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Neurological Reactivity to Personalized Odors and Sounds in Combat-related Posttraumatic Stress Disorder

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NEUROLOGICAL REACTIVITY TO PERSONALIZED ODORS AND SOUNDS IN
COMBAT-RELATED POSTTRAUMATIC STRESS DISORDER

by

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A dissertation submitted in partial fulfillment of the requirements
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ABSTRACT

Functional near-infrared spectroscopy (fNIRS) is a neurophysiological procedure that offers immense clinical utility due to its cost effectiveness, ease of use, and mobile application. Using fNIRS to measure neurological reactions to personalized trauma-related cues might strengthen diagnostic screening, tailor treatment planning, and improve detection of remission among individuals with posttraumatic stress disorder (PTSD). Odors elicit strong emotional responses but remain underutilized in clinical research. This fNIRS study examined whether personalizing combat-related odors and sounds to have a higher or lower match to distressing combat experiences increased the observed neurological effect among combat veterans with and without combat-related PTSD. This study gathered data from 58 male, right-handed combat veterans of Iraq or Afghanistan, ages 26 to 68, recruited from the community. The results indicated a significant increase in activation at the left ventral lateral prefrontal cortex (VLPFC) following an interaction between higher PTSD severity and higher match ratings for the combat-related odors ($R^2 = .20$, $p = .003$; $f^2 = .25$). Furthermore, the left VLPFC showed a significant increase in activation following an interaction between having a PTSD diagnosis and higher match ratings for the combat-related odors ($R^2 = .25$, $p = .005$; $f^2 = .33$). The findings for the combat-related sounds were less clear. The left VLPFC is associated with facilitating regulation of memory and emotional processes. Overall, the presentation of odors with higher similarity to distressing combat experiences altered the neurological response of the prefrontal cortex and may contribute to better understanding of the neurophysiological mechanisms of combat-related PTSD.

I dedicate this dissertation to my wife, Ashley for being there for me throughout the entire doctorate program. You moved across the country for me and you never left my side. After all of these years, you continue to inspire me to maintain a proper balance in life.

I also dedicate this dissertation to my parents, Martin and Catherine who encouraged me to pursue my dreams. Both of you have been my best cheerleaders.

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CHAPTER 1: INTRODUCTION

Posttraumatic stress disorder (PTSD) involves experiencing intrusive symptoms, avoidance of thoughts or external reminders, negative cognitions and mood, and alterations in arousal (e.g., hypervigilance) for at least one month following a traumatic event (DSM-5; American Psychiatric Association, 2013). PTSD is a signature injury among U.S. service men and women with point prevalence estimates of 13% in deployed military personnel and 18% in soldiers exposed to combat in Iraq or Afghanistan (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014). Despite the effectiveness of interventions for PTSD, a biological or objective marker of PTSD such as functional near-infrared spectroscopy (fNIRS) may strengthen diagnostic evaluation, bolster treatment matching, and improve detection of remission.

1.1 Delivery of Personalized Odors with Posttraumatic Stress Disorder

Among individuals with PTSD, odors directly associated with the traumatic event elicited hyperarousal and intrusive symptoms and as such, providers incorporate odors during frontline treatments such as exposure therapy (Kline & Rausch, 1985; Rizzo et al., 2010; Vermetten & Bremner, 2003). In exposure therapy, it is beneficial to provide cues that match a patient's description of the traumatic event to elicit emotional engagement. A recent review linked olfactory cues and traumatic memories to emotional processing regions of the limbic system and prefrontal cortex (PFC; Daniels & Vermetten, 2016). Combat veterans with PTSD demonstrated increased activation in the right medial prefrontal cortex (MPFC) during presentation of a combat-related odor (i.e., diesel fuel) compared to veterans without PTSD, although it was not clear that diesel fuel was a part of each veteran's traumatic event (Vermetten, Schmahl,

Southwick, & Bremner, 2007). Taken together, delivering odors that match each veteran's specific traumatic event might increase the observed neurological effect and enhance the applicability to exposure therapy for PTSD beyond non-individualized odors.

1.2 Prefrontal Cortex and Posttraumatic Stress Disorder

Two regions of the PFC associated with PTSD include the dorsal medial prefrontal cortex (DMPFC) and ventral lateral prefrontal cortex (VLPFC). The DMPFC modulates appraisal of internal or external stimuli (Etkin, Egner, & Kalisch, 2011). A meta-analysis of symptom provocation paradigms found increased activation of the right anterior DMPFC among individuals with PTSD compared to trauma-exposed controls (Sartory et al., 2013). The VLPFC is located on the lateral/anterior sides of the PFC and is associated with memory control and emotion regulation (Badre & Wagner, 2007; Burklund, Creswell, Irwin, & Lieberman, 2014). A meta-analysis of symptom provocation neuroimaging studies found decreased activation of the right inferior frontal gyrus (approximate to the VLPFC) among individuals with PTSD compared to controls (Hayes, Hayes, & Mikedis, 2012). The DMPFC and VLPFC fall within the range of depth for fNIRS imaging and are relevant regions of interest with PTSD.

1.3 Functional Near-infrared Spectroscopy and Posttraumatic Stress Disorder

Investigations have applied fNIRS imaging to emotional memory recall. Individuals who endorsed emotional stimulation during emotional memory recall displayed increased activation in the PFC, whereas individuals who denied an emotional response did not show any fluctuation in activation (Ohtani, Matsuo, Kasai, Kato, & Kato, 2005). An fNIRS study compared PFC activation before and after receiving eye movement desensitization and reprocessing therapy

among individuals with PTSD resulting from different types of traumas (Ohtani, Matsuo, Kasai, Kato, & Kato, 2009). This study found greater activation during trauma memory recall at pretreatment compared to posttreatment, and furthermore, decreased activation at posttreatment was correlated with clinical improvement. In summary, individuals with PTSD react to sounds and odors associated with their trauma and neuroimaging can be used to detect changes in brain activation associated with PTSD. Further research appeared warranted to determine if fNIRS can be used to detect distinctive patterns of brain activation when combat veterans with PTSD are exposed to sounds and odors associated with their trauma.

Only one identifiable study has measured neurological reactivity using fNIRS during presentation of odors and sounds among individuals with and without PTSD (Gramlich, Neer, Beidel, Bohil, & Bowers, 2017). This study found combat veterans with PTSD displayed increased activation in the right DMPFC during presentation of a combat-related sound (i.e., explosion) compared to combat veterans without PTSD; however, there were no significant differences in neurological reactivity during delivery of a combat-related odor (i.e., diesel fuel). The combat-related odor selected might not have been part of each individuals' distressing combat experience and thus, would not necessarily elicit an emotional response. Further research is necessary to determine whether personalized odors that correspond to individual combat experiences will differentiate combat veterans with and without PTSD.

The current study examined whether combat veterans with PTSD displayed unique neurological responses during presentation of combat-related odors and sounds that matched their distressing combat experiences. Specifically, it was hypothesized that combat veterans with PTSD display increased activation in the DMPFC and decreased activation in the VLPFC (1)

compared to combat veterans without PTSD during presentation of combat-related odors and sounds that had a high match to their distressing combat experiences, (2) as well as compared to combat veterans with and without PTSD who received combat-related cues that had a low match to their distressing combat experiences.

CHAPTER 2: METHODS AND MATERIALS

2.1 Participants

Using a quasi-experimental design, we assessed two groups of participants: (1) combat veterans who received a combat-related odor and sound that had *high match* agreement with their distressing combat experiences (HM group) and (2) combat veterans who received a combat-related odor and sound that had *low match* agreement with their distressing combat experiences (LM group). This design ensured a similar number of participants received combat-related stimuli with a high match and low match agreement to their distressing combat experiences. The degree to which a combat-related odor or sound matched their distressing combat experiences was determined by participant self-report. The study included 58 male, right-handed combat veterans of Iraq or Afghanistan who were recruited from the community. The overall sample identified as primarily Caucasian (74.1%), completed some college (31.0%), military branch history as U.S. Army (69.0%), and a minority as active duty service members (12.1%). Table 1 shows participant groups were well-matched for age, smell acuity, handedness, PTSD severity, combat exposure, depression severity, and combat-related PTSD diagnosis. In addition to PTSD, we assessed for other DSM-5 psychiatric disorders. The most common other DSM-5 psychiatric disorders were depressive or anxiety disorders. See Table 1 for more details.

Table 1: Demographic and Clinical Characteristics of Combat Veterans

	HM		LM		Overall Sample			
	<u>(n = 29)</u>		<u>(n = 29)</u>		<u>(N = 58)</u>			
Variable	<i>Mean</i>	<i>SD</i>					<i>t</i>	<i>p</i>
Age in years	38.41	7.09	39.10	8.76	38.76	7.91	0.33	.743
UPSIT ^a	34.38	2.46	35.59	2.16	34.98	2.37	1.99	.052
Laterality Index ^a	85.52	16.77	79.43	18.67	82.47	17.85	-1.31	.197
CAPS-5 ^a	21.24	16.84	21.62	21.08	21.45	18.81	0.08	.940
CES ^a	22.31	10.34	20.97	10.59	21.64	10.39	-0.49	.626
PHQ-9 ^a	9.17	6.73	8.10	7.67	8.64	7.17	-0.56	.575
Variable	<i>N</i>	%					<i>X</i> ²	<i>p</i>
PTSD Dx	12	41.4%	12	41.4%	24	41.4%	0.00	>.999
Other Dx	10	34.5%	12	41.4%	22	37.9%	0.29	.588
Depressive Dx	9	31.0%	8	27.6%	17	29.3%	0.08	.733
Anxiety Dx	4	13.8%	6	20.7%	10	17.2%	0.48	.487

Note. HM = high match group; LM = low match group; UPSIT = University of Pennsylvania Smell Identification Test (Doty et al., 1984); Laterality Index = Handedness Questionnaire (Cohen, 2008); CAPS-5 = Clinician-Administered PTSD Scale for DSM-5 (Weathers et al., 2013); CES = Combat Exposure Scale (Keane et al., 1989); PHQ-9 = Patient Health Questionnaire (Kroenke et al., 2001); Dx = DSM-5 diagnosis; Other = non-PTSD.

^a = total score.

None of the participants screened positive for a current diagnosis of psychosis, antisocial personality disorder, moderate or severe substance use disorder, or current suicidal intent or plan. In addition, none of the participants met current diagnostic criteria for a dental phobia, which was relevant since the negative sound stimulus was an operating dentist drill. All of the participants denied a lifetime history of a moderate or severe traumatic brain injury (TBI) as assessed by the Ohio State University Traumatic Brain Injury Identification Method structured interview (OSU TBI-ID). None of the participants displayed significant hearing difficulty during the diagnostic interview or experiment (e.g., difficulty hearing stimuli or interviewer questions). All of the participants displayed acceptable smell acuity (total score of at least 30) on the University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, Kimmelman, & Dann, 1984).

With regard to medication history, none of the participants reported using any benzodiazepine or beta blocker medications within at least 48 hours before the fNIRS assessment. No significant group differences for psychotropic medication use, antidepressants, antipsychotics or mood stabilizers, anxiolytics (i.e., Buspirone), or amphetamines ($ps > .05$). All participants who endorsed taking psychotropic medication reported a stable duration of at least two months prior to completing the study.

G*Power version 3.1.9 (Faul, Erdfelder, Buchner, & Lang, 2009) was used to calculate the appropriate sample size for hypotheses one and two for a moderated regression analysis (i.e., F test, linear multiple regression, fixed model, R^2 increase). The significant effect sizes (f^2) for the combat-related stimuli in the Gramlich et al. study (2017) ranged from .200 to .340 for the auditory condition and .212 for the olfactory condition. With $\alpha = .05$ and power $(1 - \beta) = .80$, 37

participants total satisfied the minimum number required (with an effect size of .340) and 59 participants total accounted for the maximum number needed (with an effect size of .200). The number of participants required between the minimum and maximum estimates was 48 participants. Taken together, a minimum of 48 participants and maximum of 58 participants were collected to allow counterbalanced delivery of olfactory and auditory stimuli.

2.2 Procedure

This research was approved by the University of Central Florida Institutional Review Board. Participants completed the study assessment with the following phases in order: (Phase 1) pre-assessment, (Phase 2) match assessment, and (Phase 3) fNIRS assessment. During the pre-assessment, participants reviewed the informed consent document, all questions were answered, and participants provided verbal confirmation that they were willing to participate in the research study. Participants completed the UPSIT, self-report measures, and structured interviews to assess for the presence of combat-related PTSD and additional psychiatric diagnoses to determine study eligibility.

At the match assessment, participants rated 18 odors (i.e., 1 negative, 1 neutral, and 16 combat-related) and 18 sounds (i.e., 1 negative, 1 neutral, and 16 combat-related) in a counterbalanced randomized fashion. Each participant rated the 18 odors and 18 sounds only one time based on the following scales: *match*, *reexperiencing*, *avoidance*, and *hyperarousal* (Cortese et al., 2018; Elsesser, Sartory, & Tackenberg, 2004). Psychometrics for the match, reexperiencing, avoidance, and hyperarousal Likert scale properties are further discussed in the Auditory and Olfactory Psychometrics section. Participants rated the 16 combat-related odors

and the 16 combat-related sounds to rate level of match to their most bothersome or distressing combat-related trauma. In addition, participants rated the negative and neutral stimuli based on level of match to verify these cues had little to no relevance to their combat-related trauma. This information verified the negative and neutral stimuli were acceptable controls.

At the fNIRS assessment, LM participants received the combat-related odor and sound that earned the lowest match rating, whereas HM participants received the combat-related odor and sound that earned the highest match rating. If a participant rated two or more combat-related odors or sounds as the highest or lowest match rating, then whichever cue had the highest or lowest total summation across the additional ratings during the match assessment (i.e., reexperiencing, avoidance, and hyperarousal) was selected. If there was still a tie among two or more combat-related odors or sounds following the summation procedure, then one of those cues was randomly selected.

This study completed a 4 (group: combat veteran with PTSD-HM, combat veteran without PTSD-HM, combat veteran with PTSD-LM, and combat veteran without PTSD-LM) x 3 (stimulus: neutral, negative, combat-related) mixed-design within separate auditory and olfactory conditions. The four-group design was used to ensure an equal number of combat veterans with and without PTSD belonged to the HM and LM groups for the analyses. The following stimuli were delivered in a counterbalanced randomized fashion: combat-related sound and odor (based on match rating); neutral sound (fan) and odor (fresh cut grass); and negative sound (dentist drill) and odor (rotten egg). The menu of combat-related stimuli were based on the most incorporated odors and sounds used by clinicians during an investigation of Trauma Management Therapy for PTSD (Beidel, Frueh, Neer, & Lejuez, 2017). The neutral and negative sounds were selected

based on the International Affective Digitized Sounds manual (IADS-2; Bradley & Lang, 2007). The UPSIT normative study by Doty, Shaman, and Dann (1984) categorized grass as a neutral odor. Prior neurophysiological studies found rotten egg as a negative odor among combat veterans (Bedwell et al., 2018; Gramlich et al., 2017). Participants were not informed which odors and sounds they would receive during the study, but only the number of stimuli.

The fNIRS assessment used a block design consisting of 36 trials total. Within the fNIRS assessment, each auditory and olfactory condition consisted of 18 trials: 6 trials of combat-related stimuli, 6 trials of neutral stimuli, and 6 trials of negative stimuli. After each stimulus was presented, participants made subjective ratings based on two dimensions: hedonic (pleasant vs. unpleasant) and intensity (weak vs. strong). Psychometrics for the hedonic and intensity Likert scale properties are further discussed in the Auditory and Olfactory Psychometrics section. The fNIRS assessment included the following sequence of events, in order: 25 s of baseline (rest), stimulus presentation for 8 s for odors and 2 to 8 s for sounds (depending on length of the sound file), 10 s of rest, and subjective ratings of the stimulus for 12 s.

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). The Medical Virtual Reality group at the University of Southern California Institute for Creative Technologies provided the combat-related sound files. The participant sat 64 in. away from the computer monitor (23 in. screen) during the fNIRS assessment. The computer monitor displayed a white fixation crosshair on a black background during the fNIRS assessment. A computer program written using C# (Microsoft Corp., Redmond, WA, USA) presented the auditory and olfactory stimuli as well as

collected the match, reexperiencing, avoidance, hyperarousal, hedonic, and intensity ratings. The participant used a mouse to select the ratings.

The mobile odor device (Global Technology Integrators, LLC, Orlando, FL, USA) presented odor stimuli using stainless steel odor tubes (8 in. length x 1 in. diameter) for the match and fNIRS assessments. The mobile device delivered fresh air during the baseline, rest, and rating phases. Odor samples were received from the manufacturers of the mobile odor device (Global Technology Integrators, LLC). Odors were released using an air pump (Gardner Denver Thomas, Inc., Sheboygan, WI, USA). The mobile odor device delivered the odor samples for the match assessment using flexible chemical resistant tubing (3 ft length x 1/8 in. diameter) to allow for quick replacement of the 18 odor tubes between presentations. For the fNIRS assessment, the delivery tube was stainless steel (30 in. length x 3/8 in. diameter) and connected to a stainless steel smell port (7 in. length x 1.5 in. diameter) positioned within 2 cm from participants' nostrils. Prior to initiating the fNIRS assessment, the researcher centered the NIRScap using the nasion, inion, and left and right preauricular points. Each participant received a \$75 gift card in compensation for completing the study.

2.3 Measures

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a semi-structured interview that contains intensity and frequency ratings of the 20 DSM-5 PTSD symptoms and was conducted to assess for the presence and overall severity of combat-related PTSD (Weathers et al., 2013). The CAPS-5 demonstrated excellent psychometric properties with strong inter-rater reliability values for CAPS-5 scores ($\kappa = .78$ to 1.00) and test-retest reliability ($\kappa = .83$), as well

as high internal consistency ($\alpha = .88$) for the CAPS-5 total severity score (Weathers et al., 2018). The internal consistencies of the CAPS-5 found for this study were acceptable (participants with PTSD: Cronbach's $\alpha = .891$; participants without PTSD: Cronbach's $\alpha = .813$). The overall sample CAPS-5 total scores ranged from 0-65.

The Mini International Neuropsychiatric Interview version 7.0.2 for DSM-5 (MINI; Sheehan, 2016) is a structured interview that was used to determine the presence of 17 common DSM-5 psychiatric diagnoses including anxiety disorders, mood disorders, substance use disorders, antisocial personality disorder, and current suicidal ideation, intent, or plan. Psychometrics are not available for the recent version of the MINI for DSM-5; however, given the minimal format revisions from the prior versions of the MINI, few psychometric differences were expected (Lecrubier et al., 1997).

Measures were administered under supervision of licensed clinical psychologists. Twenty percent of CAPS-5 and MINI screens were randomly selected for review by blinded staff members to determine inter-rater reliability and received a high rate of agreement on the CAPS-5 (PTSD diagnosis, $\kappa = 1.00$; total score, ICC = .991) and MINI (psychiatric diagnosis, $\kappa = 1.00$).

The OSUI TBI-ID (Corrigan & Bogner, 2007) is a brief, structured interview that screened for TBI history. The Handedness Questionnaire (Cohen, 2008) evaluated handedness preference by calculating the laterality index for completing different tasks and was adapted from the Edinburgh Inventory (Oldfield, 1971). The UPSIT is a self-administered assessment that examined the ability to identify scratch-and-sniff smells correctly across four booklets containing 10 smells each (scores range from 0-40; Doty, Shaman, & Dann, 1984). This assessment was the

most reliable olfactory test available (test-retest reliability exceeds $r = 0.90$; Doty, Shaman, & Dann, 1984).

The Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) was used to assess for depressive symptoms and has been validated among individuals with and without depressive disorders (Löwe, Kroenke, Herzog, & Gräfe, 2004). The Combat Exposure Scale (CES; Keane et al., 1989) measured the subjective report of wartime stressors experienced by combatants (scores range from: 0-41). The CES has strong internal consistency ($\alpha = .85$) and excellent test-retest reliability ($r = .97$; Keane et al., 1989).

The Auditory and Olfactory Psychometrics during the match assessment instructed participants to rate each neutral, negative, and combat-related stimulus based on the level of match, reexperiencing, avoidance, and hyperarousal (Cortese et al., 2018; Elsesser et al., 2004). Match asked, “How similar is this stimulus to your distressing combat experience(s)?” Reexperiencing asked, “How much does this stimulus trigger memories of your distressing combat experience(s)?” Avoidance asked, “How much would you want to avoid this stimulus?” Hyperarousal asked, “How much does this stimulus make you feel anxious?” Ratings of match, reexperiencing, avoidance, and hyperarousal were quantified on a 9-point Likert scale using the same anchor points (range: 0 = *not at all* to 8 = *extremely*). During the fNIRS assessment, participants rated each individual odor and sound stimulus after presentation on two dimensions: hedonic and intensity. Hedonic tone asked, “How pleasant is this stimulus?” and was quantified on a 9-point Likert scale (range: +4 = *very pleasant* to -4 = *offensive*; Gramlich et al., 2017). Intensity asked, “How strong or weak is this stimulus?” and was quantified on a 7-point Likert scale (range: 0 = *not detectable* to 6 = *intolerable*; Gramlich et al., 2017). The test-retest

reliabilities for the hedonic and intensity ratings were acceptable (odors for HM, $ICC \geq .863$; sounds for HM, $ICC \geq .917$; odors for LM, $ICC \geq .802$; and sounds for LM, $ICC \geq .966$).

Participants completed fNIRS imaging using the NIRSport-88, multi-channel, mobile fNIRS procedure (NIRx Medical Technologies, LLC, Berlin, Germany). The fNIRS procedure assessed neurological activation during the auditory and olfactory conditions by measuring concentrations of oxygenated hemoglobin (oxy-Hb). The fNIRS cap included an 8-source/7-detector configuration with 20 data channels and a data sampling rate of 7.8 Hz. The distance between the source-detector optodes at a measured data channel was approximately 3 cm. See Figure 1 for a configuration of the fNIRS data collection channels.

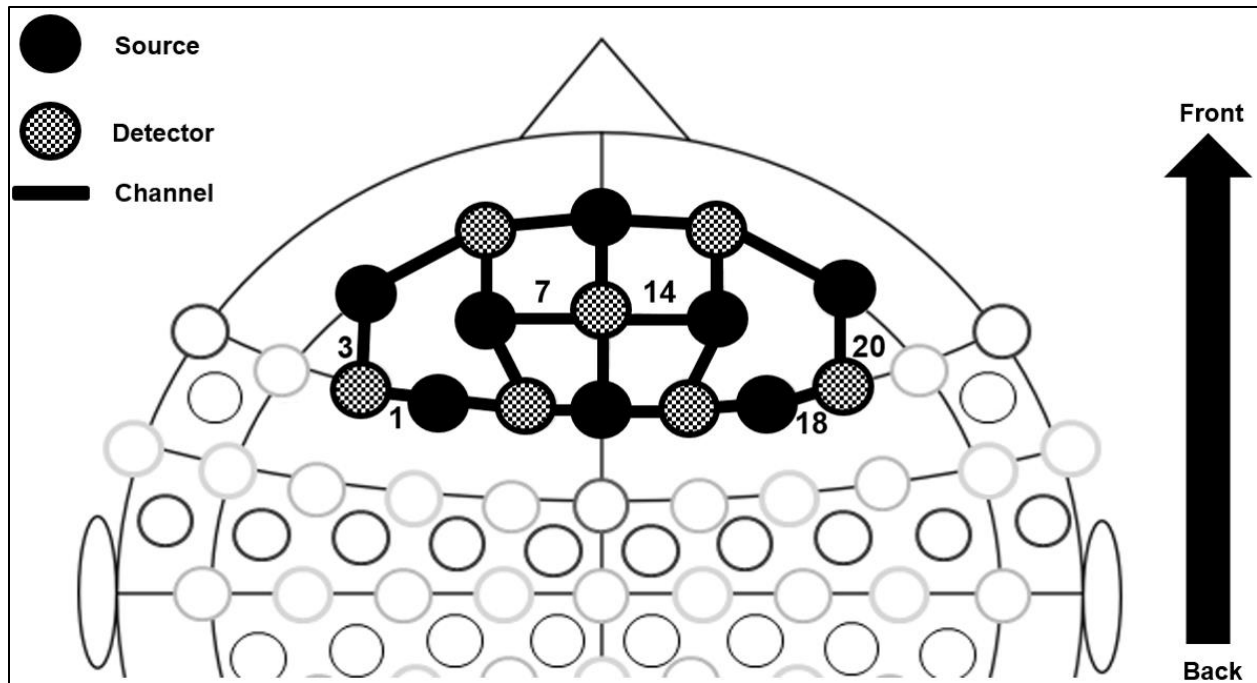


Figure 1: The Configuration of Functional Near-infrared Spectroscopy (fNIRS) Optodes and Data Collection Channels.

The black circles denote sources, the checkered circles denote detectors, and the black lines connecting sources and detectors indicate fNIRS data collection channels. Region of interest channel numbers appear adjacent to channel locations. Left ventral lateral prefrontal cortex (VLPFC): channels 1 and 3; right VLPFC: channels 18 and 20; left dorsal medial prefrontal cortex (DMPFC): channel 7; and right DMPFC: channel 14. The white circles denote idle electroencephalogram electrode positions.

2.4 Data Analysis

The primary outcomes were change in concentration of oxy-Hb as measured by fNIRS oxy-Hb beta values. An increase in oxy-Hb concentration indicated an increase in brain activation, whereas a decrease in oxy-Hb concentration suggested a decrease in brain activation. Raw optical density values were transformed to produce estimates of oxy-Hb concentrations at each sample point using the modified Beer-Lambert law in nirsLAB (version 2017.06, NIRx Medical Technologies, LLC, Brooklyn, NY, USA). The general linear model approach using statistical parametric mapping is a standard and widely used approach and was performed for level 1 analysis. Level 1 analysis included a model of three beta regressors (neutral, negative, and combat-related) to measure the influence of valence level for each individual participant. An additional nuisance beta regressor was included to partial out the data collected during the 12 s rating phase task. 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).

This study conducted *a priori* region of interest (ROI) analyses of the right/left DMPFC and right/left VLPFC corresponding to the following data channels: 14 (right DMPFC), 7 (left DMPFC); 1 and 3 (left VLPFC); as well as 18 and 20 (right VLPFC). Two models of moderated regression analyses were conducted to examine oxy-Hb concentrations in each auditory and olfactory condition:

Model A: CAPS-5 total score (PTSD severity) and match rating (moderator variable) predicting oxy-Hb concentration at an fNIRS channel (outcome variable). The total sample ($N = 58$; HM, $n = 29$; LM, $n = 29$) was included in Model A.

Model B: PTSD diagnosis (yes/no) and match rating (moderator variable) predicting oxy-Hb concentration at an fNIRS channel (outcome variable). The total sample was lowered to 50 participants for Model B to keep the number of participants with and without PTSD similar to reduce inflation of significant findings (i.e., (a) 12 HM participants with PTSD; (b) 13 HM participants without PTSD; (c) 12 LM participants with PTSD; and (d) 13 LM participants without PTSD). Significant differences were found across the four groups for PHQ-9 total score ($F(3, 46) = 13.44, p < .001$); CES total score ($F(3, 46) = 4.17, p = .011$); and CAPS-5 total score ($F(3, 46) = 40.47, p < .001$). Pairwise contrasts revealed no significant group differences for PHQ-9, CES, and CAPS-5 total scores between HM and LM participants with PTSD ($ps > .05$). We reran any significant overall model for Model B to covary for CES and PHQ-9 total scores to determine if the moderation outcomes remained consistent. No significant differences emerged across the four groups for age, handedness, or smell acuity ($ps > .05$).

Models A and B were conducted using the stimulus match rating as the moderator and the oxy-Hb concentration at the fNIRS channel for each stimulus type separately (i.e., combat-related, neutral, and negative). The moderated regression analyses were run in SPSS (version 23.0, IBM Corp. Armonk, NY, USA). PROCESS v3.3 (Hayes, 2018) was used to center variables and analyze the interactions for Models A and B. Multicollinearity of predictors was not present. Standard errors for model coefficients were based on the HC3 heteroscedasticity-constant standard error estimator due to heteroscedasticity (Hayes & Cai, 2007).

For Model A, three HM participants had bad signal recordings at channel 1 during the olfactory condition. For Model A, three HM participants and two LM participants had bad recordings at channel 1 during the auditory condition. For Model B, one HM participant had a

bad signal recording at channel 1 for the olfactory condition. For Model B, one LM participant had a bad signal recording at channel 1. No additional bad signal recordings occurred for the ROI data. Channels with bad signal recordings were not included in the ROI analyses. ROI analyses were conducted with an alpha level set to .025 to control for testing both hemispheres.

The secondary outcomes were six dependent variables: (1) match ratings; (2) reexperiencing ratings; (3) avoidance ratings; (4) hyperarousal ratings; (5) hedonic ratings; and (6) intensity ratings. Similar to the primary outcome measures, we averaged these behavioral ratings separately from each of the three stimulus independent variables within the auditory and olfactory conditions. Missing data occurred for < 10% of each participant's hedonic and intensity ratings, except for one participant during the olfactory condition due to self-reported difficulty choosing between the scaled options within 12 s (one hedonic rating per stimulus and three intensity ratings per stimulus). To deal with missing data, replacement values using the corresponding mean hedonic or intensity score were inputted; however, this did not alter the findings and therefore the available data was analyzed. Behavioral ratings were compared across groups and analyzed using SPSS (version 23.0). 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 transformations) were unsuccessful. In addition, the behavioral ratings were ordinal data and as such were analyzed using nonparametric tests using SPSS. Behavioral analyses were conducted with the alpha level set to .05.

CHAPTER 3: RESULTS

3.1 Behavioral Ratings

3.1.1 Olfactory Condition

The Mann-Whitney test showed HM participants rated the combat-related odors as significantly higher match (HM, M Rank = 43.45; LM, M Rank = 15.55; U = 825.00; p < .001); significantly higher reexperiencing (HM, M Rank = 42.38; LM, M Rank = 16.62; U = 794.00; p < .001); significantly higher avoidance (HM, M Rank = 42.24; LM, M Rank = 16.76; U = 790.00; p < .001); and significantly higher hyperarousal (HM, M Rank = 41.17; LM, M Rank = 17.83; U = 759.00; p < .001) compared to LM participants combat-related odors. See Figure 2 for the combat-related odors included in the fNIRS assessment for HM and LM participants. There were no significant group differences for the neutral or negative match, reexperiencing, avoidance, and hyperarousal ratings in the olfactory condition (ps > .05).

The Mann-Whitney test indicated that HM participants rated the combat-related odors as significantly more unpleasant compared to LM participants (HM, M Rank = 24.52; LM, M Rank = 34.48; U = 276.00; p = .024); however there was no significant group difference for the intensity of the combat-related odors (HM, M Rank = 29.97; LM, M Rank = 29.03; U = 276.00; p = .833). There were no significant group differences for the neutral or negative hedonic and intensity ratings in the olfactory condition (ps > .05).

3.1.2 Auditory Condition

The Mann-Whitney test showed HM participants rated their combat-related sound as significantly higher match (HM, M Rank = 43.36; LM, M Rank = 15.64; U = 822.50; p < .001);

significantly higher reexperiencing (HM, M Rank = 42.95; LM, M Rank = 16.05; U = 810.50; p < .001); significantly higher avoidance (HM, M Rank = 42.78; LM, M Rank = 16.22; U = 805.00; p < .001); and significantly higher hyperarousal (HM, M Rank = 42.64; LM, M Rank = 16.36; U = 801.50; p < .001) compared to LM participants. See Figure 2 for the combat-related sounds included in the fNIRS assessment for HM and LM participants. There were no significant group differences for the neutral or negative match, reexperiencing, avoidance, and hyperarousal ratings in the auditory condition (ps > .05).

The Mann-Whitney test showed HM participants rated their combat-related sound as significantly more unpleasant (HM, M Rank = 18.98; LM, M Rank = 40.02; U = 115.50; p < .001) and more intense (HM, M Rank = 38.95; LM, M Rank = 20.05; U = 694.50; p < .001) compared to LM participants. There were no significant group differences for the neutral or negative hedonic and intensity ratings in the olfactory condition (ps > .05).

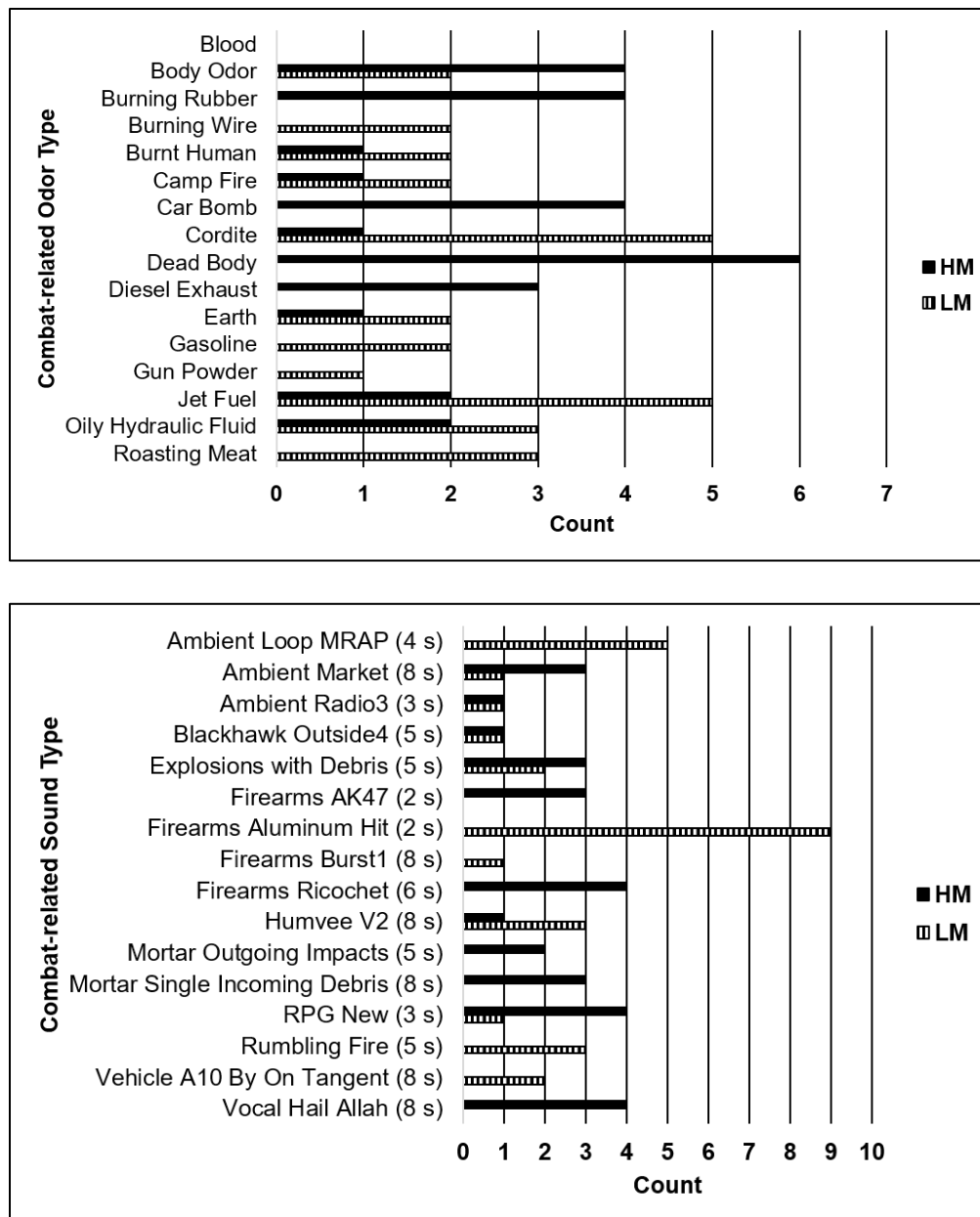


Figure 2: The Count of Combat-related Odors and Sounds Participants in the High Match (HM) and Low Match (LM) Groups Received During the fNIRS Assessment.

The duration of each sound file is listed in the figure. Mine-resistant Ambush Protected (vehicle) = MRAP; Automatic Kalashnikov 1947 (assault rifle) = AK-47; version 2 = V2; Rocket Propelled Grenade (weapon) = RPG; and military aircraft = A10.

3.2 fNIRS Model A (PTSD Severity)

3.2.1 Olfactory Condition

The overall model was significant for the combat-related odors at channel 1, $F(3,51) = 5.34, p = .003, R^2 = .20, f^2 = .25$; and channel 3, $F(3,54) = 5.73, p = .002, R^2 = .17, f^2 = .20$. There was a significant main effect for CAPS-5 total score at channel 3, $b = 0.000005, t(54) = 2.46, p = .017$. As the severity of PTSD increased, oxy-Hb concentration at channel 3 increased. There were significant interactions for CAPS-5 total score and match rating at channel 1, $b = 0.000003, t(51) = 3.44, p = .001$; and channel 3, $b = 0.000003, t(54) = 3.75, p < .001$. For a high match rating, there was a significant increase in oxy-Hb concentration when PTSD severity increased at channel 1, $b = 0.00001, t(51) = 3.79, p < .001, 95\% \text{ CI } [0.000005, 0.00002]$ and channel 3, $b = 0.00001, t(54) = 3.99, p < .001, 95\% \text{ CI } [0.000007, 0.00002]$. For a moderate match rating, there was a significant increase in oxy-Hb concentration when PTSD severity increased at channel 3, $b = 0.000005, t(54) = 2.46, p = .017, 95\% \text{ CI } [0.000001, 0.00009]$; however, there was not a significant finding for oxy-Hb concentration when PTSD severity increased at channel 1, $b = 0.000003, t(51) = 1.14, p = .259, 95\% \text{ CI } [-0.000002, 0.000007]$. For a low match rating, there were no significant differences in oxy-Hb concentrations when PTSD severity increased at channel 1, $b = -0.000005, t(51) = -1.46, p = .151, 95\% \text{ CI } [-0.00001, 0.000002]$ and channel 3, $b = -0.000003, t(54) = -1.15, p = .257, 95\% \text{ CI } [-0.000008, 0.000002]$.

When providing a combat-related odor match rating of at least 4.00 at channel 1 and 3.20 at channel 3, PTSD severity and oxy-Hb concentration were significantly related ($b = 0.000006, t(51) = 2.64, p = .011$ and $b = 0.000006, t(54) = 2.69, p = .010$, respectively). As match increased, the relationship between PTSD severity and oxy-Hb concentration became more

positive with the highest match rating (8.00) at channels 1 and 3 ($b = 0.00002$, $t(51) = 3.98$, $p < .001$ and $b = 0.00002$, $t(54) = 4.08$, $p < .001$, respectively). Figure 3 shows the interactions between the predictors at channels 1 and 3.

The overall models were not significant for the remaining ROI channels of the combat-related odors, as well as for all of the ROI channels of the neutral and negative odors ($ps > .025$). In summary, a moderate to high match rating for combat-related odors showed a significant increase in activation at channel 3 (i.e., left VLPFC) when PTSD severity increased. Furthermore, significant increases in activation were found at channels 1 and 3 (i.e., left VLPFC) for high match ratings of combat-related odors when PTSD severity increased. In contrast, there were no significant relationships between brain activation and PTSD severity for a low match rating of combat-related odors.

3.2.2 Auditory Condition

The overall models were not significant for all of the ROI channels of the combat-related, neutral, and negative sounds ($ps > .025$). Taken together, PTSD severity and level of match rating to their distressing combat experiences did not interact to affect the brain activation of combat-related, neutral, and negative sounds.

3.3 fNIRS Model B (PTSD Diagnosis)

3.3.1 Olfactory Condition

The overall models were significant for the combat-related odors at channel 1, $F(3,45) = 4.96$, $p = .005$, $R^2 = .25$, $f^2 = .33$; channel 3, $F(3,46) = 4.38$, $p = .009$, $R^2 = .21$, $f^2 = .27$; and

channel 7, $F(3,46) = 3.91, p = .014, R^2 = .14, f^2 = .16$. There were significant interactions for PTSD diagnosis and match rating at channel 1, $b = 0.0001, t(45) = 3.51, p = .001$; channel 3, $b = 0.00009, t(46) = 2.71, p = .009$; and channel 7, $b = 0.00004, t(46) = 2.71, p = .009$. After covarying for PHQ-9 and CES total scores, the overall models and interaction effects remained similar for the combat-related odors at channels 1 and 3 ($ps < .025$), whereas the overall model did not remain significant for channel 7 ($p = .051$). For a high match rating, there was a significant increase in oxy-Hb concentration with a PTSD diagnosis at channel 1, $b = 0.0004, t(45) = 3.51, p = .001, 95\% \text{ CI } [0.0002, 0.0007]$ and channel 3, $b = 0.0005, t(46) = 3.48, p = .001, 95\% \text{ CI } [0.0002, 0.0007]$. For moderate and low match ratings at channels 1 and 3, there were no significant differences in oxy-Hb concentrations and having a PTSD diagnosis ($ps > .025$).

When providing a combat-related odor match rating of at least 4.40 at channel 1 and 4.00 at channel 3, PTSD diagnosis and oxy-Hb concentration were significantly related ($b = 0.0002, t(45) = 2.52, p = .015$ and $b = 0.0003, t(46) = 2.56, p = .014$, respectively). As match increased, the relationship between PTSD diagnosis and oxy-Hb concentration became more positive with the highest match rating (8.00) at channels 1 and 3 ($b = 0.0006, t(45) = 3.79, p < .001$ and $b = 0.0006, t(46) = 3.52, p < .001$, respectively). Figure 3 shows the interactions between the predictors at channels 1 and 3.

The overall models were not significant for the remaining ROI channels of the combat-related odors and all of the ROI channels for the neutral and negative odors ($ps > .025$). In summary, significant increases in activation were found at channels 1 and 3 (i.e., left VLPFC)

following interactions between a PTSD diagnosis and high match rating for combat-related odors.

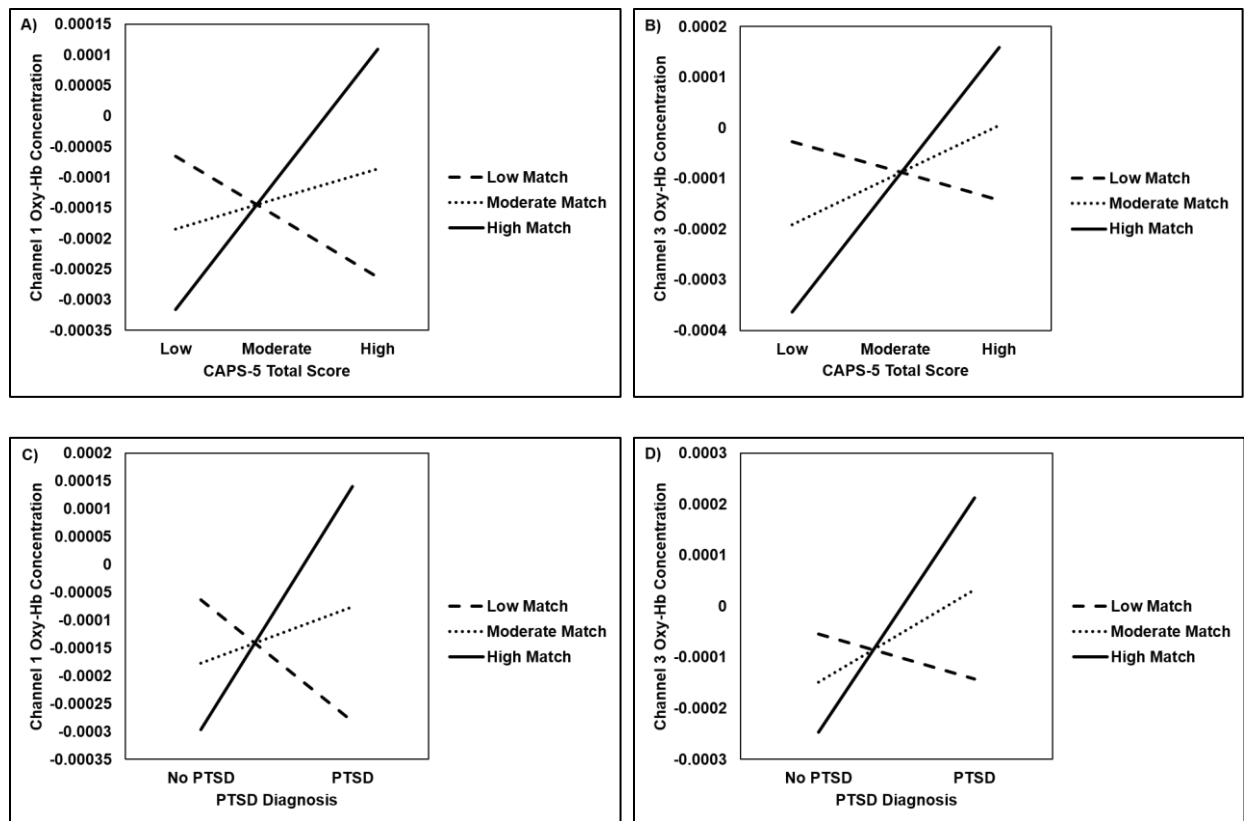


Figure 3: The Interactions Effects at Channels 1 and 3 for the Combat-related Odors.

Image A and image B show the interaction effects between the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score and match rating (low, moderate, and high) predicting oxygenated hemoglobin (oxy-Hb) concentration (i.e., Model A). Image C and image D display the interaction effects between PTSD diagnosis and match rating predicting oxy-Hb concentration (i.e., Model B). Oxy-Hb concentration values are quantified as beta values.

3.3.2 Auditory Condition

The overall model was significant for the negative sound at channel 14, $F(3,46) = 3.67$, $p = .019$, $R^2 = .14$, $f^2 = .16$. However, after covarying for PHQ-9 and CES total scores, the overall model was not significant for the negative sound at channel 14, $F(3,46) = 1.69$, $p = .16$, $R^2 = .17$, $f^2 = .20$. The overall models were not significant for any of the remaining ROI channels of the negative sounds, or the ROI channels of the combat-related and neutral sounds ($ps > .025$). Taken together, PTSD diagnosis and level of match rating to their distressing combat experiences did not interact to affect the brain activation of combat-related, neutral, and negative sounds.

CHAPTER 4: DISCUSSION

Using fNIRS, we examined whether optimizing the fidelity of combat-related odors and sounds would alter the neurological responses among combat veterans with and without PTSD. The results of Model A indicated as PTSD severity increased, greater brain activation occurred in the left VLPFC during delivery of combat-related odors with a high similarity to their distressing combat experiences. Furthermore, the results of Model B found increased activation in the left VLPFC among combat veterans with a PTSD diagnosis in response to combat-related odors with a high similarity to their distressing combat experiences, whereas no significant group differences in brain activation occurred for combat-related odors with a low similarity. Taken together, the findings indicated increasing the fidelity of combat-related odors provided meaningful changes in activation of the left VLPFC among combat veterans with PTSD.

The first and second hypotheses were not supported, as there was a significant increase in activation at the left VLPFC and no significant increase in activation at the right DMPFC for combat veterans with greater PTSD severity. Symptom provocation meta-analyses reported either a significant decrease in activation at the right VLPFC or a significant increase in activation at the right DMPFC for individuals with PTSD, among other areas (Hayes et al., 2012; Sartory et al., 2013). However, these symptom provocation meta-analyses did not include studies delivering odors. Olfactory cues are processed differently than auditory and visual stimuli. Unlike auditory and visual cues, transmission of olfactory information bypasses the thalamus and goes directly to the prefrontal cortex and limbic system (e.g., amygdala; Shepherd, 2005). Furthermore, odors elicited more emotional responses and stronger feelings of being brought back to a past event than auditory or visual cues (Herz, 2004).

The findings of increased activation in the left VLPFC converged with prior olfaction neuroimaging studies. The anatomical locations attributed to the left VLPFC includes Brodmann area 47 (BA 47). Increased activation of BA 47 was found during presentation of unpleasant odors (Gottfried, Deichmann, Winston, & Dolan, 2002); unpleasant compared to pleasant odors (Rolls, Kringelbach, & Araujo, 2003); and emotional cues compared to neutral cues for olfactory but not for auditory or visual stimuli (Royet et al., 2000). The combat-related PTSD study by Vermetten et al. (2007) did not find a significant increase in activation at the left VLPFC among combat veterans with PTSD receiving a combat-related odor. The divergence in findings compared to our study might be due to not reporting handedness, among other reasons. For instance, a study reported judging the hedonic tone of odors showed increased activation in BA 47 for right-handed participants, whereas no significant changes were found in BA 47 for left-handed participants (Royet, Plailly, Delon-Martin, Kareken, & Segebarth, 2003). Therefore, we believe it is valuable to report laterality differences in future investigations.

With regard to the auditory condition, combat-related sounds with low or high similarity did not influence different neurological responses among combat veterans with and without PTSD. Nevertheless, an fNIRS study found a combat-related sound increased activation in the right DMPFC among combat veterans with PTSD (Gramlich et al., 2017). Perhaps, sounds classified as combat-related were sufficient to cause combat veterans to think of distressing combat experiences during this study's fNIRS assessment. For instance, a combat veteran hearing radio chatter during the fNIRS assessment might be reminded of hearing the radio in a Humvee, which was later hit by an improvised explosive device (IED). The Humvee or IED sounds might have the highest match to his distressing combat experiences; however, the radio

chatter might still elicit thoughts of the distressing combat experiences after hearing it several times during the fNIRS assessment due to its relevance to combat. In contrast, odors categorized as combat-related might require higher specificity to trigger a neurological reaction.

The results provided meaningful implications for neuroimaging research and clinical interventions for combat veterans with PTSD. First, neuroimaging studies may benefit from personalizing the combat-related odors to match a distressing combat experiences due to its unique neurological responses. Second, clinicians using virtual reality exposure therapy for PTSD may benefit from incorporating odors with the highest similarities to the traumatic event to strengthen the applicability and increase the neurological engagement of the left VLPFC. Researchers found the left VLPFC supported memory encoding to create unique memory traces and memory retrieval of relevant details of past events (Badre & Wagner, 2007). Furthermore, increased activation of the left VLPFC was found to be associated with emotion regulation strategies (Burklund et al., 2014). A review article by Engen and Anderson (2018) proposed a novel theory on the link between memory control and emotion regulation. Specifically, the left VLPFC helps with retrieval of past memories and reconsolidates them via thought substitution to become innocuous or even positive. We delivered the auditory and olfactory stimuli six times each to ensure we had reliable findings. Perhaps, through repeated exposures, combat veterans with PTSD who rated the odors as a higher match were recruiting the left VLPFC to initiate this mechanism of emotion regulation. We did not compare fNIRS data trial by trial because it was beyond the scope of this study. Nevertheless, activation of the left VLPFC may support memory selection or perhaps, a neurological mechanism to facilitate memory-based emotional reactions.

4.1 Limitations and Future Directions

Several limitations and future directions should be noted. First, it is recommended to deliver this paradigm using functional magnetic resonance imaging since fNIRS cannot measure activation of other relevant brain regions (e.g., amygdala and hippocampus). Second, our list of combat-related stimuli was not an all-inclusive list available in clinical settings. Third, this study did not include females or examine non-combat traumas, and therefore, it is encouraged to further the study of personalized trauma-related odors among these diverse populations. It is recommended to measure the reactivity to odors at pre and posttreatment to confirm if neurological connections that signal successful treatment were established or strengthened. Furthermore, fNIRS measurement of neurological reactivity at posttreatment might enhance prediction of sustained remission at long-term follow-up beyond self-report evaluations.

**APPENDIX:
APPROVAL LETTER**



University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: UCF Institutional Review Board #1
FWA00000351, IRB00001138

To: Michael A. Gramlich and Co-PIs: Corey J. Bohil, Deborah Casamassa Beidel, Emy A. Willis, Krystal I. Morrison, Michelle Keck, & Sandra M. Neer

Date: September 14, 2018

Dear Researcher:

On 09/14/2018 the IRB approved the following modifications to human participant research until 08/16/2019 inclusive:

Type of Review: IRB Addendum and Modification Request Form
Expedited Review
Modification Type: Added a fourth group. Increased total number of participants from 60 to 68. Decreased total number of participants per group from 16 to 14. Revised Protocol uploaded in iRIS and revised consent and debriefing form approved for use.
Project Title: Neurological reactivity to personalized odors and sounds in combat-related posttraumatic stress disorder
Investigator: Michael A. Gramlich
IRB Number: SBE-18-14168
Funding Agency: Sigma Xi
Grant Title: N/A
Research ID: N/A

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30 days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at <https://iris.research.ucf.edu>.

If continuing review approval is not granted before the expiration date of 08/16/2019, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a copy of the consent form(s).

All data, including signed consent forms if applicable, must be retained and secured per protocol for a minimum of five years (six if HIPAA applies) past the completion of this research. Any links to the identification of participants should be maintained and secured per protocol. Additional requirements may be imposed by your funding agency, your department, or other entities. Access to data is limited to authorized individuals listed as key study personnel.

In the conduct of this research, you are responsible to follow the requirements of the [Investigator Manual](#).

This letter is signed by:

A handwritten signature in black ink that reads "Kamille Chaparro". The signature is written in a cursive style with a long horizontal line extending from the end of the name.

Signature applied by Kamille Chaparro on 09/14/2018 11:21:08 AM EDT

Designated Reviewer

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