the model not making such allowances ($\chi^2_{13} = 16.72$ [$P = .21$; CFI, 0.99; RMSEA, 0.02; SRMR, 0.02]; $\chi^2_{1\text{diff}} = 6.57$; [$P < .05$]). This establishes that the geo-operational exposure group moderated the effects of the other predictors on PTSD symptoms during deployment. To explicate this moderating effect, separate structural equation modeling analyses explored predictors within each exposure group.

Within the high-exposure group (n = 620), the model explained 34% of the variance in PTSD symptoms during deployment in the combat theater (under "medium functionality of 5-HTTLPR" in the eTable; http://www.jamapsych.com). High school completion and baseline PTSD symptoms showed significant main effects in this group. Those who did not complete high school or had greater predeployment PTSD symptoms reported more PTSD symptoms during deployment. There were no direct effects of baseline traumatic history, predeployment attention bias, or 5-HTTLPR functionality on PTSD symptoms for this high-exposure group. More important, threat-related attention bias interacted with 5-HTTLPR functionality such that in soldiers with high 5-HTTLPR functionality (under "high functionality of 5-HTTLPR" in the eTable), threat bias showed no association with deployment-related PTSD symptoms. In contrast, for soldiers with low 5-HTTLPR functionality (under "low functionality of 5-HTTLPR" in the eTable), threat bias was negatively associated with PTSD symptoms (**Figure 3**).

Within the low-exposure group (n = 465), the model explained 36% of the variance in PTSD symptoms (eTable). High school completion showed a trend, and predeployment PTSD symptoms showed a significant main effect on PTSD symptoms during deployment. However, the following had no significant effects on PTSD symptoms: baseline traumatic history, self-reported combat experience, threat bias, 5-HTTLPR functionality, and the interaction of threat bias and 5-HTTLPR.

Follow-up χ^2 difference tests confirmed that the interactions between threat bias and 5-HTTLPR status dif-

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fered significantly between the 2 exposure groups ($\chi^2_1 = 6.64$; $P < .05$). In addition, the effect of threat bias on PTSD symptoms for the group with high geo-operational exposure was significantly higher for the low-functionality 5-HTTLPR genotype than for the high- or medium-functionality genotypes ($\chi^2_1 = 9.79$ and 9.67, respectively; $P < .01$ for both).

COMMENT

The findings suggest that military deployment induces shifts in threat-related attention as measured by the dot-probe task, which in turn relate to risk for PTSD. Moreover, these shifts in biased attention interact with combat exposure and 5-HTTLPR status to predict risk for PTSD during deployment. Specifically, soldiers with low-transcription 5-HTTLPR genotypes, particularly when they display threat vigilance in combat, a "normative" response in the current sample, manifest fewer PTSD symptoms when exposed to combat stress. Risk for PTSD symptoms in combat was also predicted by soldiers' levels of predeployment symptoms and education. Interestingly, neither combat exposure alone nor prior trauma predicted PTSD symptoms in deployment.

The current results reveal complex interactions among attention, combat exposure, and PTSD susceptibility. Relative to soldiers who showed neither attention vigilance nor avoidance, both soldiers with high threat bias scores at baseline and those showing threat avoidance after basic training immediately before deployment faced higher risk for combat-related PTSD. Thus, attention-PTSD associations vary by context. Such stress-related attention plasticity is relevant to the seemingly contradictory symptoms of pathological avoidance and hypervigilance that typically occur together in PTSD.[27] Extreme adaptation challenges, such as those arising from soldiers' shifting exposures to relatively safe and acutely hostile environments, may produce shifting psychological and behavioral symptoms of hypervigilance and avoidance. These findings concur with previous reports on stress-related plasticity in stress-attention interactions.[5,6,18,28] However, more research is needed to establish whether threat-related attention patterns measured by the dot-probe task relate to actual performance in combat zones or in military training contexts.

These and other findings[5,18,29-31] on attention plasticity provide important insights on the pathophysiology of stress-related psychopathology. The current study found attentional threat avoidance under the stress of a looming deployment in soldiers who developed PTSD symptoms in combat. This finding is in line with previous reports indicating an association between threat-related bias suppression and PTSD symptoms.[5,6,18] However, these results are not easily reconciled with other findings, including those of MacLeod and Mathews,[32] who found that high-trait anxious students increased their tendency to allocate attention toward threat stimuli, whereas low-trait anxious students increased their tendency to shift attention away from such stimuli. These previously reported results suggest that under stress, bias away from threat is linked to low anxiety, whereas in the current data, bias away from threat is linked to an opposite tendency, here manifesting as high levels of PTSD symptoms. There are important differences between the 2 studies, including the nature of the populations and the stress exposure, as well as aspects of the dot-probe parameters. Any of these factors, either alone or in combination with other factors, could account for the differing patterns of results between the 2 studies. More research into these potential mediators is warranted.

The findings also carry implications for novel therapeutic treatments. Recent research indicates that threat-related attention biases can be systematically manipulated through computer-based training in a fashion that prevents or treats anxiety.[33,34] Given the complex pattern of threat-related attention in the current study, further work is needed to evaluate the potential advantages and disadvantages of such computer-based attention bias modification (ABM) protocols in the context of military deployment. However, because active threat avoidance in combat is extremely dangerous operationally and seems to also confer enhanced risk for PTSD symptoms, it may be reasonable to test whether ABM designed to enhance attendance to threats in soldiers before deployment to combat is protective against posttraumatic symptoms. Furthermore, ABM techniques could be combined with current evidence-based cognitive-behavioral therapies[35] to enhance treatment outcomes in patients with PTSD.

The current results reveal no direct effect of the 5-HTTLPR genotype on PTSD symptoms (but compare other reported findings[36,37]). Rather, a more complex pattern was revealed, in which genes and stress exposure modulate the effect of threat-related attention on risk for PTSD. In conditions of low combat exposure, threat attendance and 5-HTTLPR status did not predict PTSD symptoms. In high combat exposure, the combination of the low-transcription variant of the 5-HTTLPR genotype and threat vigilance seems to confer lower levels of PTSD symptoms. The low-transcription 5-HTTLPR genotype may play a protective role under the extreme stress of military deployment.[17] Specifically, a natural tendency of individuals with low 5-HTTLPR transcription to attend to threats may lead to enhanced maladaptive emotional responses and elevated anxiety when environmental conditions are safe and stable,[9] but which are perfectly normal and adaptive responses in combat, where vigilance toward minor threats is crucial for survival.

The current study also has some limitations. First, although considerable effort was invested in standardization of data collection, the conditions under which data were collected in combat zones were not fully uniform. The significant findings despite this variability in experimental setup suggest that the results may underestimate the robustness of the reported effects. Second, although our sample included 1085 soldiers, only 487 soldiers had complete data sets. This problem, due to high troop mobility, constrains interpretation of results, but seems inherent to research involving military combat units.[38] Third, although previous research indicates that self-reported PCL scores are correlated strongly with the Clinically Administered PTSD Scale (CAPS)

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and provide an accurate assessment of PTSD severity,[19] the primary outcome measure of PTSD in the current study relies on self-reports rather than formal clinical diagnosis. Thus, any conclusions concerning clinical PTSD are tentative and should be considered with caution. Fourth, despite stable associations between threat bias and anxiety, some concern has been voiced regarding the retest reliability of the attention bias score[39] (but see other references[40,41]). Although this potential limitation is inherent to all reaction time measures based on subtraction scores, future studies may benefit from the use of other methods, such as eye tracking, to quantify changes in threat-related attention bias in deployed soldiers.[7] Fifth, the present sample may not have been large enough to reveal all the potential interactions between threat bias, 5-HTTLPR status, and combat exposure in predicting clinical-level PTSD symptoms. This difficulty primarily relates to the relatively small number of soldiers exceeding a clinical screening cutoff on the PCL.

In conclusion, data from the current study show plasticity in attentional components of threat processing in soldiers trained and deployed to combat duties. These changes in threat processing interact with combat exposure and genetic variability in the serotonin transporter gene to predict risk for PTSD symptoms. These findings, in tandem with recent reports on ABM treatment efficacy in reducing anxiety symptoms, point to a potential application of such techniques in deployed armed forces.

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