



Original Investigation | Psychiatry

Association of War Zone–Related Stress With Alterations in Limbic Gray Matter Microstructure

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Abstract

IMPORTANCE Military service members returning from theaters of war are at increased risk for mental illness, but despite high prevalence and substantial individual and societal burden, the underlying pathomechanisms remain largely unknown. Exposure to high levels of emotional stress in theaters of war and mild traumatic brain injury (mTBI) are presumed factors associated with risk for the development of mental disorders.

OBJECTIVE To investigate (1) whether war zone–related stress is associated with microstructural alterations in limbic gray matter (GM) independent of mental disorders common in this population, (2) whether associations between war zone–related stress and limbic GM microstructure are modulated by a history of mTBI, and (3) whether alterations in limbic GM microstructure are associated with neuropsychological functioning.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was part of the TRACTS (Translational Research Center for TBI and Stress Disorders) study, which took place in 2010 to 2014 at the Veterans Affairs Rehabilitation Research and Development TBI National Network Research Center. Participants included male veterans (aged 18–65 years) with available diffusion tensor imaging data enrolled in the TRACTS study. Data analysis was performed between December 2017 to September 2021.

EXPOSURES The Deployment Risk and Resilience Inventory (DRRI) was used to measure exposure to war zone–related stress. The Boston Assessment of TBI–Lifetime was used to assess history of mTBI. Stroop Inhibition (Stroop-IN) and Inhibition/Switching (Stroop-IS) Total Error Scaled Scores were used to assess executive or attentional control functions.

MAIN OUTCOMES AND MEASURES Diffusion characteristics (fractional anisotropy of tissue [FA_T]) of 16 limbic and paralimbic GM regions and measures of functional outcome.

RESULTS Among 384 male veterans recruited, 168 (mean [SD] age, 31.4 [7.4] years) were analyzed. Greater war zone–related stress was associated with lower FA_T in the cingulate (DRRI-combat left: $P = .002$, partial $r = -0.289$; DRRI-combat right: $P = .02$, partial $r = -0.216$; DRRI-aftermath left: $P = .004$, partial $r = -0.281$; DRRI-aftermath right: $P = .02$, partial $r = -0.219$), orbitofrontal (DRRI-combat left medial orbitofrontal cortex: $P = .02$, partial $r = -0.222$; DRRI-combat right medial orbitofrontal cortex: $P = .005$, partial $r = -0.256$; DRRI-aftermath left medial orbitofrontal cortex: $P = .02$, partial $r = -0.214$; DRRI-aftermath right medial orbitofrontal cortex: $P = .005$, partial $r = -0.260$; DRRI-aftermath right lateral orbitofrontal cortex: $P = .03$, partial $r = -0.196$), and parahippocampal (DRRI-aftermath right: $P = .03$, partial $r = -0.191$) gyrus, as well as with higher FA_T in the amygdala-hippocampus complex (DRRI-combat: $P = .005$, partial $r = 0.254$; DRRI-aftermath: $P = .02$, partial $r = 0.223$). Lower FA_T in the cingulate-orbitofrontal gyri was associated with impaired

(continued)

Key Points

Question Is war zone–related stress associated with limbic gray matter (GM) microstructure?

Findings In this cohort study of US veterans, exposure to war zone–related stress was associated with alterations in limbic GM microstructure, independent of the diagnosis of mental disorder or mild traumatic brain injury. Furthermore, GM microstructure was associated with cognitive functioning.

Meaning These findings suggest that war zone–related stress may lead to limbic GM microstructure alterations, which may underlie the deleterious outcomes of war zone–related stress on brain health and that military service members may benefit from early therapeutic interventions following deployment.

+ Supplemental content

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Abstract (continued)

response inhibition (Stroop-IS left cingulate: $P < .001$, partial $r = -0.440$; Stroop-IS right cingulate: $P < .001$, partial $r = -0.372$; Stroop-IS left medial orbitofrontal cortex: $P < .001$, partial $r = -0.304$; Stroop-IS right medial orbitofrontal cortex: $P < .001$, partial $r = -0.340$; Stroop-IN left cingulate: $P < .001$, partial $r = -0.421$; Stroop-IN right cingulate: $P < .001$, partial $r = -0.300$; Stroop-IN left medial orbitofrontal cortex: $P = .01$, partial $r = -0.223$; Stroop-IN right medial orbitofrontal cortex: $P < .001$, partial $r = -0.343$), whereas higher FA_T in the mesial temporal regions was associated with improved short-term memory and processing speed (left amygdala-hippocampus complex: $P < .001$, partial $r = -0.574$; right amygdala-hippocampus complex: $P < .001$, partial $r = 0.645$; short-term memory left amygdala-hippocampus complex: $P < .001$, partial $r = 0.570$; short-term memory right amygdala-hippocampus complex: $P < .001$, partial $r = 0.633$). A history of mTBI did not modulate the association between war zone-related stress and GM diffusion.

CONCLUSIONS AND RELEVANCE This study revealed an association between war zone-related stress and alteration of limbic GM microstructure, which was associated with cognitive functioning. These results suggest that altered limbic GM microstructure may underlie the deleterious outcomes of war zone-related stress on brain health. Military service members may benefit from early therapeutic interventions after deployment to a war zone.

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Introduction

Military personnel serving in theaters of war are at increased risk for physical and mental health problems following deployment.¹⁻³ Mental health-related disorders are pervasive; up to 30% of service members returning from Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), or Operation New Dawn (OND) receive a diagnosis of a mental illness, such as posttraumatic stress disorder (PTSD), anxiety, or depression.⁴⁻⁶ Known factors associated with postdeployment mental disorders include combat exposure and associated psychosocial stressors.⁷⁻⁹ Importantly, service members exhibit symptoms related to war zone stress and experience low quality of life even if they do not meet the diagnostic criteria for a mental disorder.¹⁰ Furthermore, despite the prevalence and adversity of war zone-related stress, the majority of previous studies have not specifically investigated the impact of war zone-related stress, and even fewer have used quantitative questionnaires such as the Deployment Risk and Resilience Inventory (DRRI) to quantify perceived war zone-related stress.¹¹⁻¹⁴ Although mental health problems are highly prevalent in postdeployed military service members¹⁵ and war zone-related stress has been discussed as a risk factor, the underlying pathomechanisms remain poorly understood.

Furthermore, approximately 12% to 35% of OEF, OIF, and OND veterans have sustained a mild traumatic brain injury (mTBI).¹⁶⁻¹⁹ Evidence suggests that mTBI is not only a highly prevalent comorbidity but is also considered a potential risk factor for the development of mental disorders. In fact, service members who have sustained mTBI have a significantly increased risk for developing PTSD^{1,16,20-22} and depression.^{1,23,24} Moreover, they exhibit poorer neurocognitive functioning, worse long-term recovery,²⁵ and more severe neurological impairment^{26,27} compared with those who have not sustained mTBI. However, it is unknown whether comorbidity with mTBI modulates a possible association between war zone-related stress and alterations of brain structure and neuropsychological functioning. A better understanding of the outcomes of war zone-related stress on brain microstructure and function is critical for improving long-term health and quality of life of military service members returning from theaters of war.

Magnetic resonance imaging (MRI) provides a noninvasive way to study brain alterations as it allows for the in vivo, 3-dimensional investigation of brain macrostructure and microstructure.²⁸ Neuroimaging studies have linked neuropsychiatric disorders, including PTSD and mTBI, to

macrostructural brain alterations.²⁹ However, although an association between diagnoses and abnormal brain structure has been established, research on the outcomes of war zone-related stress on brain structure is sparse. Combat exposure has been found to be associated with lower volume of limbic or limbic-associated gray matter (GM) regions, such as the amygdala,³⁰ hippocampus,^{31,32} orbitofrontal gyrus,³³ posterior insula,³⁴ ventromedial prefrontal cortex, and dorsal anterior cingulate cortex.³⁵ Of note, although lower limbic GM volumes have been associated with PTSD symptom severity and extent of alcohol use, other disorders commonly seen in this population have previously not been considered.

Diffusion-weighted MRI (dMRI) has been shown to be sensitive to subtle microstructural brain alterations associated with neuropsychiatric disorders, such as PTSD and mTBI.²⁹ Complementary to volumetric measures, dMRI has the potential to reveal alterations in tissue composition (eg, glial changes³⁶⁻³⁸ and atrophy³⁹) and tissue morphologic changes (eg, alterations in dendritic arborization⁴⁰⁻⁴²), thereby providing insight into underlying pathomechanisms. Although most research to date has focused on the microstructure of connecting white matter (WM) fiber tracts,⁴³⁻⁴⁶ studies on the limbic GM microstructure are sparse. Importantly, to our knowledge, no study to date has investigated the association between combat exposure and limbic GM diffusion, although limbic GM constitutes an essential neuroanatomical correlate of mental and neuropsychological functioning as suggested previously by volumetric studies^{31,32,47} of limbic system structures in postdeployed veterans. The aim of this study is to investigate (1) whether war zone-related stress is associated with microstructural alterations in limbic GM independent of mental disorders, (2) whether associations between war zone-related stress and limbic GM microstructure are modulated by a history of mTBI, and (3) whether alterations in limbic system GM microstructure are associated with neuropsychological functioning.

Methods

This cohort study was approved by the institutional review board of human studies research at the Veterans Affairs Boston Healthcare System and all participants provided written informed consent. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Participants

The Translational Research Center for TBI and Stress Disorders (TRACTS) study is a longitudinal prospective cohort study that aims to assess and track the potential outcomes of psychologically and physically traumatic experiences related to military deployment over time. Inclusion criteria for enrollment into the TRACTS study were (1) age 18 to 65 years, (2) male sex, and (3) service in OEF, OIF, or OND, or scheduled deployment.⁴⁸ Exclusion criteria were (1) history of neurological illness other than TBI; (2) current diagnosis of schizophrenia spectrum or other psychotic disorders; (3) current diagnosis of bipolar or related disorders; (4) active suicidal and/or homicidal ideation, intent, or plan requiring crisis intervention; and (5) cognitive disorder due to general medical condition other than TBI. Parameters with potential impact on cerebral microstructure and resilience such as education, socioeconomic status, race and ethnicity were collected via interview.

Of the first 384 consecutively recruited veterans, 273 consented to share their data with investigators outside of TRACTS. Of these 273 veterans, several had to be excluded from the present study for the following reasons: predeployment status (ie, military service members who had not yet been deployed to combat zones) (15 participants), postenrollment report of neurological disorders (ie, history of meningitis, or brain surgery; 4 participants), history of moderate or severe TBI (15 participants), and exposure to neurotoxic chemicals or anoxia (30 participants). Another 26 cases did not pass the rigorous quality control of the MRI data, and 15 cases had missing clinical variables required for this study. The selection process is summarized in **Figure 1**.

Diagnostic and Clinical Assessment

Assessment of Psychiatric Disorders

The nonpatient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP)⁴⁹ was used to detect the presence of psychopathological disorders. The following modules were administered: module D, mood disorders; module E, substance use disorders; module F, anxiety disorders (except PTSD); module H, eating disorders; and module I, adjustment disorders. Presence and history of PTSD were determined according to the Clinician-Administered PTSD Scale (CAPS)⁵⁰ using the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV)* standard scoring rule.⁵¹

Assessment of mTBI

The Boston Assessment of TBI-Lifetime (BAT-L)¹⁷ was conducted to diagnose lifetime history of TBI. Specifically, mTBI was defined by the following criteria: loss of consciousness for 30 minutes or less, posttraumatic amnesia for 24 hours or less, or altered mental status for 24 hours or less.¹⁷

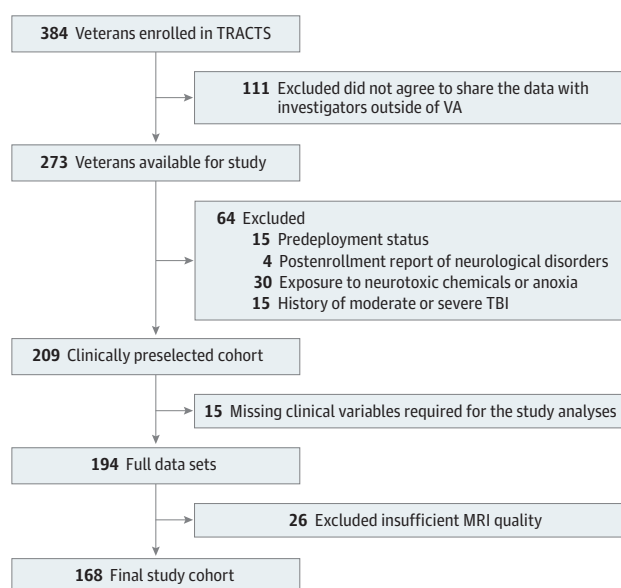
Assessment of War Zone–Related Stress

Stressors associated with deployment to war zones were assessed via selected scales from the DRRI.⁵² The combat experiences and aftermath of battle scales were used to assess perceived war zone–related stress. Both DRRI subscales (called hereafter DRRI-combat and DRRI-aftermath) consist of 16 questions concerning combat or war zone–related events. The DRRI-combat uses a 5-point Likert frequency scale (0 = never; 4 = daily or almost daily), yielding a maximum possible score of 64 points. The DRRI-aftermath scale uses a binary response (0 = no and 1 = yes), resulting in a maximum score of 16 points. Higher scores on both the DRRI-combat and DRRI-aftermath scale reflect greater exposure to deployment-related stressors.

Assessment of Functional Outcome

The World Health Organization Disability Assessment Schedule II (WHODAS II)⁵³ is a 36-item self-report questionnaire that was designed to measure disability associated with all physical and mental disorders including cognition, mobility, self-care, getting along, life activities, and participation. Functional impairments within the last 30 days are rated on a 5-point scale (0 = no disability;

Figure 1. Flowchart of the Cohort Selection Process



MRI indicates magnetic resonance imaging; TBI traumatic brain injury; TRACTS, Translational Research Center for TBI and Stress Disorders; VA, Veterans Affairs.

4 = extreme disability/cannot do). A total disability score is calculated by summing the scores across all subscales. Higher scores reflect greater disability.

The Neurobehavioral Symptom Inventory (NSI) is a 22-item self-report questionnaire used to assess postconcussion symptoms following TBI.⁵⁴ Tested symptoms include sensory, affective, vestibular, and cognitive symptoms, rated on a 5-point Likert scale (0 = none; 4 = very severe). Higher scores reflect more severe neurobehavioral symptoms.

According to identified limbic regions with GM diffusion alterations, the Digit Span Total Score (DSTot) and the Coding Raw Scores⁵⁵ were chosen from the comprehensive neuropsychological test battery,⁴⁸ as they reflect functions of the frontal and temporal lobe (ie, verbal short-term memory performance and processing speed). In addition, Stroop Inhibition (Stroop-IN) and Inhibition/Switching (Stroop-IS) Total Error Scaled Scores⁵⁶ were selected to assess more specifically executive or attentional control functions associated with the prefrontal and cingulate cortex,⁵⁷⁻⁶² whereby higher Total Error Scaled Scores reflect impaired response inhibition and vice versa.

Assessment of Hypervigilance

The CAPS criterion D was used to assess the frequency and intensity of symptoms of hypervigilance at postdeployment, including difficulty sleeping, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response. Answers were rated on a 5-point Likert scales ranging from 0 to 4 and summarized in a total score, resulting in a maximum score of 40 points.

Effort Testing

Performance validity was assessed via the Verbal Multiple Symptom Validity Test (MSVT).⁶³ The MSVT evaluates verbal learning, memory, and response consistency. It is composed of the subtests immediate recall, delayed recognition, consistency of responding across immediate recall, and delayed recognition, as well as paired associates and free recall. Study participants who failed the MSVT (8 participants) were excluded from the post hoc analyses as they were suspected of potential reduced effort or malingering.

MRI Acquisition and Data Processing

MRI of the brain was performed using a 3-Tesla TIM Trio scanner (Siemens Healthineers) located at the VA Medical Center in Boston, Massachusetts. T1-weighted (T1w) gradient-echo sequence parameters were field of view, 256 mm; 256 sections; inversion time, 1.000 ms; repetition time, 2.530 ms; echo time, 3.32 ms; flip angle, 7°; and isotropic resolution, 1 × 1 × 1 mm³. dMRI was acquired using a single-shot, echo-planar sequence with a twice-refocused spin-echo pulse and the following parameters: field of view, 256 mm; 64 axial sections with no intersection gap; 60 gradient directions with a b-value of 700 seconds/mm²; 10 b = 0 volumes; repetition time, 10 000 ms; echo time, 103 ms; and isotropic resolution, 2 × 2 × 2 mm³.

dMRI data were corrected for motion and eddy current distortions via affine registration to the first b = 0 volume using FMRIB Software Library, version 5.1 (The Oxford Centre for Functional MRI of the Brain).⁶⁴ Brain masks were created and manually edited in 3D Slicer, version 4.5 (Surgical Planning Laboratory, Brigham and Women's Hospital).⁶⁵ Automated segmentation of brain regions from the T1w data was performed using FreeSurfer⁶⁶ (version 5.1.0).⁶⁷

Free water (FW)-corrected diffusion tensor measures were derived from dMRI using in-house software.⁶⁸ FW imaging separates the dMRI signal into 2 compartments: a FW and a tissue compartment. FW in the brain is expected where water molecules are free to diffuse, such as in cerebrospinal fluid, and large extracellular spaces. We calculated a fractional anisotropy of tissue (FA_T) map from the FW-corrected diffusion tensor, which serves as a more accurate marker of anisotropy in brain tissue than the conventional FA measure. To obtain diffusion metrics for selected regions, FreeSurfer parcellation label maps were nonlinearly registered from the individual T1w space to the respective dMRI space to obtain diffusion metrics for selected regions. Eight limbic and

paralimbic GM regions in each hemisphere were evaluated—that is, cingulate gyrus, amygdala-hippocampus complex, parahippocampal gyrus, entorhinal cortex, lateral and medial orbitofrontal cortex, insula, and temporal pole. Amygdala and hippocampus were combined into 1 region of interest to ensure higher parcellation accuracy.⁶⁹ For each of these 8 bihemispheric regions of interest (16 in total), the mean of the diffusion measure (FA_T) was calculated.

Statistical Analysis

Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute). Means and SDs are displayed for continuous parameters, while absolute and relative frequencies are provided for noncontinuous variables. Generalized linear models for repeated measures using the restricted maximum likelihood approach and an unstructured covariance matrix across brain regions were used to evaluate the association of war zone-related stress with regional diffusion measures. The following parameters were selected a priori as covariates: age, diagnosis of current PTSD, mood, anxiety, substance use disorder, and weight-corrected lifetime drinking history (LDH). To test the outcomes of mTBI on the association between war zone-related stress and limbic GM diffusion, the number of lifetime mTBIs was added as fixed effect as well as modifier to the main effect.

Post hoc analyses were conducted to test for associations between diffusion measures that were significantly associated with war zone stress and neurobehavioral symptoms (NSI), cognitive (DSTot, Coding Raw Score, and Stroop IN/IS Total error scaled score), and disability (WHODAS). Participants who failed error testing (MSVT) were excluded from the post hoc analyses. Age, diagnosis of current PTSD, mood, anxiety, and substance use disorder, and LDH were included as covariates.

A false discovery rate⁷⁰ was set at 5% to correct for multiple comparisons, using the Benjamini-Hochberg method. A corrected 2-tailed $P < .05$ was considered significant. Data were analyzed December 2017 to September 2021.

Results

The final study cohort encompassed 168 male veterans with a mean (SD) age of 31.4 (7.4) years. Sample demographic characteristics are summarized in **Table 1**. The vast majority of participants were White (130 participants [77%]), followed by 24 Hispanic participants (14%) and 11 Black participants (6%) (Table 1). Although the level of education was balanced across the cohort (mean [SD] 13.9 [1.9] school years), potentially relevant differences were observed for the family status as only 38% (64 participants) were married or cohabiting.

Associations of War Zone-Related Stress With Limbic GM Diffusion

In the cohort of 168 veterans, greater war zone-related stress as assessed by DRRI-combat and DRRI-aftermath was negatively associated with FA_T in the bilateral cingulate gyri (DRRI-combat left: $P = .002$, partial $r = -0.289$, $df = 167$; DRRI-combat right: $P = .02$, partial $r = -0.216$, $df = 167$; DRRI-aftermath left: $P = .004$, partial $r = -0.281$, $df = 167$; DRRI-aftermath right: $P = .02$, partial $r = -0.219$, $df = 167$) and bilateral medial orbitofrontal gyri (DRRI-combat left medial orbitofrontal cortex: $P = .02$, partial $r = -0.222$, $df = 167$; DRRI-combat right medial orbitofrontal cortex: $P = .005$, partial $r = -0.256$, $df = 167$; DRRI-aftermath left medial orbitofrontal cortex: $P = .02$, partial $r = -0.214$, $df = 167$; DRRI-aftermath right medial orbitofrontal cortex: $P = .005$, partial $r = -0.260$, $df = 167$; DRRI-aftermath right lateral orbitofrontal cortex: $P = .03$, partial $r = -0.196$, $df = 167$). Notably, these associations were observed while controlling for age, PTSD diagnosis, mood disorder, anxiety disorder, and substance use disorder as well as LDH.

Moreover, a negative association was observed between DRRI-aftermath and the right lateral orbitofrontal gyrus FA_T and right parahippocampal gyrus FA_T ($P = .03$, partial $r = -0.191$, $df = 167$). In contrast, a positive association was found for both measures of war zone-related stress and FA_T in

the right amygdala-hippocampus complex (DRRI-combat: $P = .005$, partial $r = 0.254$, $df = 167$; DRRI-aftermath: $P = .02$, partial $r = 0.223$, $df = 167$). Results are summarized in **Table 2**.

Outcomes of mTBI on the Association of War Zone-Related Stress and Limbic GM Diffusion

The majority of veterans (109 of 168 [64.9%]) sustained at least 1 mTBI before or during deployment. They reported having experienced a mean (SD) of 1.38 (2.23) mTBIs throughout life with a maximum number of 18 mTBIs. Number of lifetime mTBIs was not associated with limbic GM diffusion and did not mediate the association between war zone-related stress and limbic GM FA_T.

Table 1. Demographics, Deployment-Related Factors, and Postdeployment Characteristics of Study Cohort

Variable	Participants, No. (%) (N = 168)
Demographics	
Age, mean (SD), y	31.36 (7.43)
Race and ethnicity	
Asian	2 (1.19)
Black	11 (6.55)
Hispanic	24 (14.29)
Unknown	1 (0.60)
White	130 (77.38)
Education mean (SD), school years	13.86 (1.93)
Married or cohabitating	64 (38.10)
Deployment factors	
OEF, OIF, or OND deployments, mean (SD), No.	1.4 (0.7)
Other stressful deployments, mean (SD), No.	0.41 (0.79)
Duration of OEF, OIF, or OND deployments, mean (SD), mo	13.82 (8.45)
Service in army branch	101 (60.12)
DRRI total score, mean (SD)	
Combat experience (DRRI-combat)	17.31 (12.02)
Aftermath exposure (DRRI-aftermath)	7.65 (4.7)
Military mTBIs, mean (SD), No.	0.63 (1.53)
Wounded or injured in combat	35 (20.83)
Postdeployment characteristics	
Time since last deployment, mean (SD), mo	40.07 (29.98)
Disorder	
Mood	35 (20.83)
Anxiety	28 (16.67)
PTSD diagnosis	112 (66.67)
Clinician-Administered PTSD Scale, mean (SD) ^a	78.35 (22.9)
Substance use disorder	25 (14.88)
Lifetime drinking history, weight corrected, mean (SD)	1790.6 (2092.7)
Lifetime TBIs, mean (SD)	1.38 (2.23)

Abbreviations: DRRI, Deployment Risk and Resilience Inventory; mTBI, mild traumatic brain injury; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; OND, Operation New Dawn; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

^a Clinician-Administered PTSD Scale score was evaluated for 112 veterans who met diagnostic criteria for postdeployment PTSD.

Association of Limbic GM Diffusion and Functional Outcome

Results of the post hoc analysis of diffusion and associated functioning are shown in **Table 3**. Decreased FA_r in the cingulate gyri and the medial orbitofrontal cortex was associated with impaired response inhibition (Stroop-IS left cingulate: $P < .001$, partial $r = -0.440$, $df = 151$; Stroop-IS right cingulate: $P < .001$, partial $r = -0.372$, $df = 151$; Stroop-IS left medial orbitofrontal cortex: $P < .001$, partial $r = -0.304$, $df = 151$; Stroop-IS right medial orbitofrontal cortex: $P < .001$, partial $r = -0.340$, $df = 151$; Stroop-IN left cingulate: $P < .001$, partial $r = -0.421$, $df = 151$; Stroop-IN right cingulate: $P < .001$, partial $r = -0.300$, $df = 151$; Stroop-IN left medial orbitofrontal cortex: $P = .01$, partial $r = -0.223$; $df = 151$; Stroop-IN right medial orbitofrontal cortex: $P < .001$, partial $r = -0.343$, $df = 151$), but with better frontotemporal functions (DSTot left amygdala-hippocampus complex: $P < .001$, partial $r = -0.574$, $df = 159$; DSTot right amygdala-hippocampus complex: $P < .001$, partial $r = 0.645$, $df = 159$; short-term memory left amygdala-hippocampus complex: $P < .001$, partial $r = 0.570$, $df = 156$; short-term memory right amygdala-hippocampus complex: $P < .001$, partial $r = 0.633$, $df = 156$). In contrast, impaired response inhibition and improved verbal short-term memory

Table 2. Association of War Zone-Related Stress and Limbic Gray Matter Diffusion Using Fractional Anisotropy of Tissue

Region	Combat exposure (DRRI-combat)				Aftermath exposure (DRRI-aftermath)			
	Left hemisphere		Right hemisphere		Left hemisphere		Right hemisphere	
	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value
Amygdala-hippocampus complex	0.158	.09	0.254	.005 ^b	0.136	.14	0.224	.02 ^b
Cingulate gyrus	-0.289	.002 ^b	-0.216	.02 ^b	-0.281	.004 ^b	-0.219	.02 ^b
Entorhinal cortex	0.020	.80	0.121	.21	-0.023	.88	0.049	.65
Insular cortex	-0.058	.52	-0.057	.52	-0.138	.14	-0.061	.57
Lateral orbitofrontal cortex	-0.081	.43	-0.151	.10	-0.083	.41	-0.196	.03 ^b
Medial orbitofrontal cortex	-0.222	.02 ^b	-0.256	.005 ^b	-0.214	.02 ^b	-0.260	.005 ^b
Parahippocampal gyrus	-0.059	.52	-0.166	.08	-0.009	.97	-0.191	.03 ^b
Temporal pole	-0.089	.40	0.053	.52	-0.224	.39	-0.003	.97

Abbreviations: DRRI, Deployment Risk and Resilience Inventory; FDR, false discovery rate. ^b Denotes significant results.

^a The higher the partial r , the stronger the linear association between 2 variables. Positive values represent positive correlations, and negative values represent negative or inverse correlations.

Table 3. Association of Limbic Gray Matter Diffusion Using Fractional Anisotropy of Tissue and Cognitive Functioning

Region	Digit Span Total Score				Coding Raw Score				Stroop inhibition			
	Digit Span Total Score		Coding Raw Score		Total error scaled score		Switching total error scaled score					
	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value	Partial r^a	FDR corrected P value				
Left amygdala-hippocampus comp	0.574	<.001 ^b	0.570	<.001 ^b	0.443	<.001 ^b	0.483	<.001 ^b				
Left cingulate gyrus	-0.393	<.001 ^b	-0.330	<.001 ^b	-0.421	<.001 ^b	-0.440	<.001 ^b				
Left lateral orbitofrontal cortex	-0.058	.74	-0.006	.94	-0.036	.79	-0.044	.78				
Left medial orbitofrontal cortex	-0.202	.02 ^b	-0.193	.03 ^b	-0.223	.01 ^b	-0.304	<.001 ^b				
Left parahippocampal gyrus	0.042	.80	0.007	.94	0.059	.79	0.013	.95				
Right amygdala-hippocampus comp	0.645	<.001 ^b	0.633	<.001 ^b	0.500	<.001 ^b	0.518	<.001 ^b				
Right cingulate gyrus	-0.290	<.001 ^b	-0.237	.007 ^b	-0.300	<.001 ^b	-0.372	<.001 ^b				
Right lateral orbitofrontal cortex	0.041	.80	0.024	.76	-0.038	.79	0.005	.95				
Right medial orbitofrontal cortex	-0.263	.002 ^b	-0.262	.003 ^b	-0.343	<.001 ^b	-0.340	<.001 ^b				
Right parahippocampal gyrus	-0.001	.99	-0.021	.79	-0.032	.79	-0.103	.35				

Abbreviation: FDR false discovery rate. ^b Denotes significant results.

^a The higher the partial r , the stronger the linear association between 2 variables. Positive values represent positive, and negative values represent negative or inverse correlations.

performance and processing speed were associated with increased FA_T in the amygdala-hippocampal region (Figure 2). No significant associations were revealed for limbic GM diffusion and (postconcussion) neurobehavioral symptoms or disability (eTable 1 in the Supplement).

Association of Limbic GM Diffusion and Hypervigilance State

Hypervigilance at postdeployment was positively associated with FA_T in the amygdala-hippocampal region (left: $P < .001$, partial $r = 0.325$, $df = 165$; right: $P < .001$, partial $r = 0.309$; $df = 165$) and negatively associated with FA_T in the cingulate gyri (left: $P < .01$, partial $r = -0.253$ $df = 165$; right: $P < .01$; partial $r = -0.261$ $df = 165$). The results are summarized in eTable 2 in the Supplement.

Discussion

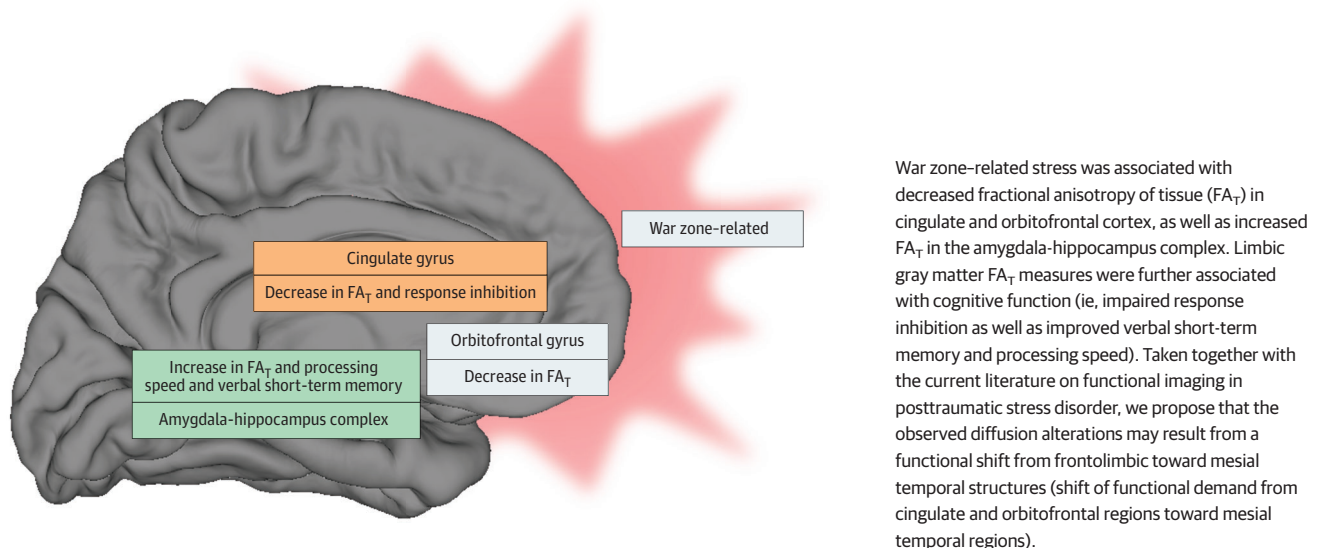
This cohort study found an association between war zone-related stress and microstructure of limbic GM in veterans. Importantly, these findings were observed while accounting for common comorbidities, including PTSD, mood, anxiety, and substance use disorder. Furthermore, mTBI had no significant effect on the association between war zone-related stress and limbic GM microstructure. Finally, characteristics of limbic GM microstructure were associated with cognitive performance including verbal short-term memory, processing speed, and response inhibition, while no associations with overall disability and neurobehavioral symptoms were found.

War Zone-Related Stress and Limbic GM Diffusion

This study revealed a co-occurring decrease and increase in limbic GM FA_T. More specifically, the greater the experienced war zone-related stress, the lower FA_T was in the cingulate gyri, the medial orbitofrontal gyri, the right lateral orbitofrontal gyrus, and the right parahippocampal gyrus. Moreover, the greater the experienced war zone-related stress, the higher the FA_T in the amygdala-hippocampus complex. Importantly, associations described previously were independent of diagnosis of mental disorders as well as mTBI.

The interpretation of diffusion measures in GM is challenging as data linking diffusion to histologic profile is sparse.^{37,71-74} FA in GM likely reflects diffusion properties of the main GM components (ie, astroglia, neurons, and axons). For example, a study in mice reveals an association

Figure 2. Model of Structural Brain Alterations and Associated Cognitive Function in the Context of War Zone-Related Stress



between decreased FA and decreased astrocyte density in the hippocampus.⁷¹ Astrocytes play a crucial role in complex brain functions, such as neurotransmitter homeostasis and blood-brain barrier maintenance.⁷⁵ Moreover, a decrease in astrocytes predisposes the brain to inflammatory states.^{75,76} Another dMRI study⁷⁷ in a murine model of Parkinson disease found an association between decreased FA_T in the substantia nigra and neuronal loss. Taken together, the association between war zone-related stress and decreased FA_T in the cingulate, orbitofrontal gyri, and right parahippocampal gyrus may potentially be due to a decrease in astrocytes and/or neurons.

Interestingly, a positive association was found for greater war zone-related stress and higher FA_T in the amygdala-hippocampus complex. Increased FA_T in GM and WM has been associated with neuroplastic remodeling.^{72,73} In rodents, long-term learning and memory tasks induced an FA increase, particularly in limbic system structures such as the amygdala, the parahippocampal gyrus, and the cingulate cortex, which correlated with an increase in a myelin marker (myelin basic protein) in the histological analysis.^{72,73} The authors^{72,73} hypothesized that oligodendrocytes, which form the myelin sheaths in the central nervous system, produced more myelin basic protein postlearning to allow for the required flow of information. Taken together, findings of our study suggest regional differences in the association between war zone-related stress and alterations in GM microstructure that may be due to neurodegenerative and neuroplastic processes.

Association Between Limbic GM Diffusion and Functional Outcome

We observed improved frontotemporal brain functions (ie, short-term memory and processing speed) in association with increased FA_T in the amygdala-hippocampal complex (Figure 2), which is in line with previous studies that report a link between processing speed and hippocampal FA.⁷⁸⁻⁸⁰ Our study results further suggest an association between improved frontotemporal brain functions with war zone-related stress.⁸¹ It has been hypothesized that hypervigilance and readiness to respond to combat-related challenges may be advantageous adaptations to the highly stressful environment. However, it may be challenging to transition back to normal states of alertness when returning from deployment. The chronic activated state may consequently lead to a functional overuse of frontotemporal brain functions. This overuse may induce neuroplastic changes as suggested by the increased FA_T in the amygdala-hippocampal complex⁷³ found in this study. This hypothesis is supported by our finding of a significant association between hypervigilance state at postdeployment and increased FA_T in the amygdala-hippocampal complex.

At the same time, we observed impaired prefrontal-cingulate functions (response inhibition) in association with lower FA_T in prefrontal regions. This is thought to result from functional (emotional or stress) overuse of mesial temporal structures, as described previously, which may, in turn, lead to poorer performance in other cognitive tasks, a phenomenon called interference.⁸²⁻⁸⁴ Interference or shift of emotion and cognition has previously been described in patients with PTSD⁸⁵ as well as in veterans. More specifically, impaired memory consolidation and reduced learning speed were observed in veterans returning from OEF, OIF, or OND.^{86,87} Of note, those functions are typically associated with the prefrontal-cingulate cortex,⁸⁶⁻⁸⁹ regions that have been found to have lower FA_T in association with war zone stress in the current study.

Taken together, we hypothesize that the outcomes of war zone-related stress outlast deployment, leading to attentional interference with increased functional use of mesial temporal structures and decreased use or impaired retrieval of prefrontal-cingulate functions. This hypothesis is further supported by functional MRI studies,⁹⁰ which have reported a hypoconnectivity of mesial temporal and prefrontal brain regions under conditions of stress. The functional interference may, in turn, lead to microstructural adaptations, reflected by increased FA_T in the amygdala-hippocampus complex and decreased FA_T in the cingulate and orbitofrontal gyri (Figure 2). This biological adaptive response may potentially, in addition to preexisting biological predisposition for deployment, mean that service members with outstanding processing speed and verbal short-term memory might be more likely to join the military and to be deployed.

No significant associations were found between limbic GM diffusion and more general measures of functional outcome following mTBI (ie, the WHODAS and NSI). We thus speculate that abnormalities in the limbic system may need to be more severe to cause impairments in everyday functioning. Furthermore, the observed limbic alterations may represent a minor contributor to everyday functioning as assessed using WHODAS and NSI, whereas the individual comorbidities may be the main drivers of the functional impairment.

Limitations

Our study has limitations. We investigated a representative subsample of OEF, OIF, or OND veterans⁴⁸ and we accounted for common comorbidities in the statistical analysis. However, we used dichotomous variables based on the *DSM-IV* classifications to account for the presence of psychopathologic disorders. Future studies should consider using dimensional assessments of psychopathologic disorders, to further investigate the spectrum of psychopathologic disorders. Furthermore, we did not account for service branch, race, or socioeconomic status,⁹¹⁻⁹⁸ which might be of importance for resilience, stress exposure, management, and rehabilitation and should be considered in future analyses. The vast majority of participants were White, followed by Hispanic and Black participants (Table 1). Although the level of education was balanced across the cohort, potentially relevant differences were observed for the family status as only 38% were married or cohabiting. A further limitation is that this study was limited to male participants only. The cross-sectional design of this study further limits the interpretation of our findings as well as the identification of additional factors associated with risk and causal relationship between war zone-related stress and alterations in limbic GM may not be drawn. Moreover, we did not differentiate between the amygdala and hippocampus as we aimed for the highest possible accuracy in the segmentation. Previous research of imaging data has demonstrated that the use of the combined amygdala-hippocampus complex represents a methodologically more rigorous and accurate approach of segmentation using FreeSurfer.⁶⁹ Against the background of our study findings, future studies should strive to retest our hypothesis on manually segmented limbic GM. Additionally, although all interviews were conducted by doctoral level psychologists, their administration at long-term follow-up might have been inevitably biased by participant subjective memory and reporting. Of further note, multishell dMRI data would have improved the FW model fit but was not available in the study. In addition, the analysis of GM is highly sensitive to misalignment of the diffusion space and T1 space, which may have caused inflation in the FW measure. Despite the FW-correction, the FA_T measures remain unspecific and can only serve as a gross estimation of the underlying microstructure.

Conclusions

In this study, war zone-related stress was associated with alterations in limbic GM microstructure, which, in turn, were associated with cognitive function independent of the diagnosis of mental disorders and mTBI commonly observed in this population. Taken together, findings from this study suggest that alterations in limbic GM microstructure may underlie the deleterious outcomes of exposure to war zone-related stress. Thus, military service members exposed to war zone-related stress may benefit from early therapeutic intervention even in the absence of a diagnosed mental disorder.

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SUPPLEMENT.

eTable 1. Association of Limbic Gray Matter Diffusion (FAT) and Disability/Neurobehavioral Symptoms

eTable 2. Association of Limbic Gray Matter Diffusion (FAT) and Hypervigilance State