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A Functional Near-Infrared Spectroscopy Study of Trauma-Related Auditory and Olfactory Cues: Posttraumatic Stress Disorder or Combat Experience?

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The prevalence of posttraumatic stress disorder (PTSD) among U.S. veterans deployed to Iraq or Afghanistan necessitates the need for comprehensive assessment and treatment strategies. This study investigated the utility of a combat-related PTSD symptom provocation paradigm to elicit unique neurological responses across three groups: combat veterans with PTSD, combat veterans without PTSD, and nonmilitary participants without PTSD. Using functional near-infrared spectroscopy (fNIRS) the results indicated that combat veterans with PTSD demonstrated significant activation to a trauma-related sound compared with nonmilitary personnel, channel 14: $d = 1.03$, 95% confidence interval (CI) [0.28, 1.76]; channel 15: $d = 1.30$, 95% CI [0.53, 2.06]; and combat veterans without PTSD, channel 14: $d = 0.87$, 95% CI [0.14, 1.59]. Specifically, this increased neural activation was approximately located in the right medial superior prefrontal cortex (Brodmann areas 9/10), an area associated with experiencing negative or threatening stimuli and emotional detachment. There were no differences across the groups for nontrauma-related sounds. Results were less clear with respect to a combat-related odor. These results suggest a specific neurophysiological response to trauma-related cues and, if replicated, may offer a biomarker for combat-related PTSD. Such a response could provide incremental validity over diagnostic assessments alone and assist in planning and monitoring of treatment outcome.

The current prevalence of posttraumatic stress disorder (PTSD) is approximately 13% among U.S. combat veterans who served in Iraq or Afghanistan (Kok, Herrell, Thomas, & Hoge, 2012). Currently, clinicians rely primarily on diagnostic interviews and self-report measures, which are always vulnerable to bias or malingering (Frueh et al., 2003). Biological markers such as functional near-infrared spectroscopy (fNIRS) may offer additional benefits including improved diagnosis, determination of optimal treatment course, objective markers of treatment outcome, and remission of the disorder. Presently, no validated biological assessment for PTSD is available.

Extant literature on the neurobiology of PTSD postulates a disruption of neural circuits across the medial prefrontal cortex (mPFC), amygdala, and hippocampus (Ross et al., 2017). The dorsomedial PFC (dmPFC) and ventromedial PFC (vmPFC) are vital for the appraisal of negative stimuli and regulating negative emotions (Etkin, Egner, & Kalisch, 2011). In one investigation, veterans with PTSD demonstrated increased activation of the dmPFC during anticipation of threat compared to anticipation of safe trials (Grupe, Wielgosz, Davidson, & Nitschke, 2016). Additional findings from this study found a positive correlation with the severity of reexperiencing symptoms and activation of the vmPFC during anticipation of threat compared to anticipation of safety. In another study, participants with PTSD displayed greater activation of the vmPFC during construction of negative autobiographical memories and decreased activation of this region during positive autobiographical memories compared with healthy controls (Jacques, Botzung, Miles, & Rubin, 2011). A meta-analysis of symptom provocation paradigms found increased activation by participants with PTSD in the right superior/middle frontal gyrus compared to trauma-exposed controls (Sartory et al., 2013). The right superior/middle frontal gyrus and other regions of PFC are located near the surface of the brain and within the range of depth for fNIRS measurement (Tian & Liu, 2014). As such, this brain region is applicable to fNIRS investigation, which is less susceptible to motion artifacts, emits no acoustic noise, and allows naturalistic body positioning during imaging compared to functional magnetic resonance imaging (fMRI).

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As an added benefit, fNIRS is a portable device that includes models with a wireless design.

Extant data suggest that fNIRS reliably measures neural functioning of the PFC during emotional processing of affective or threatening stimuli (Doi, Nishitani, & Shinohara, 2013). Ernst et al. (2013) found increased activation in the right dorsolateral prefrontal cortex (dlPFC) during incompatible (avoid positive, approach negative) compared to compatible (avoid negative, approach positive) tasks. Although fNIRS studies have found enhanced activation during processing of fear-relevant compared to disgust and neutral auditory stimuli, the majority of these investigations have focused on the temporal and/or parietal lobes (Köchel, Schöngassner, & Schienle, 2013). Nevertheless, increases in self-reported negative emotion and arousal while listening to music corresponded to greater activation of the PFC; additionally, researchers found adequate classification of emotional response based on fNIRS measurement of PFC activation (Moghimi, Kushki, Power, Guerguerian, & Chau, 2012). With regard to olfactory stimuli and fNIRS, researchers have found that delivery of rose and orange odors decreased activation of the right PFC and increased self-report of relaxation (Igarashi, Ikei, Song, & Miyazaki, 2014). To our knowledge, only one study has examined a symptom provocation paradigm on individuals with PTSD using fNIRS imaging (Matsuo et al., 2003). Specifically, this study examined participants who had experienced the Tokyo subway sarin attack in 1995 (with and without PTSD) and healthy volunteers who had not been exposed to the traumatic event. This study found only participants with PTSD displayed overall patterns of increased activation in the PFC during presentation of traumatic images. There appear to be no fNIRS studies that examined trauma-related stimuli and combat-related PTSD. Given these findings, further investigation using the combination of fNIRS and trauma-related sounds or odors may aid neurophysiological understanding of emotional processing and combat-related PTSD.

Several neuroimaging investigations have revealed neurophysiological differences between veterans with and without combat-related PTSD during exposure to combat sounds (Bremner et al., 1999; Liberzon et al., 1999). The use of combat sounds to simulate combat exposure is a promising method to identify unique neurological responses. In comparison to other sensory modalities, olfaction has been widely understudied when examining neurophysiological reactions to trauma-related stimuli (Sartory et al., 2013), even when there is evidence that olfactory cues (of any type) impact memory. For example, Herz (2004) found odor-evoked autobiographical memories elicited more emotionality and evocativeness, but similar vividness and specificity in comparison to verbal, visual, and auditory cues. This study indicated that olfactory stimuli add a unique connection between memories and emotional experiences, but should not be misinterpreted as eliciting more accurate memories over other cues. Olfactory stimuli connected to the traumatic event may provoke posttraumatic symptoms among individuals with PTSD. Specifically, clinicians have documented instances of olfactory cues (e.g., diesel fuel, vomit, specific aftershaves) as triggers of military, first responder, and sexual trauma–related PTSD, respectively (Vermetten & Bremner, 2003).

No identifiable study has looked at whether combat experience can be distinguished from combat-related PTSD via fNIRS response to trauma-related sounds or odors. This study examined whether veterans with a current diagnosis of combat-related PTSD display distinct neurological markers in response to a trauma-associated sound (i.e., explosion) and odor (i.e., diesel fuel). Specifically, we hypothesized that combat veterans with PTSD will display increased activation in the PFC during the presentation of trauma-related stimuli relative to civilian and combat-exposed participants without PTSD, and that combat veterans with PTSD will rate the trauma-related odor and sound as more unpleasant and intense than both combat veteran and nonmilitary participants without PTSD.

Method

Participants

Using a quasi-experimental design, we assessed three groups of participants: (1) veterans with combat-related PTSD (PTSD+), (2) combat veterans without PTSD (CV), and (3) nonmilitary participants without PTSD (NM). Participants within the NM group endorsed no current or past history of military service. The study included 48 male participants (PTSD+, $n = 16$; CV, $n = 16$; NM, $n = 16$), ages 18 to 56 years ($M = 32.02$, $SD = 8.47$), who had been recruited from the community. The PTSD+ participants were beginning an exposure-based treatment for combat-related PTSD and had PTSD as their primary diagnosis. All PTSD+ participants completed the study before receiving treatment.

The sample was 70.8% Caucasian, 12.5% Hispanic, 10.4% African American, 4.2% Asian/Pacific Islander, and 2.1% American Indian/Alaskan. No significant group differences found for race (Fisher's exact test, $p = .140$). With regard to education, 45.8% completed some college, 22.9% earned a master's degree, 16.7% earned a bachelor's degree, and 14.6% completed high school. No significant group differences found for education (Fisher's exact test, $p = .425$). The CV group included more Marine Corps veterans (37.5%) than the PTSD+ group (6.25%; Fisher's exact test, $p = .047$); however, the majority of CV (50%) and PTSD+ (68.75%) participants were Army veterans. None of the participants included in the CV group meet current diagnostic criteria for any psychiatric diagnoses, except for agoraphobia ($n = 1$). Comorbid diagnoses in the PTSD+ group included current major depressive disorder ($n = 8$), panic disorder with agoraphobia ($n = 2$), and adjustment disorder with depressed mood ($n = 1$), which is representative of comorbidity rates among U.S. veterans of Iraq and Afghanistan with PTSD (e.g., Rauch et al., 2015). No participants in the NM group met criteria for any clinical diagnoses.

The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID; Corrigan & Bogner, 2007),

Table 1
Frequency (%) of Age, Worst Traumatic Brain Injury (TBI) History, and Medications Across Groups

	CV		NM		PTSD+			
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F* (2, 45)	*p*
Age	31.19	5.10	27.38	8.12	37.5	8.76	7.44	.001[a]
	N	%	*N*	%	*N*	%		
Worst TBI history ($N = 38$)[c]								
No history	9	56.3	—	—	1	6.7		.012[b]
Mild TBI w/o LOC	3	7.9	—	—	4	26.7		
Mild TBI w/ LOC	4	25.0	—	—	10	66.7		
Medications ($N = 39$)								
No medications	12	75.0	5	71.4	3	18.8		.003[b]
Antidepressants	2	12.5	0	0.0	11	68.8		<.001[b]
Anxiolytics	1	6.3	1	14.3	4	18.8		.389[b]
Antipsychotics and mood stabilizer	1	6.3	0	0.0	7	43.8		.023[b,e]
Over the counter	1	6.3	0	0.0	11	78.6		<.001[b]
Other prescribed[d]	1	6.3	1	6.3	3	21.4		.592[b]

Note. CV = combat veterans without posttraumatic stress disorder (PTSD); NM = nonmilitary personnel without PTSD; PTSD+ = combat veterans with PTSD; LOC = loss of consciousness.
[a]Tukey HSD test revealed a significant group difference for age between the PTSD+ and NM groups only. [b]Fisher's exact tests. [c]NM participants recontacted denied TBI history and as such they were not included in the Fisher's exact tests. [d]Prescribed medications including albuterol (CV participants); amphetamine (NM participants); and methylphenidate, levothyroxine, and rizatriptan (PTSD+ participants). [e]Nonsignificant following Bonferroni correction for multiple tests (i.e., $p > .008$).

Handedness Questionnaire (Cohen, 2008) adapted from the Edinburgh Inventory (Oldfield, 1971), and medication log form were not originally administered among PTSD+ and NM groups. We attempted to recontact these previously studied participants by calling or electronically messaging each participant a maximum of three times. The researchers successfully followed up and administered the OSU TBI-ID, Handedness Questionnaire, and medication log forms with some of the NM participants ($n = 7$ out of 16). All of the CV and PTSD+ participants, as well as the NM participants who had been successfully recontacted, screened positive for right-handedness. On the OSU TBI-ID assessment, nearly all of the PTSD+ participants completed the interview ($n = 15$ out of 16). However, we are confident that the one missing case did not have any significant traumatic brain injury (TBI) history (e.g., moderate or severe TBI) because the individual reported no diagnosis of TBI and denied any receipt of service-connected disability related to head or neck injury on the demographics form. No participants included in the study endorsed history of moderate or severe TBI. All NM participants who were recontacted endorsed no history of TBI and as such TBI comparisons were conducted only between combat veteran groups (displayed in Table 1).

None of the participants reported using any benzodiazepines within at least 24 hours before the assessment. Because individual participants endorsed medications across classes, we performed separate Fisher's exact tests for each medication category to ensure each participant contributed to only one cell of the contingency table (i.e., assumption of independence for chi-square). As a result, we applied a Bonferroni correction for multiple tests, which set the p value at .008 to be significant at the $p < .05$ level (displayed in Table 1). "Other" medications included predominately over-the-counter medications (e.g., vitamin D, aspirin, or antacid).

Procedure

Using a 3 × 3 between-subjects design with two separate auditory and olfactory conditions, the following stimuli were administered in a randomized counterbalanced fashion: trauma-related sound (explosion) and odor (diesel fuel), negative sound (dentist drill) and odor (rotten egg), and neutral sound (phone ringing) and odor (n-butanol). The sounds were selected based on the International Affective Digitized Sounds manual (IADS-2; Bradley & Lang, 2007), which provides ratings on pleasure, arousal, and dominance from over 100 male college students. For odors, we chose n-butanol based on prior normative research establishing this odor as a standardized indicator of odor threshold (Kobal et al., 2000) and rotten egg given its incorporation as a negative odor in several neuroscience publications (e.g., Bensafi, Sobel, & Khan, 2007). Diesel fuel was chosen based on its presence in prior neuroimaging investigations of combat-related PTSD (e.g., Vermetten, Schmahl, Southwick, & Bremner, 2007) and higher distress ratings among combat

veterans with PTSD compared to healthy controls (Cortese, Leslie, & Uhde, 2015).

The auditory/olfactory task paradigm used a block design consisting of 72 trials total. Each auditory and olfactory condition presented 36 trials: 12 trials of neutral stimuli, 12 trials of negative stimuli, and 12 trials of trauma-related stimuli. The paradigm consisted of the following sequence of events, in order: 25 seconds of rest, stimulus presentation for 7 seconds, 10 seconds of rest, and subjective ratings of respective stimulus for 12 seconds. Following presentation of each negative, neutral, and trauma-related stimulus, the participant rated the stimulus on two dimensions: hedonic (pleasant vs. unpleasant) and intensity (weak vs. strong).

A Windows 8.1. Dell OptiPlex 9020 AIO (Dell Inc., Round Rock, TX, USA) computer presented the auditory cues through speakers ($M = 69.33$ dB). An air compressor (California Air Tools, Inc., San Diego, CA, USA; CAT – 1610A; 1.0 Hp) pressurized the Scentroid SC300 (IDES Canada, Inc., Stouffville, ON, Canada) mobile olfactometer, which delivered the odors, with the smell port positioned 2 cm from participants' nostrils. We received the liquid samples from the manufacturers of the mobile olfactometer (IDES Canada, Inc.). Based on the natural odorant intensity of the liquid samples, the n-butanol and rotten egg odor samples each derived from 1μL liquid odorant, whereas the diesel fuel odor sample contained 0.75 mL liquid odorant.

This research was approved by the University of Central Florida Institutional Review Board. The study was conducted in an 18 ft × 14 ft experimental room with the participant sitting 64 in. away from the computer monitor (23 in. screen). After consent and psychiatric screening, the researcher centered the NIRScap using the nasion, inion, and left and right preauricular points. The participant used a mouse to select hedonic and intensity ratings during the trials. During presentation of the auditory and olfactory stimuli, the computer monitor displayed a white fixation crosshair on a black background. Each participant received $75 in compensation for completing the study.

Measures

We screened for PTSD using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). The CAPS has good internal consistency (Cronbach's $\alpha = .80$ to .90), strong convergent validity ($r = .70$ to .90), and sensitivity and specificity values typically above .80 and .90, respectively (Weathers, Keane, & Davidson, 2001). The internal consistencies of the CAPS found for this study were acceptable (CV: Cronbach's $\alpha = .72$; PTSD+: Cronbach's $\alpha = .93$). Within the CV participant group, we verified combat exposure by DD-214 paperwork or official military documentation among active-duty personnel. Of participants, 50.0% of the PTSD+ group and 66.7% of the CV group reported one of their Criterion A events directly involved an explosion (e.g., improvised explosive device [IED]). Among the CV participants who endorsed a combat-related Criterion A event (i.e., 15 out of 16), the mean CAPS total score was 14.80 ($SD = 9.81$, range = 1 to 32), whereas the PTSD+ participants earned a mean CAPS total score of 93.81 ($SD = 21.00$, range = 53 to 127).

We excluded any participants who met criteria for substance use disorders, antisocial personality disorder, or psychotic disorders using the following assessments: Structured Clinical Interview for DSM-IV (SCID-CV; First, Spitzer, Gibbon, & Williams, 1996), Structured Clinical Interview for DSM-IV Personality Disorders, Personality Questionnaire (SCID-II-PQ; First, Gibbon, Spitzer, Williams, & Benjamin, 1997), and MINI International Neuropsychiatric Interview 6.0 version (MINI; Sheehan et al., 1997). Within the PTSD+ group, we screened participants using the SCID-CV and SCID-II-PQ assessments, whereas among the NM and CV participants we completed a psychiatric screening using the MINI. The MINI has shown good reliability and diagnostic utility compared to the SCID for DSM disorders and the average duration of administration for the MINI is relatively short (i.e., approximately 15 minutes; Sheehan et al., 1997).

Measures were administered under the supervision of licensed clinical psychologists. We selected 20% of CAPS and MINI screens to be reviewed by a blinded staff member to determine interrater reliability, which demonstrated a high degree of agreement on the CAPS (total score ICC = .996; PTSD diagnosis $\kappa = 1.00$) and MINI (psychiatric diagnosis $\kappa = 1.00$).

The remaining measures assessed for lifetime history of TBI, handedness, and smell acuity: OSU TBI-ID (Corrigan & Bogner, 2007), Handedness Questionnaire (Cohen, 2008) adapted from the Edinburgh Inventory (Oldfield, 1971), and University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, & Dann, 1984). The UPSIT is considered the gold standard of smell identification tests and is the most reliable olfactory test available (test-retest reliability exceeds $r = .90$; Doty et al., 1984). All participants included in the study scored at least a 30 or higher on the UPSIT, which indicated acceptable smell acuity (i.e., normosmia to mild microsmia ranges). With regard to hearing capability, clinicians did not observe any hearing difficulty during the diagnostic interview or experiment (e.g., wearing hearing aids, or reporting difficulty hearing stimuli or interviewer questions).

The hedonic and intensity ratings during the auditory/olfactory task paradigm were similar to German Standard VDI 3882 guidelines (as cited in Frechen, 2000). Hedonic tone was quantified on a 9-point Likert scale (range: +4 = *very pleasant* to −4 = *offensive*). The hedonic ratings displayed excellent internal consistencies within each respective group for the auditory (Cronbach's $\alpha = .955$ to .969) and olfactory (Cronbach's $\alpha = .955$ to .973) stimuli. Intensity was quantified on a 7-point Likert scale (range: 0 = *not detectable* to 6 = *intolerable*). The internal consistencies were excellent within each respective group for the intensity ratings of auditory (Cronbach's $\alpha = .944$ to .974) and olfactory (Cronbach's $\alpha = .891$ to .961) stimuli.

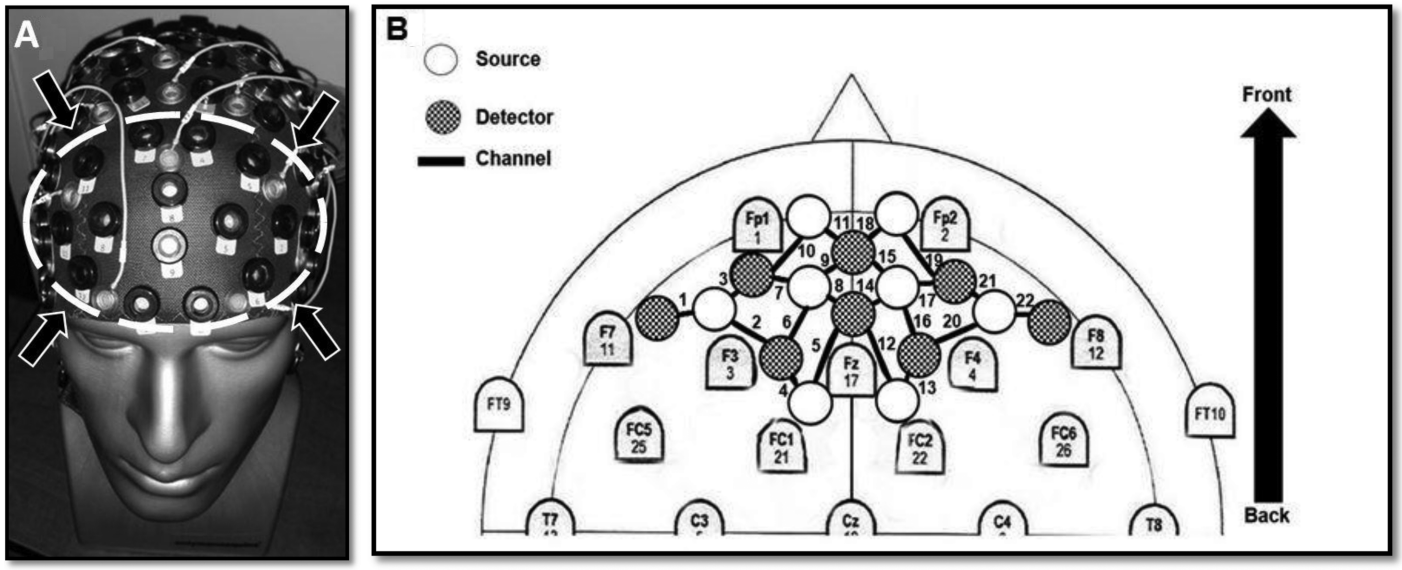

Figure 1. Functional near-infrared spectroscopy (fNIRS) data collection channels. NIRScap and outline of measured area (image A). Channel numbers (1–22) appear adjacent to channel locations and semicircle markers denote standard electroencephalogram (EEG) 10–20 positions (image B).

NIRSport-88 is a multi-channel, mobile fNIRS device (NIRx Medical Technologies, LLC, Berlin, Germany) that measured changes in concentration of oxygenated and deoxygenated hemoglobin during the olfactory and auditory tasks. This system has an 8-source/8-detector configuration with 22 data channels covering right and left PFC hemispheres (displayed in Figure 1). The distance between each source-detector at a measured data channel was approximately 3 cm. Channel positions were based on the International 10–20 system commonly used in electroencephalogram (EEG) data collection. Localization to Brodmann area (BA) is approximate due to individual differences in brain structure and the lack of anatomical magnetic resonance imaging brain scans for this study. We used NIRS Acquisition Software (NIRStar; release 2014, NIRx Medical Technologies, LLC, Glen Head, NY, USA) for data collection.

Data Analysis

Behavioral ratings. An analysis of the behavioral ratings indicated violation of parametric assumptions of normality and attempts to normalize the data through various transformations (e.g., log transformation) were unsuccessful. Additionally, the behavioral ratings were ordinal data and as such were analyzed through nonparametric tests using SPSS (version 23.0, IBM Corp., Armonk, NY, USA). Missing data of the participants included in the analyses was $\leq$ 20.0% of each participant's total behavioral ratings. To deal with missing data, we inputted replacement values using each participant's corresponding mean hedonic or intensity score; however, this did not alter the findings and therefore we analyzed the available data only. Analyses were conducted with the alpha level set to .05 unless specified otherwise.

fNIRS. Initially, spike artifacts and discontinuities were detected and eliminated automatically. A change between adjacent data points larger than five standard deviations from the mean for each channel's time course was considered an artifact. Next data were bandpass-filtered to remove slow data drift (low cutoff frequency = .01Hz) and high frequency noise (high cutoff frequency = .2Hz).

After preprocessing, raw optical density values were transformed to produce estimates of oxygenated hemoglobin (oxy-Hb) concentration changes at each sample point using the modified Beer-Lambert Law in nirsLAB (version 2016.01, NIRx Medical Technologies, LLC, Brooklyn, NY, USA). Hemodynamic state conversion parameters were based on Gratzer and Kollias (2009). In nirsLAB, we performed the standard and widely used method of general linear model-based data analysis that uses statistical parametric mapping (SPM; e.g., Tian & Liu, 2014). For level 1 (individual participant) analysis, three regressors were included in the model to measure the influence of each valence level (neutral, negative, and trauma-related). An additional nuisance regressor was included to partial out the data collected during the 12-second rating phase of the task, because participants were likely to move more during this phase than during trial presentation. For each individual data set, a canonical hemodynamic response function was convolved with a boxcar function to model task-related activity. Serial correlation was removed by precoloring with a Gaussian kernel (FWHM = 4s). The SPM level 2 (group) analysis was carried out on beta values estimated during level 1 modeling. The SPM level 1 and 2 sequence constitutes a random effects model analysis (Mumford & Poldrack, 2007). There were no missing fNIRS data among all participants.

A two-way repeated measures analysis of variance (ANOVA; group [PTSD+, CV, and NM] x stimulus [negative, neutral, and

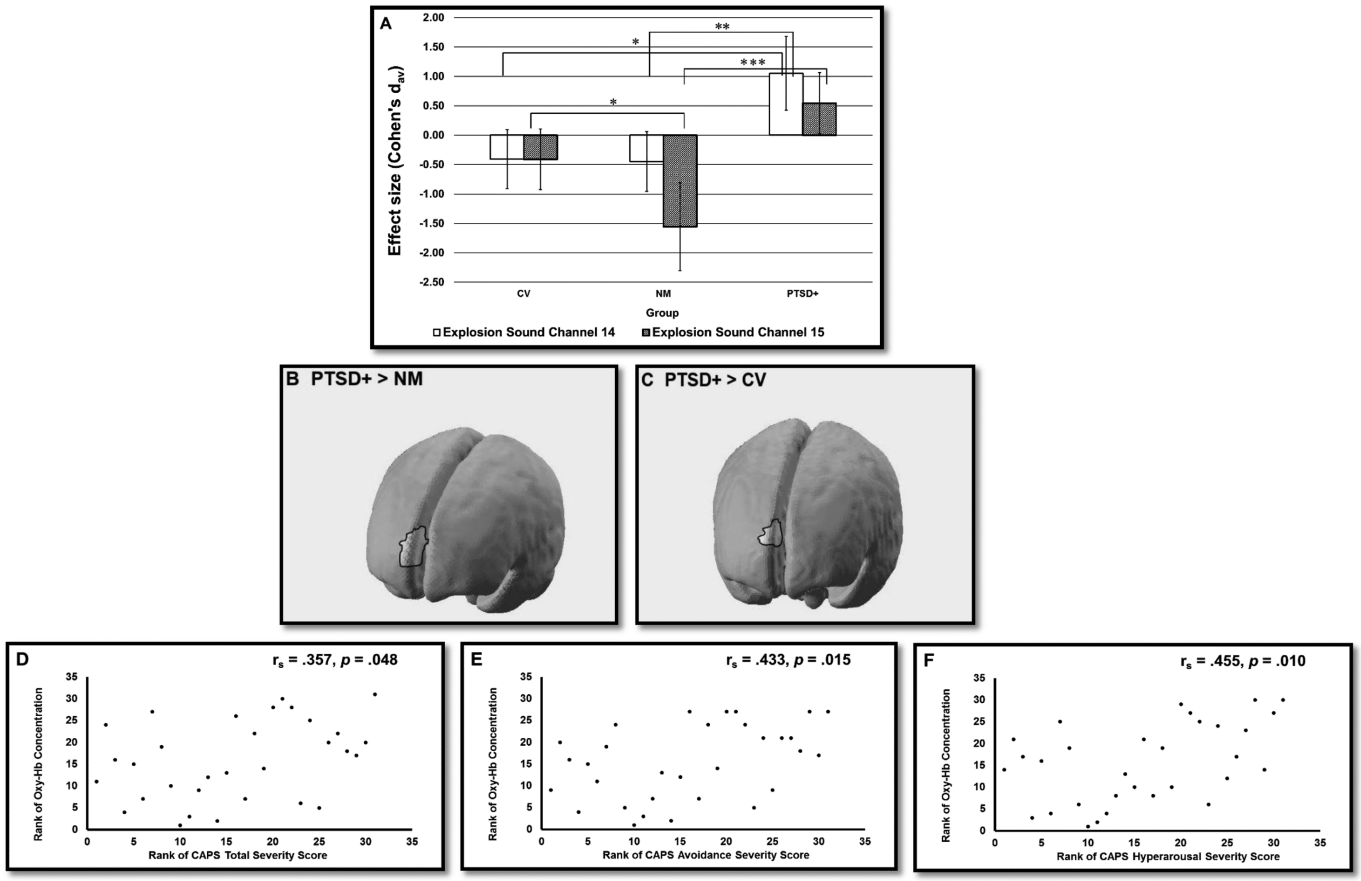

Figure 2. Results of oxygenated hemoglobin (oxy-Hb) concentrations during presentation of the explosion (trauma-related) sound at channels 14 and 15. Bar graphs indicate within-subjects effect sizes; positive values indicate higher, whereas negative values indicate lower concentrations of oxy-Hb during the explosion sound compared to the rest (baseline) phases (image A). Asterisks indicate significant group differences at channels 14 or 15 (image A). Statistical parametric mapping images of oxy-Hb concentrations during the explosion sound for combat veterans with posttraumatic stress disorder (PTSD) [PTSD+] compared with nonmilitary personnel without PTSD [NM] (image B) and combat veterans without PTSD [CV] (image C). Spearman's rank-order correlation scatter plots for explosion sound at channel 14 and Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) scores among PTSD+ and CV participants ($N = 31$; images D, E, and F).
$^*p < .05$. $^{**}p < .01$. $^{***}p < .001$.

trauma-related]) examined oxy-Hb beta values in each auditory and olfactory condition. Two-way repeated measures ANOVAs were performed in SPSS (version 23.0). We conducted planned comparisons of Group × Stimulus at each channel based on the literature showing increased activation of PFC among participants presented with trauma-related stimuli (Sartory et al., 2013). To control for Type I error, we used the false discovery rate (FDR) approach (Benjamini & Hochberg, 1995). Based on the mean beta values, we calculated the between-subjects effect for each significant channel as Cohen's *d* (Cohen, 1988). Additionally, we calculated the within-subjects effect size (i.e., d_{av}) to display the amount of oxy-Hb concentration between the experimental (e.g., trauma-related) and rest (baseline) phases (Cumming, 2012; displayed in Figure 2). For the within-subjects effect size (d_{av}), positive values indicate higher, whereas negative values indicate lower concentrations of the oxy-Hb. Increased concentrations of oxy-Hb suggest increased neural activation. Effect sizes were performed using Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA).

Results

Behavioral Ratings

Auditory condition. The Kruskal-Wallis test indicated a significant group effect for trauma-related hedonic ratings, $H(2) = 6.40$, $p = .041$. Step-down follow-up analysis showed that PTSD+ participants rated the trauma-related sound as significantly more unpleasant (M Rank = 17.28) compared to NM and CV participants (M Rank = 27.84 and M Rank = 28.38, respectively); however, there was no difference between the NM and CV groups, $p = .792$. There were no significant group differences for the neutral or negative hedonic ratings, as well as for the intensity ratings in the auditory condition.

Olfactory condition. There was a significant group effect for trauma-related hedonic ratings, $H(2) = 6.120$, $p = .047$. Step-down follow-up analysis revealed that the PTSD+ participants rated the trauma-related odor as significantly more unpleasant (M Rank = 18.09) than CV participants

(M Rank = 30.28); however, there were no significant differences between NM participants (M Rank = 25.12) and PTSD+ ($p = .168$) or CV ($p = .317$) participants. No significant group differences emerged for neutral or negative hedonic ratings, as well as for the intensity ratings in the olfactory condition.

fNIRS

Auditory condition. Results of the oxy-Hb auditory condition repeated measures ANOVA revealed significant group differences for the trauma-related sound at channel 14, $F(2,45) = 4.495$, $p = .017$, $\eta_p^2 = .167$; and channel 15, $F(2,45) = 7.671$, $p = .001$; $\eta_p^2 = .254$. Pairwise comparisons indicated significant differences between NM and PTSD+ groups at channel 14, $p = .006$; $d = 1.03$, 95% confidence interval (CI) [0.28, 1.76] and channel 15, $p < .001$; $d = 1.30$, 95% CI [0.53, 2.06]; between NM and CV groups at channel 15, $p = .03$; $d = 0.84$, 95% CI [0.11, 1.55]; and between the CV and PTSD+ groups at channel 14, $p = .036$; $d = 0.87$, 95% CI [0.14, 1.59]. After controlling for multiple testing using FDR, only channel 15 remained significant between NM and PTSD+ groups (i.e., $p \leq .002$).

There was a significant group difference for age between the PTSD+ and NM groups. We conducted a multivariate analysis of covariance (MANCOVA) using trauma-related oxy-Hb values at channels 14 and 15 with age as a covariate. When controlling for age, the overall MANCOVA was significant, $F(2, 28) = 3.592$, $p = .041$, Wilks' Lambda = .796; $\eta_p^2 = .204$. In addition, age was not a significant covariate, $F(2, 28) = 1.485$, $p = .244$, Wilks' Lambda = .904; $\eta_p^2 = .096$. Furthermore, age and trauma-related oxy-Hb values at channels 14 and 15 were not significantly correlated within any group (i.e., ps $> .05$). Thus, age does not appear to drive the significant effects found at channels 14 and 15.

Overall, the PTSD+ group displayed an increase in oxy-Hb at channels 14 and 15 during the trauma-related sound, which corresponded to the right medial superior PFC (BA 9/10). Conversely, the NM and CV participants exhibited a decrease in oxy-Hb at both of the respective channels (displayed in Figure 2). See Figure 2 for oxy-Hb SPM images between groups during the trauma-related sound.

Olfactory condition. With regard to the oxy-Hb repeated measures ANOVA for the olfactory condition, a significant group difference emerged at channel 3 for the trauma-related odor, $F(2,45) = 4.773$, $p = .013$; $\eta_p^2 = .175$, and neutral odor, $F(2,45) = 3.456$, $p = .04$; $\eta_p^2 = .133$. Pairwise comparisons indicated significant differences between CV and NM groups at channel 3 for the trauma-related odor, $p = .005$, $d = 0.92$, 95% CI [0.18, 1.64], and neutral odor, $p = .019$, $d = 0.74$, 95% CI [0.02, 1.45], as well as significant differences between CV and PTSD+ groups at channel 3 for the trauma-related odor, $p = .028$, $d = 0.68$, 95% CI [−0.04, 1.39], and neutral odor, $p = .044$, $d = 0.62$, 95% CI [−0.10, 1.32]. No significant differences emerged between NM and PTSD+ participants. Following FDR correction, no channels remained significant (i.e., $p > .002$). Overall, each group produced a decrease in concentration of oxy-Hb during the trauma-related and neutral olfactory tasks at channel 3, which coincided to the left middle frontal gyrus (BA 46).

Impact of PTSD severity on fNIRS activity. We conducted an exploratory analysis to determine whether a relationship existed between the severity of PTSD symptoms among combat veterans and neural activity at the explosion sound/channel 14 and the diesel fuel odor/channel 3 (based on the significant pairwise comparisons described earlier). For severity of PTSD, we examined the CAPS total score ($M = 55.55$, $SD = 7.79$) and CAPS subscale scores: reexperiencing ($M = 15.29$, $SD = 2.31$), avoidance ($M = 20.74$, $SD = 3.54$) and hyperarousal ($M = 19.19$, $SD = 2.31$). We performed Spearman's rank-order correlation tests due to bias of non normality and outliers among CAPS total and subscale scores. There were significant positive correlations between explosion sound/channel 14 and the following PTSD severity scores: CAPS total score, avoidance subscale score, and hyperarousal subscale score (displayed in Figure 2). These findings suggest that higher levels of overall PTSD severity, avoidance, and hyperarousal were moderately correlated to increased concentrations of oxy-Hb in the right medial superior PFC (BA 9/10) during presentation of the explosion sound.

Discussion

This is the first fNIRS investigation examining the neurophysiological response of combat veterans with PTSD when presented with a trauma-related sound and odor. The results indicated combat veterans with PTSD displayed increased activation in the right medial superior PFC (BA 9/10) during presentation of an explosion sound compared to individuals without history of combat exposure. Furthermore, combat veterans with PTSD endorsed higher ratings of unpleasantness for the explosion sound compared with both combat veterans and nonmilitary participants without PTSD, while no group differences emerged for neutral or negative sounds.

During the explosion sound, channel 14 (right medial superior PFC) failed to withstand FDR correction between combat veterans with PTSD compared with both nonmilitary personnel and combat veterans without PTSD. Nevertheless, if we had conducted a region of interest (ROI) analysis based on literature (Sartory et al., 2013), these group differences would be significant for channel 14. The FDR correction is common for multiple tests in neuroimaging, yet this conservative approach might exclude meaningful effects. Moving forward, one might run a ROI analysis and use a less conservative correction.

The outcome of this investigation is consistent with other recent investigations where increased activation in the right superior/middle frontal gyrus differentiated participants with PTSD and trauma-exposed controls during presentation of trauma-related stimuli (Sartory et al., 2013; Vermetten et al.,

2007). The results correspond with a recent fNIRS investigation that found greater activation of the right compared to the left PFC during exposure to negative affective stimuli among nonpsychiatric participants (Balconi, Grippa, & Vanutelli, 2015a).

This study supports the hypothesis that the PFC is activated among veterans with combat-related PTSD exposed to trauma-related stimuli. Neuroscience investigations have found increased activation of the right PFC linked with processing negative and threat-related stimuli (Kalisch & Gerlicher, 2014). Several investigations have implicated increased functioning of the right medial superior frontal gyrus during emotional distancing tasks aimed at reducing emotional arousal (Falquez et al., 2014; Koenigsberg et al., 2010). Although distancing oneself may offer an adaptive strategy to reduce immediate negative emotions and arousal among healthy individuals encountering new stimuli, this mechanism could be detrimental to those trying to emotionally detach from past adversity. Avoidance of thoughts, feelings, activities, or people that remind an individual of the trauma are hallmark symptoms of PTSD. Perhaps combat veterans with PTSD displayed increased activation in the right medial superior PFC during presentation of the explosion sound due to attempts to emotionally detach and reduce arousal, whereas those participants with or without history of combat did not experience the trauma-related cues as negative and therefore did not feel the need to detach.

The inability to self-regulate negative emotions related to the trauma may be a key neurophysiological feature of PTSD. Perhaps a superior strategy might involve changing the meaning of trauma-related internal or external cues through behavioral or cognitive therapy approaches. Rabinak and colleagues (2014) found decreased activation in the left dlPFC during presentation of negative stimuli in combat veterans with PTSD compared to combat veterans without PTSD following brief cognitive reappraisal training. Investigations using fNIRS have suggested that right frontal activity is related to emotions or approach behaviors towards negative stimuli, whereas activation of left PFC corresponds with emotions or approach behaviors towards positive stimuli (Balconi, Grippa, & Vanutelli, 2015b; Ernst et al., 2013). Future research should examine whether combat veterans with PTSD display increased functioning of the left dlPFC or decreased activation of the right medial superior PFC following successful treatment.

Although the PTSD+ group rated the trauma-related odor as significantly more unpleasant than the CV participants, differences in neural activity were not confirmed by fNIRS. This lack of significant group differences may have involved the selection of diesel fuel as the single trauma-related odor. Vermetten et al. (2007) found increased activation in the right medial PFC (BA 10) during presentation of diesel fuel for combat veterans with PTSD compared to those without PTSD, which is similar to the area identified for our findings in the trauma-related auditory condition between combat exposed groups. However, Vermetten et al. did not describe the index trauma for each participant. We found over 50% of our combat-exposed groups reported an event related to an IED or explosion (e.g., mortar attack) during the CAPS diagnostic screening for combat-related PTSD. Nevertheless, it was not determined whether diesel fuel was associated with each combat veteran's traumatic event. Moving forward, delivering a combat-related odor that specifically matches the traumatic event and is reported as a trigger of PTSD symptoms may improve the external validity and strengthen the observed effect.

This study has several limitations. First, fNIRS resolution has limited spatial localization and depth of approximately 3 cm and therefore, areas supporting fear and memory circuitry such as the amygdala and hippocampus were inaccessible (Tian & Liu, 2014). A potential solution may involve conducting investigations using fNIRS and fMRI simultaneously to establish the best neurological picture. Second, the strength of the oxy-Hb signal detected by this study may be diminished due to extracranial confounds such as skin blood flow (SBF; Haeussinger et al., 2014). Haeussinger and colleagues developed a correction method for SBF that increased levels of detected oxy-Hb concentration. Further fNIRS research could apply this method to vigilance or evoked arousal tasks. Third, although we screened for benzodiazepine medications, combat veterans with PTSD reported significantly greater use of antidepressant medications. Given the high rates of comorbid depression with PTSD, we could not expect to find a sample with little to no antidepressant use. Future research should extend this paradigm among medication-free participants, if available. Lastly, we did not gather data on level of combat exposure between combat veteran groups with and without PTSD. In future research, using a measure such as the Combat Exposure Scale (Keane et al., 1989) to control for degree of combat in comparison to PTSD symptoms may further clarify the nature of this relationship.

We believe this study has direct applications to the assessment and treatment of combat-related PTSD. First, neural examinations during the presentation of trauma-related cues might offer clinicians access to biomarkers that could extend incremental validity to diagnostic assessment. Among service-connected military personnel, it is vital to determine which men and women are experiencing PTSD beyond self-report to ensure available treatment resources are being channeled efficiently. Similarly, this approach should be examined among individuals currently diagnosed with noncombat PTSD (e.g., sexual assault). Furthermore, neurological assessment could benefit clinicians using first-line treatment approaches such as exposure therapy. Examining the autonomic and neurological responses of patients in response to cues would allow clinicians to identify and incorporate the most physiologically provoking triggers during exposure therapy sessions. Additionally, this added information would allow clinicians to monitor progress throughout the course of treatment using an objective indicator during trauma-related exposure beyond patient self-report. At this time, although neurological assessment cannot replace patient report of PTSD symptoms, it could promote an individualized, comprehensive approach to further assessment and treatment of this chronic disorder.

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